



GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

www.esmo.org



CARDIOVASCULAR



NEUROLOGICAL

RESPIRATORY



RENAL &
UROLOGICAL



METABOLIC

GASTRO-
INTESTINAL



IMMUNE-
HAEMATOLOGICAL

ESMO HANDBOOK OF ONCOLOGICAL EMERGENCIES

Edited by Mariano Provencio Pulla

2ND EDITION

CANCER PAIN



PSYCHOLOGICAL



ESMO Handbook Series



ESMO HANDBOOK OF **ONCOLOGICAL EMERGENCIES**



ESMO HANDBOOK OF **ONCOLOGICAL EMERGENCIES**

Edited by

Mariano Provencio Pulla

*Medical Oncology Department, Hospital Universitario
Puerta de Hierro, Madrid, Spain*

ESMO Press

First edition published in 2005 by Taylor & Francis. This edition first published in 2016 by ESMO Press.

© 2016 European Society for Medical Oncology

All rights reserved. No part of this book may be reprinted, reproduced, transmitted, or utilised in any form by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying, microfilming, and recording, or in any information storage or retrieval system, without written permission of the publisher or in accordance with the provisions of the Copyright, Designs, and Patents Act 1988 or under the terms of any license permitting limited copying issued by the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, USA (www.copyright.com/ or telephone 978-750-8400). Product or corporate names may be trademarks or registered trademarks, and are used only for identification and explanation without intent to infringe.

This book contains information obtained from authentic and highly regarded sources. Reprinted material is quoted with permission and sources are indicated. A wide variety of references are listed. Reasonable efforts have been made to publish reliable data and information, but the authors and publisher cannot assume responsibility for the validity of all materials or for the consequence of their use.

Although every effort has been made to ensure that drug doses, treatments, and other information are presented accurately in this publication, the ultimate responsibility rests with the prescribing physician. Neither the publisher nor the authors can be held responsible for errors or for any consequences arising from the use of information contained herein. For detailed prescribing information on the use of any product or procedure discussed herein, please consult the prescribing information or instructional material issued by the manufacturer.

A CIP record for this book is available from the British Library.

ISBN: 978-88-906359-9-1

For orders, corporate sales, foreign rights, and reprint permissions, please contact:

ESMO Head Office
Guidelines and Publishing Department
Via Luigi Taddei 4
6962 Viganello-Lugano
Switzerland
Tel: +41 (0)91 973 19 00
www.esmo.org
Email: publishing@esmo.org

Printed through s|s|media limited, Rickmansworth, Hertfordshire, UK

Contents

Contributors	xii
Reviewers	xvi
Acknowledgements	xvii
Preface	xviii

I CARDIOVASCULAR COMPLICATIONS

1 Cardiac Complications of Cancer and Anticancer Treatment	3
Introduction	3
Malignant Pericardial Effusion and Cardiac Tamponade	3
Chemotherapy-related Heart Failure	5
Arterial Hypertension	10
Myocardial Ischaemia	12
Arrhythmias	13
QT Prolongation	14
Radiation Therapy-induced Cardiotoxicity	15
Further Reading	16
2 Venous Thromboembolism in Cancer Patients	17
Introduction	17
Pathophysiology	18
Diagnosis	20
Prevention of Cancer-associated Thromboembolism	22
Treatment	23
Further Reading	28

3	Superior Vena Cava Syndrome	30
	Introduction	30
	Physiology of SVC Obstruction (SVCO)	30
	Aetiology	31
	Investigations	32
	Treatment	34
	Summary	38
	Further Reading	38
4	Complications of Central Venous Devices	39
	Introduction	39
	Intravascular Catheter-related Infections	39
	Catheter-related Thrombosis	45
	Catheter Malfunction	47
	Further Reading	47
5	Septic Shock	49
	Definition	49
	Management of Septic Shock	49
	Antimicrobial Therapy	51
	Treatment of Cardiovascular Insufficiency	53
	Oxygen Support	54
	Nutrition	55
	Hyperglycaemia	55
	Treatment with Corticosteroids	55
	Treatment with Coagulation Inhibitors	55
	Cytokines and Haematopoietic Growth Factors	56
	Transfusion Management in Sepsis	56
	Further Reading	56
6	Extravasation of Chemotherapy	58
	Introduction	58
	Differential Diagnosis and Grading	58
	Epidemiology	59
	Risk Factors – Intravenous Infusion	59
	Management	63

Documentation and Follow-up	66
Further Reading	68

II NEUROLOGICAL COMPLICATIONS

7 Spinal Cord Compression	71
Introduction	71
Clinical Manifestations	72
Evaluation of SCC	72
Differential Diagnosis	72
Management	73
Further Reading	76
8 Complications of Brain Metastases	77
Introduction	77
Evaluation and Treatment of Brain Metastases	77
Important Complications of Brain Metastases	78
Leptomeningeal Carcinomatosis	81
Future Strategies	81
Further Reading	82

III RENAL AND UROLOGICAL COMPLICATIONS

9 Renal Failure and Urological Emergencies in Cancer Patients	85
Introduction	85
Urological Emergencies	85
Acute Renal Failure	88
Further Reading	90

IV METABOLIC COMPLICATIONS

10 Hypercalcaemia	95
Definition	95
Aetiology	95
Differential Diagnosis	96
Evaluation	97

Treatment	98
Further Reading	101
11 Tumour Lysis Syndrome	103
Introduction	103
Signs and Symptoms	105
Risk Stratification	105
Prevention	107
Treatment	111
Further Reading	112
12 Other Endocrine and Metabolic Complications of Advanced Cancer	114
Hyponatraemia and the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)	114
Lactic Acidosis	119
Hypoglycaemia	120
Complication of Forced Diuresis	121
Further Reading	122
V RESPIRATORY COMPLICATIONS	
13 Dyspnoea and Respiratory Failure	125
Introduction	125
Aetiology	126
Evaluation	127
Anamnesis of Dyspnoea	127
Clinical Examination	129
Complementary Investigations	130
Evaluation of Tolerance	130
Management of Dyspnoea	131
Further Reading	134
14 Pulmonary Infections in Cancer	136
Introduction	136
Aetiology	136

Clinical Manifestations and Presentations	137
Diagnosis	139
Treatment	140
Conclusions	142
Further Reading	143
15 Haemoptysis and Intractable Hiccups	144
Haemoptysis	144
Persistent and Intractable Hiccups	148
Further Reading	152
VI GASTROINTESTINAL COMPLICATIONS	
16 Nausea and Vomiting	157
Introduction	157
Aetiology	158
Pathophysiology	160
Risk factors	160
Obstructive Bowel Disease	161
Treatment	161
Further Reading	163
17 Mucositis	164
Definition	164
Technical Procedures Involved	165
Description of the Processes Involved in Their Essential/Critical Steps	166
Management of OM	167
Potential Future Developments	170
Further Reading	171
18 Diarrhoea	172
Introduction	172
Oncological Therapies Associated with Diarrhoea	173
Other Causes of Diarrhoea in Cancer Patients	177
Patient Assessment	178

Management and Treatment	179
Conclusions	181
Further Reading	181
19 Abdominal Infections in Neutropaenic Patients	183
Introduction	183
Definitions	184
Risk Factors	185
Pathophysiology	186
Clinical Manifestations	187
Diagnosis	188
Management	191
Conclusion	193
Further Reading	193
 VII IMMUNE-HAEMATOLOGICAL EMERGENCIES	
20 Anaemia in Cancer	197
Introduction	197
Aetiology	197
Evaluation	198
Treatment	201
Iron Supplementation	206
Conclusion	206
Further Reading	207
 21 Febrile Neutropenia in Cancer Patients	 208
Aetiology and Epidemiology	208
Initial Assessment and Investigations	209
Risk Factors/Risk Groups	210
Treatment	212
Follow-up and Duration of Therapy	217
Further Reading	218
 22 Immune-Haematological Emergencies in Cancer Patients	 221
Drug-induced Hypersensitivity	221

Infusion-related Reactions with Drugs	223
Adverse Transfusion Reactions with Blood Components	226
Disseminated Intravascular Coagulation	228
Further Reading	231
23 Bleeding Disorders	233
Introduction	233
Aetiology	234
Evaluation	236
Prevention and Treatment	238
Conclusion	242
Further Reading	242
 VIII CANCER PAIN	
24 Management of Cancer Pain	245
Introduction	245
Basic Science of Pain	245
Aetiology	246
Evaluation	247
Treatment	249
Further Reading	258
 IX PSYCHOLOGICAL COMPLICATIONS	
25 Psychological Complications	263
Definition	263
Description of the Process	264
Technical Procedures Involved	266
Predictive and Prognosis Markers	267
Clinical Results	269
Potential Future Developments	270
Further Reading	270
 Index	 272

Contributors



Aguiar P.N. Jr. Department of Oncology and Haematology, Division of Medical Oncology, Federal University of São Paulo, São Paulo, Brazil

Alonso M. Medical Oncology Department, University Hospital Virgen del Rocío, Seville, Spain

Andrade de Mello R. Department of Biomedical Sciences and Medicine, Division of Medical Oncology, University of Algarve, Faro, Portugal; Department of Medicine, Faculty of Medicine, University of Porto, Porto, Portugal; Department of Medical Oncology, Centro Oncológico São Mateus, Ceará Cancer Institute, Fortaleza, Brazil

Araújo A. Service of Medical Oncology, Centro Hospitalar do Porto - Unit for Multidisciplinary Research in Biomedicine, Institute of Biomedical Sciences Abel Salazar, University of Porto, Porto, Portugal

Ballová V. Národný onkologický ústav, Hemato-oncological Department, Bratislava, Slovakia

Blanco-Piñero N. Department of Psychiatry, Faculty of Medicine, University of Seville, Seville, Spain

Califano R. Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; Department of Medical Oncology, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK

Calvo V. Medical Oncology Service, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain

Cardone C. Faculty of Medicine, Second University of Naples, Naples, Italy

Castañon Alvarez E. Phase I – Early Clinical Trials Unit, Oncology Department, Antwerp University Hospital and Center for Oncological Research, Antwerp University, Antwerp, Belgium

Chiramel J. Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK

Corral J. Medical Oncology Department, University Hospital Virgen del Rocio, Seville, Spain

de la Cruz-Merino L. Medical Oncology Department, Hospital Universitario Virgen Macarena, Seville, Spain

de Mattos-Arruda L. Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, UK; Vall d’Hebron Institute of Oncology, Vall d’Hebron University Hospital, Barcelona, Spain; Universitat Autònoma de Barcelona, Barcelona, Spain

Duran I. Virgen del Rocio University Hospital, Seville, Spain

Febra J. Service of Medical Oncology, Centro Hospitalar do Porto - Unit for Multidisciplinary Research in Biomedicine, Institute of Biomedical Sciences Abel Salazar, University of Porto, Porto, Portugal

Foy V. The Christie NHS Foundation Trust, Manchester, UK

Griguolo G. Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy; Division of Medical Oncology 2, Istituto Oncologico Veneto, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padova, Italy

Guarneri V. Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy; Division of Medical Oncology 2, Istituto Oncologico Veneto, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padova, Italy

Köksoy E.B. Ankara University School of Medicine, Department of Medical Oncology, Ankara, Turkey

Kurup R. The Christie NHS Foundation Trust, Manchester, UK

Magalhães M. Service of Medical Oncology, Centro Hospitalar do Porto - Unit for Multidisciplinary Research in Biomedicine, Institute of Biomedical Sciences Abel Salazar, University of Porto, Porto, Portugal

Martinelli E. Faculty of Medicine, Second University of Naples, Naples, Italy

Mediano M. Virgen del Rocio University Hospital, Seville, Spain

Moiseenko F. Saint-Petersburg Scientific Practical Center of Specialized Kinds of Medical Care (Oncological), St-Petersburg, Russian Federation

Morgillo F. Faculty of Medicine, Second University of Naples, Naples, Italy

Mountzios G. University of Athens School of Medicine, Athens, Greece

Nogales-Fernández E. Medical Oncology Department, Hospital Universitario Virgen Macarena, Seville, Spain

Öztürk M.A. Department of Medical Oncology, Marmara University Faculty of Medicine, Istanbul, Turkey

Padua T. Department of Medical Oncology, Federal University of São Paulo, São Paulo, Brazil

Papadimitriou K. Phase I – Early Clinical Trials Unit, Oncology Department, Antwerp University Hospital and Center for Oncological Research, Antwerp University, Antwerp, Belgium

Pérez-Callejo D. Medical Oncology Service, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain

Petrova M. MHAT Nadezhda (Multiprofile Hospital of Active Treatment), Sofia, Bulgaria

Poulsen L. Department of Oncology, Aalborg University Hospital, Aalborg, Denmark

Preusser M. Department of Medicine I and Comprehensive Cancer Center CNS Unit, Medical University of Vienna, Vienna, Austria

Punie K. Medical Oncology, Leuven University Hospitals, Leuven, Belgium

Qvortrup C. Department of Oncology, Odense University Hospital, Odense, Denmark

Rolfo C. Phase I – Early Clinical Trials Unit, Oncology Department, Antwerp University Hospital and Center for Oncological Research, Antwerp University, Antwerp, Belgium

Sag A.A. Division of Interventional Radiology, Department of Radiology, Koc University School of Medicine, Istanbul, Turkey

Salih Z. Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK

Sforza V. Faculty of Medicine, Second University of Naples, Naples, Italy

Strijbos M. Medical Oncology, AZ Klina, Iridium Cancer Network, Antwerp, Belgium

Tadokoro H. Department of Oncology and Haematology, Division of Medical Oncology, Federal University of São Paulo, São Paulo, Brazil

Thallinger C. Department of Internal Medicine I, Section of Oncology, Medical University of Vienna, Austria

Troiani T. Faculty of Medicine, Second University of Naples, Naples, Italy

Unsel M. Department of Internal Medicine I, Section of Oncology, Medical University of Vienna, Austria

Ürün Y. Ankara University School of Medicine, Department of Medical Oncology, Ankara, Turkey

Volkov N. Saint-Petersburg Scientific Practical Center of Specialized Kinds of Medical Care (Oncological), St-Petersburg, Russian Federation

Yazıcı O. Department of Medical Oncology, Ankara Numune Research & Education Hospital, Ankara, Turkey

Reviewers



We would like to thank all the authors who took the time to review the chapters.

Acknowledgements



This book is the result of the effort, work and experience of many people. I would like to thank the members of the ESMO Publishing Working Group and also the ESMO Educational Steering Committee for their support and unstinting assistance.

We must recognise and thank the authors for the many hours they have devoted to this work – without them, this update would not have been possible.

I would also like to thank Aude Galli and Claire Bramley of ESMO for their collaboration, patience and interest in the success of this book.

Above all, I would like to thank you, dear reader, for your trust in us.

Mariano Provencio Pulla
Medical Oncology Department,
Hospital Universitario Puerta de Hierro,
Madrid, Spain

Preface



In 2010 ESMO decided to structure its educational material into disease-oriented books (“Essentials for Clinicians”), while reviewing the more general topics (such as anticancer drugs, special clinical situations, nutrition, prevention, etc) in the “Handbook” series.

The previous edition of the Handbook of Oncological Emergencies was prepared by the ESMO Young Oncologists Group, which produced an excellent and very successful book, published in 2005.

As this needed to be updated and extended, the Publishing Working Group took over this task. Professor Mariano Provencio Pulla from Madrid and Aude Galli at the ESMO Office carried out the task to co-ordinate the review, involving former or new authors to update their chapters, introducing new chapters and restructuring the table of contents.

I am very grateful to both of them for the immense work of reading and re-reading the texts, asking the authors to add or correct where it was needed, so that an oeuvre has now been produced which will again be very useful for all European oncologists.

I also thank all the young authors and their senior tutors who helped complete the work on time for publication.

Besides being published on paper, the Handbook will be available for members on the ESMO OncologyPRO website.

Professor Michele Ghielmini
Chair of the Publishing Working Group 2012–2015
Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

I - Cardiovascular complications



Cardiac Complications of Cancer and Anticancer Treatment

G. Griguolo^{1,2}

V. Guarneri^{1,2}

¹*Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy*

²*Division of Medical Oncology 2, Istituto Oncologico Veneto, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padova, Italy*

Introduction

Neoplastic diseases can be associated with severe, sometimes fatal, cardiac complications such as pericardial effusion and cardiac tamponade. In addition, several anticancer agents can induce potentially irreversible cardiac dysfunction, and the development of targeted therapies has recently widened the cardiotoxic spectrum of antineoplastic drugs.

Increasing the chance of survival as a consequence of improvements in cancer diagnosis and treatment highlights the relevance of this topic, since cardiac complications can adversely affect survival and quality of life independently of cancer prognosis. In this chapter, we briefly review the cardiac complications of both neoplastic diseases and cancer treatments, describing their incidence and aetiology, and focusing on strategies to evaluate, treat and prevent this wide spectrum of disorders.

Malignant Pericardial Effusion and Cardiac Tamponade

Aetiology

Malignant cardiac involvement is not an infrequent event, its incidence at autopsy being around 10% in patients with known malignancies.

Neoplastic diseases that most frequently present involvement of the pericardium are advanced lung cancer (approximately 30% of patients with lung cancer present pericardial involvement), breast cancer (approximately 25% of patients), malignant melanoma (40%–70% of patients) and leukaemia and lymphomas (around 15% of patients). In addition, chemotherapy-related effusions are occasionally observed (up to 1%–2% incidence) following exposure to busulfan, cytarabine, cyclophosphamide or tretinoin, especially when these drugs are used at high doses or in combination for the treatment of haematological malignancies.

Evaluation

As fluid accumulates in the pericardium, the increase in intrapericardial pressure affects diastolic filling of the heart, leading to decreased cardiac output. Symptoms may arise gradually or rapidly, depending on fluid accumulation rate, and may range from dyspnoea, chest pain, cough, palpitations and orthopnoea, to fatigue, anxiety and confusion. At physical examination, tachycardia, decreased heart sounds, neck vein distension, peripheral oedema and pericardial friction rubs may be present. Pulsus paradoxus, defined as an inspiratory decrease of more than 10 mmHg in systolic pressure, is a rare but suggestive sign of pericardial effusion. As cardiac tamponade develops, patients may show signs of low-output shock.

At initial evaluation, a chest radiograph may provide evidence of an enlarged cardiac silhouette, while at electrocardiography (ECG) low-voltage complexes and electrical alternans are suggestive of pericardial effusion. However, two-dimensional echocardiography is considered the standard method for diagnosing pericardial effusion.

Pericardiocentesis is usually needed to establish aetiology, the malignant nature of pericardial effusion being confirmed by identification of malignant cells at cytological examination.

Treatment

Treatment depends on the underlying aetiology and symptom progression. In patients with minimal symptoms without haemodynamic implications, systemic management is warranted, especially in chemosensitive cancers, and radiotherapy may also be indicated.

In patients with mild hypotension, rapid volume expansion by infusion of normal saline or Ringer's lactate may increase the right ventricular filling pressure above the pericardial pressure, improving cardiac output. However, immediate pericardiocentesis is mandatory and life-saving for patients with tamponade. If no systemic therapy can control the pericardial effusion, local measures, such as subxiphoid pericardiostomy, with or without intrapericardial instillation of sclerosing or cytotoxic agents, percutaneous balloon pericardiotomy and pericardial window, may be considered.

Chemotherapy-related Heart Failure

Aetiology

One of the most common manifestations of cardiotoxicity associated with anticancer therapies is the development of left ventricular dysfunction (LVD) and overt heart failure (HF). According to the definition proposed by the Cardiac Review and Evaluation Committee, LVD is characterised by:

- A decrease in cardiac LV ejection fraction (LVEF), that is either global or more severe in the septum;
- Symptoms of congestive heart failure (CHF);
- Associated signs of CHF, including but not limited to S3 gallop, tachycardia or both;
- Decline in LVEF of at least 5% to below 55% with accompanying signs or symptoms of CHF, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms.

Two distinct forms are identifiable. Type I cardiac dysfunction, typically induced by cytotoxic agents, is due, at least in part, to oxidative stress on the cardiac muscle, resulting in free radical formation and cell death. It is irreversible and typically associated with significant ultrastructural changes at biopsy.

Type II, typically induced by biological agents, is associated with reversible myocardial dysfunction rather than structural damage. It is highly reversible (up to 79%) and generally not dose-related.

Anthracyclines and cytotoxics with cumulative dose-related cardiotoxicity: type I agents

Even if several cytotoxic agents have been associated with cardiac toxicity (Table 1), anthracycline-induced cardiotoxicity is the most studied, given their frequency of use and resulting morbidity.

It may present as acute, subacute or late. Acute toxicity occurs during or immediately after infusion, and includes arrhythmias sometimes accompanied by an acute, transient decline in myocardial contractility, which is usually reversible and not dose-dependent. Subacute toxicity occurs within a few weeks of treatment, and clinically resembles myocarditis with oedema and thickening of the LV walls, accompanied by diastolic dysfunction. These two forms are, however, rare (1%–4%).

The most significant cardiac effect of anthracyclines is chronic cardiac toxicity leading to LVD and congestive HF. Symptoms usually appear during the first post-treatment year, but may occur even after 10–20 years. Prognosis is poor, with a 50% 2-year mortality in untreated established LVD.

Table 1 Antineoplastic Drugs Associated with Left Ventricular Dysfunction (LVD)

Compound	Incidence
Type I agents	
Doxorubicin 400 mg/m ²	7%–26%
Doxorubicin 550 mg/m ²	18%–48%
Epirubicin	0.9%–3.3%
Liposomal anthracyclines	2%
Mitoxantrone >150 mg/m ²	2.6%
Cyclophosphamide (high dose)	7%–28%
Ifosfamide	17%
Type II agents	
Trastuzumab	2%–27%
Lapatinib	1.5%–2.2%
Sunitinib	2%–11%
Bevacizumab	1.7%–3%
Imatinib	0.5%–1.7%
Trametinib	5%–7%

The most important risk factor for late cardiac toxicity is cumulative anthracycline dose. The associated incidence of HF is about 3%–5% with a doxorubicin cumulative dose of 400 mg/m², and 18%–48% with a

cumulative dose of 700 mg/m². For this reason, a cumulative doxorubicin dose of 450–550 mg/m² is empirically considered as the highest allowed in clinical practice. Other anthracyclines, such as epirubicin, idarubicin and daunorubicin, induce cardiotoxicity less frequently (0.9%–3.3%), allowing administration of different cumulative doses (900–1000 mg/m² for epirubicin, 100 mg/m² for idarubicin, 600 mg/m² for daunorubicin).

However, there is a considerable variability in the individual dose–response relationship for cardiac toxicity, and symptoms of CHF may also occur at lower doses. Additional risk factors for anthracycline cardiotoxicity include extremes of age, female gender, underlying cardiovascular (CV) diseases, and predisposing factors such as hypertension and smoking. Moreover, intravenous bolus administration and higher single doses of anthracyclines, concomitant use of cyclophosphamide, taxanes or trastuzumab, and previous mediastinal irradiation can increase the risk of developing cardiac toxicity. Liposomal anthracyclines are generally associated with a lower rate of cardiotoxicity compared to standard anthracyclines; for pegylated liposomal doxorubicin, which has been the most extensively studied, clear evidence shows a better cardiac safety profile. However, high cumulative doses of liposomal anthracyclines may still be associated with cardiac damage (Safra 2003).

The use of cardioprotectants such as dexrazoxane, which acts by chelating iron and decreasing iron-mediated free radical formation, has confirmed efficacy against anthracycline-related cardiac damage. Use of dexrazoxane, however, is recommended, both in the USA and in Europe, only for adult patients with advanced or metastatic breast cancer who have already received >300 mg/m² doxorubicin, and who may benefit from continued doxorubicin-containing therapy.

Monoclonal antibodies and targeted agents not associated with cumulative dose-related cardiotoxicity: type II agents

Several targeted agents have been identified as causing type II cardiac dysfunction (Table 1), trastuzumab being one of the first shown to adversely affect cardiac function. In patients with advanced disease, the incidence of LVD ranges from 2%–7% when trastuzumab is used as monotherapy, to 2%–13% up to 27% when in combination with paclitaxel

and anthracyclines plus cyclophosphamide, respectively. Trastuzumab-related cardiotoxicity includes various degrees of asymptomatic decreased LVEF or, less frequently, symptomatic CHF. Typically, it does not appear to be dose-dependent. Patients who develop cardiotoxicity generally improve once trastuzumab is discontinued, and retreatment is usually possible with a low incidence of LVD recurrence.

Risk factors include partially altered baseline LVEF values, elderly age, prior cardiac diseases, previous cardiotoxic treatments (including mediastinal irradiation and anthracyclines) and CV risk factors.

The temporary cardiomyocyte dysfunction caused by trastuzumab is probably secondary to inhibition of cardiomyocyte human ErbB2 signalling, thereby interfering with normal growth, repair and survival. Apart from HER2-targeting agents, other target agents, such as the antiangiogenic drugs sunitinib and bevacizumab and some tyrosine kinase inhibitors (TKIs) such as imatinib, are also known for their association with LVD.

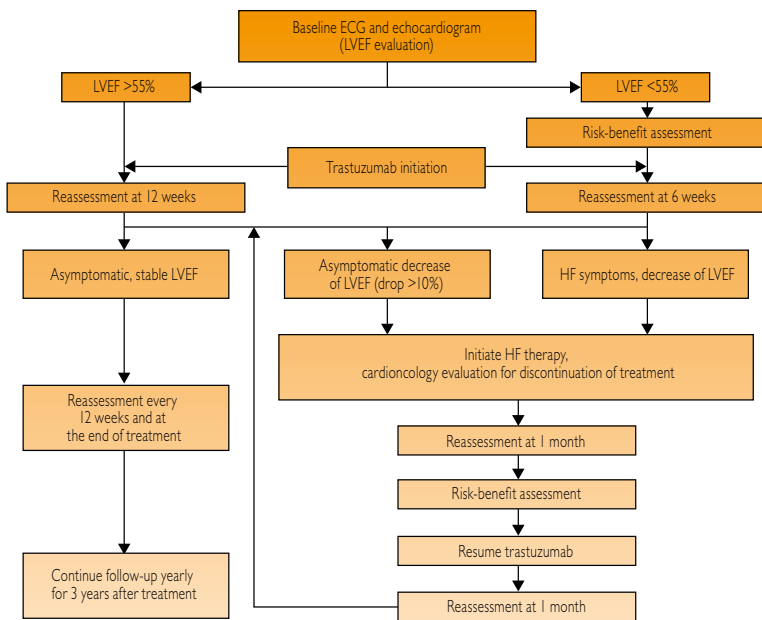
Evaluation and Treatment

Prevention is the best approach to minimise chemotherapy-induced cardiotoxicity. Careful drug selection should be based on a detailed patient history focused on CV risk factors, pre-existing CV disorders and previous exposure to chemotherapeutic agents or mediastinal irradiation. The introduction of a drug-free interval between anthracyclines and trastuzumab, or the administration of anthracycline-free regimens, can lower the potential risk of cardiac damage. Additionally, patients should be encouraged to actively reduce CV risk through blood pressure (BP) control, lipid level reduction, smoking cessation and lifestyle modifications. Even so, careful serial monitoring of the LV, using Doppler echocardiography or gated radionuclide scan with multiple acquisitions (MUGA scan), is advisable. Serial evaluation should always be conducted using the same procedure.

The monitoring schedule can be adapted according to the drug, cumulative dose, length of treatment and CV risk profile of the patient. Generally, in the adjuvant setting, serial monitoring of cardiac function every 3 months has been proposed, while patients treated for metastatic disease can be monitored less frequently in the absence of symptoms.

An assessment of cardiac function is recommended 4 and 10 years after anthracycline therapy in patients who were treated at <15 years of age, or even older if the cumulative dose of doxorubicin is >240 mg/m² or epirubicin >360 mg/m².

Cardiospecific biomarkers, such as troponin I and brain natriuretic peptide (BNP) concentrations, have also been shown to be valid diagnostic tools for the early identification and monitoring of cardiotoxicity. They are minimally invasive and less expensive than echocardiography. Nevertheless, the standardisation of their use in clinical practice is still under debate.



ECG, Electrocardiogram; HF, heart failure; LVEF, left ventricular ejection fraction.

Figure 1 An example of trastuzumab-related cardiotoxicity management.

Modified from: Todaro MC, Oreto L, Qamar R, et al. *Cardiology: state of the heart. Int J Cardiol* 2013; 168:680–687, with permission from Elsevier.

If a decline in LVEF does occur, even in the absence of symptoms, early treatment with angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers and beta-blocker administration, unless contraindicated, should be considered.

When using anthracycline-containing regimens, a reduction in LVEF of $\geq 20\%$ from baseline or a confirmed LVEF decrease $< 50\%$ requires discontinuation of therapy, evaluation of medical LVD treatment and further clinical and echocardiographic re-evaluations. If LVEF declines to $< 40\%$, chemotherapy should be stopped and alternatives discussed.

When managing trastuzumab-related cardiotoxicity, “stopping/restarting” rules are usually effective, and their use is recommended (Figure 1).

Arterial Hypertension

Hypertension is a relatively common and dose-related side effect of several antiangiogenic drugs (Table 2). It can occur at any time after therapy initiation; however, pre-existing hypertension is an important risk factor for complications.

Clinical trials of bevacizumab reported grade 3–4 hypertension in approximately 10% of patients, with rare cases of hypertensive crisis, encephalopathy or intracranial haemorrhage. In trials with antiangiogenic multitarget kinase inhibitors, such as sunitinib or sorafenib, the incidence of grade 3–4 hypertension was even higher, and in some rare cases hypertension was associated with reversible posterior leukoencephalopathy syndrome, a clinical event characterised by headache, seizures, impaired vision and acute hypertension (Todaro et al, 2013).

Several mechanisms have been proposed to explain antiangiogenic-induced hypertension, including decreased nitric oxide signalling in the wall of arterioles, increased endothelin-1 production and capillary rarefaction. Arterial hypertension developing through these mechanisms is an on-target side effect, and may play a role as a pharmacodynamic biomarker for vascular endothelial growth factor (VEGF) inhibition.

However, hypertension may also be secondary to renal thrombotic microangiopathy or to glomerular damage, hence the importance of

Table 2 Antineoplastic Agents Associated with Arterial Hypertension

Agent	Mechanism of action	Incidence of G3–G4 hypertension
Bevacizumab	Anti-VEGF-A Ab	0.4%–1.8%
Sorafenib	Multitarget TKI	0.35%–30.7%
Sunitinib	Multitarget TKI	2.4%–14.8%
Pazopanib	Multitarget TKI	7.0%–11.0%
Axitinib	Multitarget TKI	23%
Ramucirumab	Anti-VEGFR2 Ab	7.6%–14.7%
Aflibercept	Anti-VEGF trap	19.3%–23%

Ab, Antibody; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.

investigating renal abnormalities through evaluation of creatinine clearance, proteinuria and microscopic haematuria while on active therapy. Proteinuria is usually monitored during treatment by dipstick urine analysis. Patients who develop proteinuria (confirmed using 24-hour urine collection) or reduced renal function (glomerular filtration rate [GFR] <60 ml/min per 1.73 m²) should be referred to a nephrologist. It should also be considered whether to put on hold, or definitively discontinue, treatment according to the severity of proteinuria, based on the manufacturer's recommendations.

As hypertension and cancer can frequently coexist in the same patient, patients who are candidates for treatment with antiangiogenic agents should be screened at baseline for hypertension and for existing kidney disease. Anti-hypertensive therapy should be implemented or optimised before starting treatment, to prevent antiangiogenic-induced uncontrolled hypertension and avoid the development of serious complications. Repeated BP measurements are recommended during treatment with antiangiogenic drugs, with the aim of implementing early active anti-hypertensive therapy to maintain BP <140/90 mmHg, rather than withdrawing treatment. Since these patients are at increased risk of LVD, preferred anti-hypertensive agents should include ACE inhibitors and dihydropyridine calcium channel blockers (CCBs), although there are minimal data to suggest the superiority of a class of agents. Non-dihydropyridine CCBs should be avoided in sorafenib-induced hypertension, due to drug interactions that

may result in higher levels of sorafenib. Discontinuation of treatment may be applicable if systolic BP is >200 mmHg, diastolic BP >100 mmHg, or in case of hypertensive crisis.

Myocardial Ischaemia

Aetiology

Several antineoplastic agents are associated with an increased risk of coronary artery disease and/or acute coronary syndrome (Table 3).

Table 3 Antineoplastic Agents Associated with Myocardial Ischaemia

Agent	Incidence
5-Fluorouracil	7%–10%
Capecitabine	3%–9%
Paclitaxel	0.29%–5%
Docetaxel	1.7%
Bevacizumab	0.6%–1.5%
Sorafenib	2.7%–3%

The most common is 5-fluorouracil (5-FU), especially when used as a continuous infusion (7%–10% incidence), in combination with cisplatin or in patients with a history of coronary artery disease. Although it appears less toxic than 5-FU, capecitabine may also elicit myocardial ischaemia. These acute coronary syndromes seem to be related to endothelial dysfunction and vasospasm of coronary arteries.

By contrast, for antiangiogenic agents, inhibition of VEGF itself seems to be responsible for the increased risk of cardiac ischaemia and infarction through reduction of the regenerative capacity of endothelial cells, thus causing defects that expose procoagulant phospholipids on the luminal plasma membrane, leading to thrombosis.

Evaluation and Treatment

Baseline ECG evaluation is recommended when treating patients with drugs known to be associated with myocardial ischaemia. Thoracic pain is usually the presenting symptom, but some cases may present with

ventricular arrhythmias and cardiac arrest. If chest pain occurs during 5-FU infusion, the infusion must be stopped immediately, and antianginal therapy and a work-up for ischaemia should be initiated. ECG may show evidence of an ST-segment elevation, while coronary angiography is usually consistent with coronary artery spasm.

While nitrates and calcium channel blockers are used to treat 5-FU-related coronary syndromes, their usefulness as a prophylactic measure to prevent ischaemia during therapy is still controversial.

Re-challenging patients after treatment-related myocardial ischaemia remains a questionable practice. It should be reserved for patients having no alternative therapeutic interventions, and administered in a supervised environment.

Arrhythmias

Aetiology

Multiple conditions may cause arrhythmias in cancer patients. Fibrosis due to old age or radiation therapy, or coronary or myocardial disease secondary to cancer therapy, can all affect the cardiac conduction system. Several chemotherapeutic agents have been associated with bradycardia and heart block, the most clinically significant being paclitaxel (incidence of asymptomatic bradycardia up to 30% in phase II studies) and thalidomide (incidence ranging from 0.12% up to 55%). In addition, some new target agents such as crizotinib have also been associated with profound asymptomatic sinus bradycardia (in 5% of patients).

Evaluation and Treatment

Generally, bradycardia presents with an asymptomatic heart rate <50 beats/min; nevertheless, some patients may have associated symptoms such as fatigue, syncope or dizziness. Diagnostic tests include an ECG, Holter monitoring and screening for underlying disorders, such as thyroid disease or electrolyte abnormalities.

Bradycardia associated with paclitaxel is generally without clinical significance, as many cases are asymptomatic. However, if patients develop

bradycardia with progressive atrioventricular conduction disturbances and/or clinically significant haemodynamic effects, paclitaxel discontinuation is warranted, and some patients might require pacemaker implantation. Whenever haemodynamic instability is imminent or life-threatening, active intervention according to advanced cardiac life-support protocols is mandatory.

With crizotinib, bradycardia presents as a pharmacodynamic effect, with heart rate progressively decreasing when serum concentrations of this agent increase. Thus, special attention should be given to drug–drug interactions, which might result in an increased concentration of crizotinib. In addition, concurrent heart rate-lowering agents such as beta-blockers or CCBs should be used with caution in these patients.

QT Prolongation

Aetiology

QT interval prolongation is an abnormality of the electrical activity of the heart, which places individuals at risk for life-threatening ventricular arrhythmias, including torsade de pointes (TdP) and sudden cardiac death.

Cancer patients are particularly prone to QT prolongation (16%–36% incidence at baseline), probably due to the high prevalence of concomitant diseases, as well as concomitant medications that are known to prolong the QT interval (e.g. antiemetics, antifungals, quinolone antibiotics). Furthermore, electrolyte disturbances caused by nausea, vomiting and diarrhoea increase the risk for QT prolongation.

Several novel anticancer therapies including histone deacetylase inhibitors, multitargeted TKIs, and Src/Abl kinase inhibitors are associated with QT prolongation. Arsenic trioxide, a uniquely effective drug in relapsed acute promyelocytic leukaemia, is also known to provoke QT prolongation (incidence ranging from 26%–93%) and TdP.

Evaluation and Treatment

Drugs known to provoke QT prolongation should be used cautiously in patients with risk factors. ECGs should be performed at baseline, and

regularly while on therapy, using Bazett or Fridericia formulae to correct QT for heart rate (QTc). A baseline QTc >450 ms in men and >470 ms in women should be considered abnormal, and conditions associated with QT prolongation, such as hypomagnesaemia and hypokalaemia, should be investigated and treated before starting therapy.

Non-cancer medications that may prolong the QTc interval should be administered cautiously and, due to drug interactions, treatment with CYP3A4 inhibitors should also be carefully evaluated. Patients should be informed to report any cardiac symptoms such as palpitations.

Manufacturers' recommendations on QTc-prolonging agents usually include details on baseline and periodic ECG monitoring requirements, as well as dosage adjustments necessary in case of QT prolongation. Increases of >60 ms from baseline or QTc >500 ms usually raise concern about the potential risk of arrhythmia, and treatment withdrawal should be evaluated.

In case of TdP, the involved drug should be stopped and patients should be monitored closely in an intensive care unit. Magnesium infusion and shortening of the QT interval by increasing heart rate should be undertaken. Non-synchronised defibrillation may be indicated if sustained, haemodynamically unstable polymorphic ventricular tachycardia or fibrillation develop.

Radiation Therapy-induced Cardiotoxicity

Chest radiation, used to treat lymphoma, breast and lung cancers, is associated with an increased risk of late cardiovascular effects through two mechanisms: microvascular disruption leading to cellular death and fibrosis, and accelerated macrovascular atherosclerosis. These affect not only the myocardium but also the pericardium, coronary arteries, and the heart valvular and conduction systems.

The risk of cardiac disease depends mostly on the radiation dose (dose >30 Gy), volume of the heart exposed (improvements in radiation techniques seem to reduce it) and radiation delivery techniques (dose per fraction >2 Gy). However, other risk factors include age (younger patients are at higher risk), longer time since exposure (incidence of

heart disease continues to increase even 30 years after radiation), gender, exposure to other cardiotoxic treatments, or other CV risk factors.

High-risk patients, such as those who received a mediastinal/heart dose of >30 Gy as children or young adults, should be followed up closely.

Declaration of Interest:

Dr Griguolo has reported no conflicts of interest.

Dr Guarneri has reported no conflicts of interest.

Further Reading

- Brana I, Tabernero J. Cardiotoxicity. *Ann Oncol* 2010; 21(Suppl 7):vii173–vii179.
- Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol* 2012; 23(Suppl 7):vii155–vii166.
- DeVita VT Jr, Lawrence TS, Rosenberg SA (Editors). DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology, 10th edition. Philadelphia: Lippincott-Raven, 2014.
- Izzedine H, Ederhy S, Goldwasser F, et al. Management of hypertension in angiogenesis inhibitor-treated patients. *Ann Oncol* 2009; 20:807–815.
- Niederhuber JE, Armitage JO, Doroshow JH, et al (Editors). *Abeloff's Clinical Oncology*, 5th edition. Philadelphia: Elsevier Churchill Livingstone, 2014.
- Safra T. Cardiac safety of liposomal anthracyclines. *Oncologist* 2003; 8 Suppl 2:17–24.
- Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. *N Engl J Med* 1998; 339:900–905.
- Todaro MC, Oreto L, Qamar R, et al. Cardioncology: state of the heart. *Int J Cardiol* 2013; 168:680–687.

Venous Thromboembolism in Cancer Patients

2

J. Chiramel¹

Z. Salih¹

R. Califano^{1,2}

¹*Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK*

²*Department of Medical Oncology, University Hospital of South Manchester NHS Foundation Trust, Manchester, UK*

Introduction

The association between venous thromboembolism (VTE) and cancer was firstly described in 1823 by Jean-Baptiste Bouillaud. In 1865, Armand Trousseau highlighted the association again, lending his name to the condition – Trousseau’s syndrome.

VTE is the second leading cause of death in cancer patients, and the risk of developing VTE in patients with cancer is around 20%. The incidence of VTE varies with cancer type and is highest among patients initially diagnosed with metastatic disease. Patients with advanced cancer of the pancreas, stomach, colon, kidney, brain and lymphoma have the highest incidence of VTE. Cancer patients with VTE have a poor survival outcome compared with non-cancer patients with VTE.

The most common thromboembolic events are pulmonary embolism (PE) and deep venous thrombosis (DVT), usually in the legs, but they can also develop in the vena cava, arm or neck veins and the cerebral or portal circulation. Notably, cancer patients have a three-fold increased risk of recurrent VTE.

Pathophysiology

The pathogenesis of a pro-thrombotic state in cancer involves:

- Production of procoagulants by tumour cells
- Suppression of fibrinolytic activity
- Platelet activation

There is a close link between malignant transformation, tumour angiogenesis, metastasis and thrombosis. Tissue factor (TF), a transmembrane glycoprotein, is a procoagulant expressed by tumour cells. Overexpression of TF spontaneously releases microparticles into the bloodstream and these microparticles are procoagulant. TF induces production of vascular endothelial growth factor (VEGF) in human tumour cells, independently of its ability to activate factor Xa-catalysed conversion of prothrombin. The TF–VIIa complex and factor Xa are among the known activators of G-protein-coupled protease-activated receptor-2 (PAR-2) in tumour cells, while the TF–VIIa–Xa complex and thrombin efficiently activate PAR-1. Both PARs have been implicated in signalling pathways leading to angiogenesis and metastasis. The genetic mechanism responsible for malignant transformation, such as oncogene activation (*RAS* or *MET*), or tumour suppressor gene inactivation (*P53* or *PTEN*), also directly induces the expression of genes regulating haemostasis.

Factors contributing to the pro-thrombotic state in cancer

- Plasminogen activator inhibitor-1 is a potent inhibitor of the fibrinolytic system, promoting tumour growth and angiogenesis
- Proinflammatory cytokines such as tumour necrosis factor, interleukin-1, interleukin-6 and interferons activate coagulation
- Platelet P-selectin leads to platelet aggregation and platelet-rich thrombus formation
- Chemotherapy induces endothelial cell activation, leading to increased TF expression, elevated levels of plasma von Willebrand factor and factor VIII coagulant protein, and decreased level of anti-thrombin and protein C and S.

Risk Factors for Thromboembolic Events

Disease-related

- Primary site of cancer (gastrointestinal [GI], brain, lung, gynaecological, renal malignancy, lymphoma, myeloma)
- Initial period after diagnosis (highest in the first 3–6 months)
- Histology (higher for high-grade tumours and adenocarcinoma)
- Stage (higher with regional and metastatic disease)

Treatment-related

- Major surgery (2-fold increased risk of postoperative DVT and 3-fold risk of PE)
- Chemotherapy
- Antiangiogenic therapy (i.e. bevacizumab, sunitinib, sorafenib for arterial events)
- Hormonal therapy (tamoxifen)
- Immunomodulatory agents (i.e. thalidomide or lenalidomide)
- Erythropoiesis-stimulating agents
- Central venous access devices
- Transfusions of blood products

Patient-related

- Age
- Ethnic origin (higher in African–Americans, lower in Asian–Pacific Islanders)
- Comorbidities (concomitant infection, renal disease, lung disease and anaemia)
- Previous history of thromboembolism
- Inherited pro-thrombotic mutations (factor V Leiden, prothrombin gene mutation)
- Poor performance status
- Varicose veins

Biomarkers

- Pre-chemotherapy leukocyte count $>11\,000/\text{mm}^3$
- Pre-chemotherapy platelet count $>350\,000/\text{mm}^3$
- Haemoglobin $<10\text{ g/dl}$
- TF (antigen expression, circulating microparticles, antigen or activity)
- D-dimer
- C-reactive protein
- Soluble P-selectin
- Peak thrombin generation
- Factor VIII

Diagnosis

The Wells Criteria are a clinical prediction tool for estimating the probability of DVT and PE; they are shown in Tables 1 and 2.

Table 1 Two-level DVT Wells Score.

Adapted from: Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 2003; 349: 1227–1235. Copyright © 2003 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Clinical features	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within 12 weeks, requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	-2
DVT likely if ≥ 2 points DVT unlikely if ≤ 1 point	

DVT, Deep venous thrombosis.

Table 2 Two-level PE Wells Score.

Adapted from: Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. *Thromb Haemost* 2000; 83:416–420.

Clinical features	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate >100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months or palliative)	1
PE likely if >4 points PE unlikely if ≤4 points	

DVT, Deep venous thrombosis; PE, pulmonary embolism.

Clinical presentation

- Dyspnoea
- Chest pain
- Pain and swelling in the lower limbs
- Dry cough
- Haemoptysis

Investigations

- Physical examination and vital signs (respiratory rate, oxygen saturation, blood pressure, heart rate)
- Chest X-ray
- Electrocardiogram
- Arterial blood gas
- Ultrasound Doppler
- Computed tomography pulmonary angiogram (CTPA)
- Ventilation-perfusion scan (V-Q scan)

Prevention of Cancer-associated Thromboembolism

The majority of hospitalised patients with cancer confined to bed require thromboprophylaxis, which is not routinely recommended for ambulatory patients with cancer, but should be considered for high-risk groups. It has been demonstrated that the risk of VTE in cancer patients receiving chemotherapy can be reliably predicted using a simple risk assessment model based on five clinical and laboratory parameters, such as:

- Primary site of cancer
- Pre-chemotherapy platelet count $\geq 350 \times 10^9/l$
- Haemoglobin < 100 g/l, or use of red cell growth factors
- Leukocyte count more than $11 \times 10^9/l$
- Body mass index ≥ 35 kg/m² (Khorana et al, 2008)

Prophylaxis should be commenced pre-operatively for cancer patients undergoing surgery. Oncology professionals should educate their patients regarding signs and symptoms of VTE.

Pharmacological Thromboprophylaxis

Unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux are used for thromboprophylaxis. A meta-analysis of VTE prophylaxis in medical patients suggested that thromboprophylaxis with LMWH (including fondaparinux) or UFH is effective in reducing the risk of DVT and PE. A prospective study, PROSPECT-CONKO-004, showed that patients in the enoxaparin arm had lower VTE rates at 12 months compared to the control group, but there was no difference in median survival (Kuderer et al, 2009).

In a Phase II randomised study of chemo-anticoagulation (gemcitabine–dalteparin) versus chemotherapy alone (gemcitabine) for locally advanced and metastatic pancreatic adenocarcinoma (FRAGEM), VTE rates were 28% and 12% for the control group and dalteparin group, respectively. Fatal VTE rates were 8.3% in the control group versus 0% in the dalteparin group. Recommended regimens for prophylaxis with UFH and LMWH are shown in Table 3.

Table 3 Recommended Regimens for Thromboembolism Prophylaxis

Unfractionated heparin	5000 units every 8 hours
Dalteparin (LMWH)	5000 units once a day
Enoxaparin (LMWH)	40 mg once a day
Fondaparinux	2.5 mg once a day

LMWH, Low molecular weight heparin.

Mechanical Methods of Prophylaxis

Graduated compression stockings or intermittent pneumatic calf compression devices can lower the risk of VTE, but are less effective than anticoagulants. Their use should be limited to patients in whom anticoagulation is contraindicated.

Duration of Prophylaxis

Most hospitalised cancer patients require thromboprophylaxis throughout their stay in the hospital. Patients undergoing major surgery should receive prophylaxis starting before surgery and continuing for at least 7–10 days. Extending postoperative prophylaxis up to 4 weeks should be considered in high-risk patients. A multicentre, placebo-controlled trial showed that extended prophylaxis with enoxaparin significantly reduced the rate of VTE by 60% at one month, and this benefit was maintained at 3 months (Bergqvist et al, 2002).

The increased risk of post-discharge symptomatic VTE was shown to peak at 3 weeks after cancer surgery in two large prospective studies. The American Society of Clinical Oncology (ASCO) and American College of Chest Physicians (ACCP) recommend that extended prophylaxis in patients undergoing cancer surgery should be considered in patients with high-risk features, such as previous history of VTE, anaesthesia lasting >2 hours, bed rest for >4 days, advanced malignancy and older age (Khorana et al, 2009).

Treatment

The aim of treatment is to prevent recurrence, progression and embolism while minimising the risk of bleeding.

Initial Treatment

Unfractionated heparin

Regular UFH was the standard of care until the introduction of LMWH. UFH is administered by continuous intravenous (i.v.) infusion of nearly 30 000 IU over 24 hours, following a bolus dose of 5000 IU. UFH has a short half-life, so is ideal in unstable patients with high risk of bleeding. Heparin-induced thrombocytopenia is a recognised complication of UFH.

Low molecular weight heparin

LMWH is ideal for stable, ambulatory cancer patients, due to its improved bioavailability, long half-life and subcutaneous (s.c.) dosing. Its activity is measured in units of factor X inactivation, and monitoring of activated partial thromboplastin time (aPTT) is not required. LMWH dose is adjusted according to the patient's weight. LMWH is cleared by the kidneys and has a significant cumulative effect in patients with impaired renal function. Anti-factor Xa activity monitoring is recommended in patients with renal failure (glomerular filtration rate [GFR] <25–30 ml/min) receiving UFH or LMWH.

A systematic review of anticoagulation for the initial treatment of VTE in cancer concluded that LMWH is superior to UFH in reducing mortality in the initial treatment of VTE in cancer patients (Akl et al, 2014). Clinical trials have now established that LMWH is the preferred long-term treatment for VTE. The largest study, CLOT, was a multicentre, international, randomised trial comparing 6 months of warfarin versus dalteparin in cancer patients with acute VTE. Dalteparin was more effective in reducing the risk of recurrent thromboembolism (9% vs 17%) without increasing the risk of bleeding (Lee et al, 2003).

Recommended LMWH regimens for the treatment of thromboembolism are shown in Table 4.

Table 4 Recommended LMWH for Thromboembolism Treatment

Enoxaparin	1 mg/kg twice daily or 1.5 mg/kg daily
Dalteparin	100 U/kg twice a day or 200 U/kg daily
Tinzaparin	175 IU/kg once daily

LMWH, Low molecular weight heparin.

Fondaparinux

Fondaparinux is a pentasaccharide and inhibits factor Xa. Two randomised trials have shown that fondaparinux and enoxaparin, for the initial treatment of symptomatic DVT/PE, were at least as effective and safe as LMWH and UFH (Büller et al, 2004). Fondaparinux is dosed according to the patient's body weight. For a body weight <50 kg, the dose is 5 mg s.c. daily; for a body weight 50–100 kg, 7.5 mg daily; for a body weight >100 kg, 10 mg daily. Fondaparinux is excreted via the kidneys, and is contraindicated in patients with GFR \leq 30 ml/min.

Novel oral anticoagulants (NOACs)

NOACs are now approved by the US Food and Drug Administration and European Medicines Agency for selected indications in VTE prevention and treatment, but are not routinely recommended in cancer patients. These agents inhibit activated factor X (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran etexilate). The major concerns about NOACs in cancer patients include unpredictable absorption and higher risk of GI bleeding in patients with mucositis, inability to measure the anticoagulant activity by using standard assays, potential interaction with hormonal and chemotherapeutic agents, altered metabolism in patients with renal dysfunction or hepatic metastasis, and lack of antidote when patients are actively bleeding. Adequately powered randomised controlled trials are needed to evaluate the efficacy and safety of these drugs in cancer patients.

Thrombolytic therapy

Thrombolysis is indicated in patients with PE and severe right ventricular dysfunction, and in patients with massive iliofemoral thrombosis at risk of limb gangrene. Urokinase, streptokinase and tissue type plasminogen activator are commonly used.

Inferior vena cava (IVC) filter

Patients with active bleeding or who are at high risk of bleeding may have an IVC filter placed to prevent new or recurrent PE. An IVC filter is also indicated in patients with recurrent PE despite adequate anticoagulant

treatment. Once bleeding is stopped or risk of bleeding is reduced, patients with IVC filters should receive anticoagulant therapy.

Long-term Treatment

LMWH is preferred over vitamin K analogues (VKAs) for long-term treatment of VTE in cancer patients. Current evidence suggests that cancer patients treated with VKAs are more likely to have recurrent episodes of VTE compared with non-cancer patients. Common problems with VKAs in cancer patients are drug interactions, serious bleeding, difficulties with maintaining the international normalised ratio (INR) within the therapeutic range, and frequent interruption due to thrombocytopenia or invasive procedures. European Society for Medical Oncology (ESMO), ASCO, ACCP and National Comprehensive Cancer Network (NCCN) guidelines recommend LMWH as long-term treatment for cancer patients with DVT or PE.

Duration of extended treatment

In clinical practice, the majority of cancer patients with VTE are treated for 3–6 months. There is no high-level evidence to guide the duration of extended treatment. The decision of extending treatment beyond 6 months should take into account the potential benefit of preventing recurring thrombosis and death, but also be based on patients' preferences, comorbidities, type of anticancer treatment, prognosis and impact on quality of life.

Management of recurrence for patients already on anticoagulation

- If the patient is on sub-therapeutic dose of warfarin, change the dose to achieve a target INR of 2–3. If INR is therapeutic, switch warfarin to LMWH
- If the patient is on LMWH, check anti-factor Xa level at 4 hours since last dose
- If the peak anti-factor Xa level is sub-therapeutic (<0.5 units), adjust dose of LMWH to achieve a peak anti-factor Xa level of 0.5–1.5 units
- If the peak anti-factor Xa level is therapeutic, then increase the dose of LMWH by 20%

- If the anti-factor Xa level is therapeutic and the patient is symptomatic from VTE, then consider IVC filter

Contraindications to anticoagulation

Absolute contraindications

- Cerebral haemorrhage, or haemorrhage in the eye or vital organ
- Neurosurgery, ocular surgery or intracranial bleeding within past 10 days

Relative contraindications

- Brain metastasis conferring risk of bleeding (renal cell cancer, choriocarcinoma, melanoma, thyroid cancer)
- Spinal procedure
- Major trauma or head trauma
- Major abdominal surgery within 48 hours
- Severe hypertension (systolic >200 mmHg and diastolic >120 mmHg)
- Endocarditis, pericarditis
- GI bleeding within past 14 days
- Pre-existing coagulopathy
- Platelet count <50 000/mm³
- Hypersensitivity to heparin or heparin-induced thrombocytopenia
- Bleeding diathesis

Anticoagulation in patients with brain metastases

Around 20% of patients with brain metastases develop VTE, and the main concern for anticoagulation in this group of patients is the risk of intracranial haemorrhage. There are not enough data to suggest that the risk of bleeding is due to vascularity of the tumour or supra-therapeutic levels of anticoagulation. Brain metastasis from melanoma, renal cell carcinoma, choriocarcinoma and thyroid have higher propensity for intracranial haemorrhage. There are limited data supporting the safety of use of LMWH in patients with brain metastasis. A retrospective cohort study has shown that intracranial haemorrhage is frequently observed in

patients with brain metastasis, but therapeutic anticoagulation does not increase the risk of intracranial haemorrhage. A series from the Memorial Sloan Kettering Cancer Center suggests that anticoagulation is safe when maintained within the therapeutic range, and is more effective than the IVC filter in preventing and treating VTE (Schiff et al, 1994). The risk of intracranial haemorrhage must be weighed against the potential risk of death from VTE.

Declaration of Interest:

Dr Chiramel has reported no conflicts of interest.

Dr Salih has reported no conflicts of interest.

Dr Califano has reported no conflicts of interest.

Further Reading

Akl EA, Kahale L, Neumann I, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. *Cochrane Database Syst Rev* 2014; 6:CD006649.

Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med* 2002; 346:975–980.

Büller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004; 140:867–873.

DeVita, Hellman, and Rosenberg's *Cancer: Principles and Practice of Oncology*, 10th edition. Chapter 134, Cancer-associated thrombosis. Philadelphia: Lippincott, 2014; 1969–1975.

Falanga A, Zacharski L. Deep vein thrombosis in cancer: the scale of the problem and approaches to management. *Ann Oncol* 2005; 16:696–701.

Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th edition. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl):e195s–e226S.

Khorana AA. The NCCN Clinical Practice Guidelines on Venous Thromboembolic Disease: strategies for improving VTE prophylaxis in hospitalized cancer patients. *Oncologist* 2007; 12:1361–1370.

- Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008; 111:4902–4907.
- Khorana AA, Streiff MB, Farge D, et al. Venous thromboembolism prophylaxis and treatment in cancer: a consensus statement of major guidelines panels and call to action. *J Clin Oncol* 2009; 27:4919–4926.
- Kuderer NM, Ortel TL, Khorana AA, et al. Low-molecular-weight heparin thromboprophylaxis in ambulatory cancer patients: A systematic review and meta-analysis of randomized controlled trials. *Blood (ASH Annual Meeting Abstracts)* 2009; 114:490.
- Lee AY, Levine MN. The thrombophilic state induced by therapeutic agents in the cancer patient. *Semin Thromb Hemost* 1999; 25:137–145.
- Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; 349:146–153.
- Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013; 31:2189–2204.
- Mandalà M, Falanga A, Roila F, on behalf of the ESMO Guidelines Working Group. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol* 2011; 22(Suppl 6):vi85–vi92.
- Oo TH. Low-molecular weight heparin prophylaxis should not be recommended even in highly selected patients with solid cancer receiving outpatient chemotherapy. *J Clin Oncol* 2013; 31:4380–4381.
- Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002; 100:3484–3488.
- Schiff D, DeAngelis LM. Therapy of venous thromboembolism in patients with brain metastases. *Cancer* 1994; 73:493–498.
- Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the model's utility with the SimpliRED D-dimer. *Thromb Haemost* 2000; 83:416–420.
- Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 2003; 349:1227–1235.
- Yu JL, May L, Lhotak V, et al. Oncogenic events regulate tissue factor expression in colorectal cancer cells: implication for tumor progression and angiogenesis. *Blood* 2005; 105:1734–1741.

Superior Vena Cava Syndrome

3

V. Foy*

R. Kurup*

The Christie NHS Foundation Trust, Manchester, UK

Introduction

Superior vena cava syndrome (SCS) encompasses a range of signs and symptoms resulting from external compression or intrinsic obstruction of the superior vena cava (SVC) or associated greater veins. 73%–97% of cases of SCS are secondary to malignancy, and clinical presentation can be acute or subacute.

The syndrome is rarely an oncological emergency in the absence of tracheal compression and airway compromise; however, development of the syndrome has an impact on prognosis, with a median survival of 46 weeks for patients who receive treatment, and 6 weeks for patients who do not receive therapy or develop mentation changes and airway compromise.

Physiology of SVC Obstruction (SVCO)

The SVC is a thin-walled, compliant and easily compressible vein. SVC carries one third of the total venous return to the heart, predominantly from the head, neck and upper extremities. SVC compression or obstruction can result in compromise of cardiac output in the acute setting, but, within a few hours, extensive collateral vessels can achieve steady-state blood return to the azygous vein or inferior vena cava. The severity of symptoms depends on the degree of narrowing of the SVC and on the speed of onset.

In the acute onset of SVCO, elevated venous pressures cause interstitial oedema, which can result in laryngeal oedema, resulting in breathing

*These authors contributed equally to this work.

compromise or cerebral oedema, leading to cerebral ischaemia, herniation and death (Figure 1).

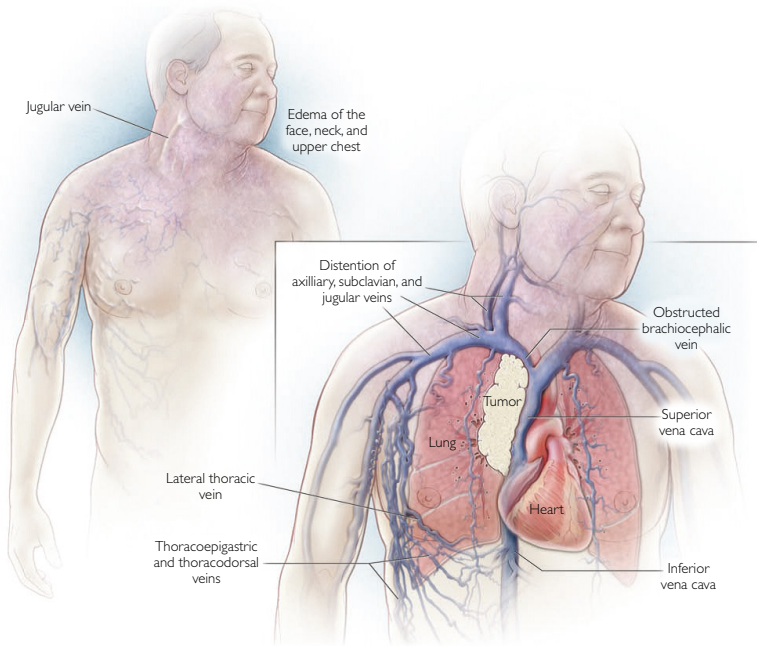


Figure 1 The physiology of SVCO.

Reprinted with permission of the Massachusetts Medical Society, from: Wilson LD, Detterbeck FC, Yahalom J. Clinical practice. Superior vena cava syndrome with malignant causes. *N Engl J Med* 2007; 356:1862–1869; permission conveyed through Copyright Clearance Center Inc.

Aetiology

SVCO results from compression, invasion or thrombosis of the SVC. This can be the result of inflammatory, benign or neoplastic processes. Lung cancer is its most frequent malignant cause (Table 1).

Table 1 Principal Causes of SVCO.

Reprinted from: Costovici CN, Badulescu F. Superior vena cava syndrome. In: Kosmidis PA, Schrijvers D, André F, Rottey S (Editors). *ESMO Handbook of Oncological Emergencies*. Oxon: Taylor and Francis, 2005; 18–24.

Lung cancer (52%–81%)
• Small-cell cancer
• Non-small-cell cancer
• Diffuse large-cell cancer
Lymphoma (2%–20%)
• Lymphoblastic
Metastatic disease to mediastinum (8%–10%)
• Breast cancer
• Germ cell cancer
• Gastrointestinal cancers
• Other
Primary mediastinal tumours
• Thymoma
• Sarcomas (e.g. malignant fibrous histiocytoma)
• Melanomas
• Thymic carcinoma
Non-malignant causes
• Infectious disease – syphilis, tuberculosis and histioplasmosis
• Central line thrombus and other iatrogenic causes
• Idiopathic fibrosing mediastinitis
• Congestive heart failure
• Goitre

Investigations

Clinical Evaluation

The most common signs and symptoms of SVCO are summarised in Tables 2 and 3. Signs can be graded to indicate SVCO severity (Table 4).

All patients presenting with suspected SVCO should have a thorough clinical history to assess the duration and speed of symptom onset. History should also note previous invasive procedures and any history of malignancy.

Detailed examination can rule out common differentials, including congestive cardiac failure and Cushing's syndrome. Examination should include

Table 2 Symptoms of SVCO.

Reprinted from: Costovici CN, Badulescu F. Superior vena cava syndrome. In: Kosmidis PA, Schrijvers D, André F, Rottey S (Editors). *ESMO Handbook of Oncological Emergencies*. Oxon: Taylor and Francis, 2005; 18–24.

Dyspnoea	Nasal stuffiness
Facial oedema	Tongue swelling
Cough	Nausea
Headache	Light headedness
Distorted vision	Stridor
Hoarseness	

Table 3 Signs of SVCO.

Reprinted from: Costovici CN, Badulescu F. Superior vena cava syndrome. In: Kosmidis PA, Schrijvers D, André F, Rottey S (Editors). *ESMO Handbook of Oncological Emergencies*. Oxon: Taylor and Francis, 2005; 18–24.

Jugular venous distension	Lethargy, stupor and coma
Upper extremity swelling	Syncope
Facial and upper body plethora	Cyanosis
Chemosis	Papilloedema
Mental status changes	

a careful evaluation of neurological function, as impairment may be subtle but life-threatening if attributable to cerebral oedema.

Radiological Evaluation

Chest X-ray is often abnormal and can identify superior mediastinal masses or mediastinal widening. Other common findings include hilar masses and pleural effusion.

Contrast computed tomography (CT) or magnetic resonance imaging (MRI) is the gold standard investigation to localise the level of SVCO and underlying pathology, including tumour mass size. CT/MRI can also assess SVC diameter, length of stenosis/obstruction, evidence of SVCO thrombus and formation of collateral vessels.

Treatment of SVCO is determined by the underlying pathology. In the sub-acute setting, if malignancy is suspected, tissue diagnosis should be obtained. This can be obtained via bronchoscopy, endobronchial ultrasound, mediastinoscopy, fine needle aspiration, excision biopsy or CT-guided biopsy. Safe and efficient means of obtaining tissue should be guided by results of imaging and multidisciplinary team discussion.

Table 4 Proposed Grading System for SCS.

Republished with permission of Elsevier from: Yu JB, Wilson LD, Detterbeck FC. Superior vena cava syndrome – a proposed classification system and algorithm for management. *J Thorac Oncol* 2008; 3:811–814; permission conveyed through Copyright Clearance Center Inc.

Grade	Category	Estimated incidence (%)	Definition ^a
0	Asymptomatic	10	Radiographic SVCO in the absence of symptoms
1	Mild	25	Oedema in head or neck (vascular distension), cyanosis, plethora
2	Moderate	50	Oedema in head or neck with functional impairment (mild dysphagia, cough, mild or moderate impairment of head, jaw, or eyelid movements, visual disturbances caused by ocular oedema)
3	Severe	10	Mild or moderate cerebral oedema (headache, dizziness) or mild/moderate laryngeal oedema or diminished cardiac reserve (syncope after bending)
4	Life-threatening	5	Significant cerebral oedema (confusion, obtundation) or significant laryngeal oedema (stridor) or significant haemodynamic compromise (syncope without precipitating factors, hypotension, renal insufficiency)
5	Fatal	<1	Death

^aEach sign or symptom must be thought due to SVCO and the effects of cerebral or laryngeal oedema or effects on cardiac function. Symptoms caused by other factors (e.g. vocal cord paralysis, compromise of the tracheobronchial tree, or heart as a result of mass effect) should not be considered as they are due to mass effect on other organs and not SVCO.

SCS, Superior vena cava syndrome; SVCO, superior vena cava obstruction.

Treatment (Figure 2)

Conventional measures such as head elevation and supplementary oxygen are important while obtaining investigations. Pharmacological interventions such as glucocorticoid steroids and diuretics are often used, but their effects are not well studied and supportive evidence is sparse. Anxiolytics/morphine can also be used in the initial supportive management.

Stenting in SVCO

SVC stenting is safe and effective with rapid resolution of SVCO symptoms. Endovascular stenting relieves SVCO in 95% of patients with lung cancer, although 11% have symptom recurrence in the period of follow-up, often due to thrombus of the SVC.

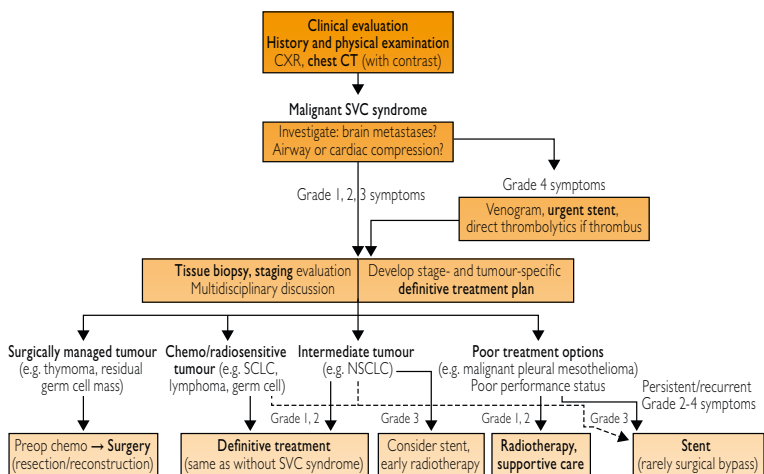


Figure 2 Proposed management algorithm.

Republished with permission of Elsevier from: Yu JB, Wilson LD, Detterbeck FC. Superior vena cava syndrome – a proposed classification system and algorithm for management. *J Thorac Oncol* 2008; 3:811–814; permission conveyed through Copyright Clearance Center Inc.

CT, computed tomography; CXR, chest X-ray; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; SVC, superior vena cava.

Stenting can often be accomplished even if there is complete SVCO or thrombosis. Stents are percutaneously delivered into the vena cava under fluoroscopic guidance, and are available in two fundamental designs: self-expanding or expandable.

Patients presenting with life-threatening symptoms such as haemodynamic compromise, laryngeal oedema or cerebral oedema should be considered for immediate endovascular stenting, to provide rapid relief from symptoms. Stenting should be strongly considered for patients in whom effective treatment approaches are very limited, e.g. in mesothelioma. It is of questionable value in patients with chemosensitive tumours such as small-cell lung cancer (SCLC), lymphoma and germ cell tumours, although it can be considered in individuals with resistant disease.

Complications of SVC stenting are rare, reported to be between 3% and 7% (Table 5). The risk of complication is increased with anticoagulation, often recommended after stenting.

Table 5 Complications of Stenting

Infection	Perforation
Pulmonary emboli	Bleeding
Pericardial tamponade	Stent failure due to extrinsic tumour compression, infiltration of tumour through the stent or thrombus
Stent migration	

Radiotherapy

Radiotherapy is an effective treatment modality for certain tumour types, as an initial intervention or as an adjuvant treatment after stenting. After the initiation of therapy, subjective improvement is often apparent within 72 hours. As many as 75% of all patients with malignancy-associated SCS notice symptomatic improvement within 3–7 days of starting radiotherapy or chemotherapy, and 90% experience major relief within 1 week, with objective responses requiring 1–3 weeks.

Doses ranging from 30 Gy in 10 fractions to 50 Gy in 25 fractions have been used. Daily doses of 1.8 to 2.0 Gy are recommended for the majority of lymphomas. SCLC and non-small-cell lung cancer (NSCLC) are usually treated with higher daily fractions of 2.0 to 3.0 Gy.

All locoregional diseases, including involved hilar and supraclavicular regions with appropriate margins, should be treated.

Side effects of radiotherapy include initial worsening of symptoms secondary to oedema, tumour necrosis with fever, myelosuppression, alopecia, nausea and vomiting, stomatitis, oesophagitis and infection.

Obstructive thrombosis is the most likely cause of failure of radiation therapy. Other causes include tumour recurrence, radiation fibrosis and failure of development of collaterals secondary to fibrosis.

The 2-year survival for patients with SCS secondary to SCLC and NSCLC treated with radiation therapy is identical at 5%. The mean post-treatment survival is 6–7 months.

Chemotherapy

In patients presenting with non-Hodgkin's lymphoma, germ cell tumours

and SCLC, chemotherapy seems to be the treatment of choice for SCS and may provide fast relief, as these tumours are exquisitely chemosensitive. Complete relief of symptoms of vena cava obstruction is achieved with chemotherapy in approximately 80% of patients with non-Hodgkin's lymphoma or SCLC, and in 40% of patients with NSCLC. With chemotherapy as the sole treatment modality for these tumour types, symptoms usually improve within 1–2 weeks of treatment initiation. For NSCLC or SCLC, sequential treatment with chemotherapy following radiotherapy or vice versa can be used accordingly.

In SCLC, chemotherapy and/or radiotherapy relieves SVCO in 77% of patients, and 17% of those treated have a recurrence of SVCO. In NSCLC, 60% have relief of SVCO following chemotherapy and/or radiotherapy, and 19% of those treated have a recurrence of SVCO.

No data on targeted therapies are available to date in the treatment of SCS.

Surgery

Surgical procedures to bypass or resect tumours to decompress the venous system are effective in selected patients. However, invasive surgery in this predominantly palliative situation has a very limited role, due to the range of alternative effective therapies available, and has largely become redundant. The only exception is in patients with malignant thymoma and thymic carcinoma, where surgery should be evaluated as part of a multimodal treatment strategy.

Thrombolytics and Anticoagulation

The benefit of anticoagulation in SVCO is unclear. Slow relief of symptoms on initiation of treatment can be due to the presence of intraluminal thrombus, and thrombolytics can be useful in this setting. 30%–50% of patients with SVCO have evidence of a thrombosis at post mortem.

Most experts recommend anticoagulation after thrombolysis, to prevent reoccurrence of thrombus and reduce the risk of pulmonary emboli. Aspirin is often recommended after stent placement in the absence of thrombus.

Summary

SCS is often clinically striking, but rarely requires emergency intervention. Treatment planning should be multidisciplinary. Tissue biopsy is warranted to guide diagnosis and optimise therapy. In patients with life-threatening symptoms or signs of obstruction of the SVC, the placement of an intravascular stent can provide rapid relief. With the advent of stenting, emergency external beam radiation therapy is less often used, because it usually does not relieve symptoms for 5–10 days. In patients with malignancy, after stenting, radiotherapy/chemotherapy is advised to optimise outcome and prevent tumour growth near the stent, which could cause recurrence of SCS. In chemotherapy-naive or immunotherapy-naive patients with non-Hodgkin's lymphoma or germ cell tumour, systemic therapy as the sole treatment may be recommended. The presence of the SCS does not reduce the likelihood of cure of the underlying malignant condition, and should not compromise the choice of appropriate therapy.

Declaration of Interest:

Dr Foy has reported no conflicts of interest.

Dr Kurup has reported no conflicts of interest.

Further Reading

- Lepper PM, Ott SR, Hoppe H, et al. Superior vena cava syndrome in thoracic malignancies. *Respir Care* 2011; 56:653–666.
- Rowell NP, Gleeson FV. Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus. *Cochrane Database Syst Rev* 2001; (4): CD001316.
- Wilson LD, Detterbeck FC, Yahalom J. Clinical practice. Superior vena cava syndrome with malignant causes. *N Engl J Med* 2007; 356:1862–1869.
- Wudel LJ Jr, Nesbitt JC. Superior vena cava syndrome. *Curr Treat Options Oncol* 2001; 2:77–91.
- Yu JB, Wilson LD, Detterbeck FC. Superior vena cava syndrome – a proposed classification system and algorithm for management. *J Thorac Oncol* 2008; 3: 811–814.

Complications of Central Venous Devices

N. Volkov

F. Moiseenko

Saint-Petersburg Scientific Practical Center of Specialized Kinds of Medical Care (Oncological), St-Petersburg, Russian Federation

Introduction

Central venous catheters (CVCs) are essential for the delivery of appropriate medical cancer care. Stable venous access through central catheters is important for the primary prevention of peripheral phlebitis and delivery of high-intensity infusion therapy, chemotherapy, blood products or parenteral nutrition. It also positively impacts patients' quality of life by abrogating the need for repeated diagnostic venepunctures. Several types of central venous access devices are used: percutaneous non-cuffed or tunnelled catheters for short-term use, peripherally inserted CVCs (PICCs), surgically implanted cuffed, tunnelled CVCs, and subcutaneous implanted ports for durable venous access.

Besides the range of immediate complications of CVC placement, such as pneumo- or haemothorax, arrhythmia, catheter malposition and air embolism, which will not be discussed here, these devices carry the risk of intravascular catheter-related infections and thrombosis.

Intravascular Catheter-related Infections

Intravascular catheter-related infections (ICRI) may arise either through violation of dermal structures, or through direct contact of the catheter with outside polluted air.

They can be grouped into three categories:

- Localised entrance- or exit-site infections
- Tunnel and/or port-pocket infections
- Catheter-related blood stream infections (CRBSI).

Prevention

Primary prevention measures lead to a reduction in the incidence of ICRI and to decreased health care costs. The mainstay of ICRI prevention is the education of staff involved in catheter placement and care. The main measures are:

- Hand hygiene, maximal barrier precautions, optimal skin antisepsis (>0.5% chlorhexidine alcoholic solution is the preferred option)
- Optimal choice of catheterisation site (femoral catheterisation is discouraged, due to higher risk of infection and thrombosis)
- Routine preventive use of antibiotic or antiseptic lock solutions is not recommended, but may be considered in patients with long-term catheters who have a history of multiple CRBSI despite appropriate application of aseptic technique
- The use of antibacterial-/antiseptic-impregnated short-term catheters and chlorhexidine dressings can be considered in high-risk patients, such as bone transplant recipients and leukaemia patients
- Prophylactic use of systemic antibiotics is not recommended.

Clinical Presentation

ICRI should be considered in every patient with a CVC who experiences:

- Local symptoms of infection (erythema, tenderness, induration, purulence) at the catheter entrance or exit site, port-pocket or along the subcutaneous tract of a tunnelled catheter
- Systemic symptoms of infection without other evident source

- Fever
- Sudden fever or rigors just after initiation of the infusion through the CVC
- Blood stream infection without other cause
- Septic shock
- Endocarditis
- Pulmonary abscesses or other pus focus.

Clinical symptoms have low specificity for establishing CVC as the source of blood stream infection.

Evaluation

- Clinical evaluations for local signs of infection at the catheter entrance or exit site, port-pocket or along the subcutaneous tract of a tunnelled catheter are:
 - If positive signs present, consider catheter removal for microbiology; the catheter tip should be cultured
 - In case of implantable ports, port lumen culture should also be performed
 - Catheter exit-site exudate swab cultures should be performed in case of suspicion of exit-site infection.
- Clinical evaluations for symptoms suggestive of bacteraemia secondary to catheter-related infection are:
 - Paired blood cultures should be obtained prior to antibiotic therapy initiation
 - Paired blood samples from the central catheter, peripheral vein (and exit site, if possible) should be obtained
 - Strongly consider skin and catheter tip preparation prior to blood draw
 - If no peripheral vein access is available, consider ≥ 2 samples drawn from different catheter lumens.

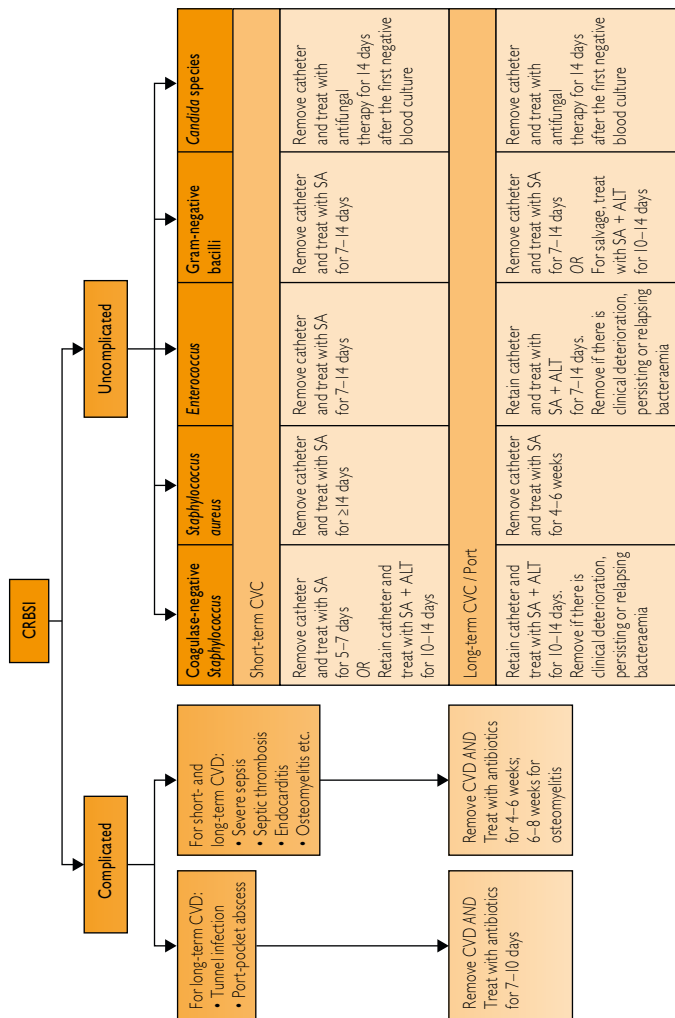
- Catheter colonisation is demonstrated by growth of 15 colony-forming units (CFU) from a 5 cm segment of the catheter tip by semi-quantitative (roll-plate) culture, or by growth of $>10^2$ CFU from a catheter by quantitative (sonication) broth culture method.
- The diagnosis of CRBSI is proved if the same organism grows from at least 1 percutaneous blood culture and from a culture of the catheter tip (in case of catheter removal).
- Quantitative paired blood cultures are essential for a diagnosis of CRBSI without catheter removal. Positivity is considered either in the presence of quantitative differences between the catheter and peripheral blood culture (≥ 3 -fold higher colonisation of the culture from the catheter, or >100 CFU/ml in the catheter-drawn sample), or in differential time to positivity (the catheter-drawn sample becomes positive >2 hours earlier than the peripheral vein-drawn culture). Qualitative blood cultures are also possible, but have low specificity.
- Also consider transoesophageal echocardiography in case of *Staphylococcus aureus* infection, or if the patient presents signs and symptoms that suggest endocarditis, prolonged bacteraemia or fever despite appropriate antimicrobial therapy, septic pulmonary emboli, or has a prosthetic valve or other endovascular foreign bodies.

Treatment

A treatment algorithm is provided in Figure 1.

If CRBSI is suspected or proven

- Removal of the central line access device is the most cost-effective procedure in ICRI. The catheter should be removed in the following cases:
 - The central line is no longer needed
 - Severe entrance- or exit-site, tunnel or port-pocket infection
 - Complications (endocarditis, suppurative phlebitis)
 - Severe sepsis



ALT, Antifungal lock therapy; CRBSI, catheter-related blood stream infection; CVC, central venous catheter; SA, systemic antibiotic.

Figure 1 Management of catheter-related blood stream infections.

Adapted from: Mermel LA, Alon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 49:1–45. By permission of Oxford University Press.

- Infections due to *Staphylococcus aureus*, *Pseudomonas aeruginosa*, fungi, or mycobacteria or Gram-negative bacilli for long-term catheters; infections due to *Staphylococcus aureus*, enterococci, fungi and mycobacteria for short-term catheters
 - If the patient's condition worsens and/or bacteraemia persists after 48–72 hours of adequate antibiotic therapy
 - If bacteraemia recurs with the same pathogen less than 2 weeks after completion of antibiotics, given that no other source of infection is identified.
- Empirical antimicrobial therapy covering Gram-negative bacilli should be initiated based on local susceptibility data (e.g. fourth-generation cephalosporin, carbapenem, or beta-lactam/beta-lactamase with or without aminoglycoside).
 - Vancomycin should be considered, based on the prevalence of methicillin-resistant *Staphylococcus aureus* in the health care setting and in case of serious sepsis, septic shock, presence of abscesses, endocarditis, thrombophlebitis and neutropaenia.
 - Empirical combinations for multi-drug-resistant Gram-negative bacilli may be considered in critically ill, neutropaenic patients.
 - Empirical antifungal therapy should be considered in patients on total parenteral nutrition or with haematological malignancies, with prolonged use of broad-spectrum antibiotics. Echinocandins or fluconazole (for selected patients unexposed to azoles in the previous 3 months) should be used.
 - Upon availability of the microbiology report, antibiotics should be adjusted accordingly.
 - If catheter salvage is pursued, antibiotic lock therapy (ALT) should be used along with systemic antimicrobials. Antibiotic solutions with 100–1000 times higher than systemic concentration with heparin are used for 10–14 days. Reinstallation should be performed every 24–48 hours.
 - Duration of systemic antibiotic therapy depends on the pathogen, catheter status (removed or not), presence of complications (endo-

carditis, suppurative phlebitis) and response to antimicrobial therapy within 48–72 hours:

- Coagulase-negative *Staphylococcus* species: 5–7 days if the catheter is removed, and 10–14 days if the catheter is retained
- *Staphylococcus aureus*: catheter removal and at least 14 days of antibiotic therapy; 4–6 weeks is recommended for long-term catheters
- Gram-negative bacilli or *Enterococcus* species: 7–14 days if the catheter is removed, and 10–14 days if the catheter is retained
- Fungi: 14 days beginning from the day of the first negative blood culture
- Infective endocarditis, suppurative thrombophlebitis or if bacteraemia persists more than 72 hours after catheter removal on adequate antimicrobial therapy: 4–6 weeks
- Osteomyelitis: 6–8 weeks.

Only if local infection is present

- Uncomplicated exit-site infections without purulence, systemic signs of infection and/or bacteraemia are managed with topical antimicrobial agents only, according to exit-site culture results. Systemic antibiotics are indicated in case of ineffective local treatment.
- Tunnel or port-pocket infection without concomitant bacteraemia or candidaemia is managed with catheter removal and 7–10 days of systemic antibiotic therapy.

Catheter-related Thrombosis

Prevention

- No routine prophylactic procedures are recommended
- Catheter placement by appropriately trained staff is essential, as making several attempts at catheter installation and malpositioning of the catheter are among the most common risk factors

- Routine flushing with saline is recommended. Heparin addition is not proven to decrease the risk of thrombosis.

Clinical Presentation

- Clot formation and/or asymptomatic thrombosis are more frequent
- Mechanical catheter occlusion by an intraluminal clot or external fibrin sheath may accompany asymptomatic thrombosis
- Arm swelling, oedema, discolouration, visible venous collaterals
- Rare: face or neck swelling, headache, superior vena cava syndrome
- Pulmonary embolism (rare, less common compared to lower limb deep vein thrombosis).

Evaluation

- Doppler ultrasonography
- If suspicion is high and ultrasonography is negative, then perform venography
- Consider evaluation for pulmonary embolism
- D-dimer testing is not routinely recommended, but negative results rule out catheter-related thrombosis.

Treatment

- Immediate catheter removal is not recommended
- Low molecular weight heparin for 5–7 days, followed by oral anti-coagulation or continuation of low molecular weight heparin for 3–6 months, is recommended.
- Consider catheter-directed or systemic thrombolysis in case of massive deep vein thrombosis with extensive swelling and functional impairment of the arm, if the risk of bleeding complications is low
- Consider catheter removal in case of:
 - Catheter infection

- Persistent catheter malfunction
- Contraindications for anticoagulation
- Persistent symptoms despite anticoagulation
- Catheter is no longer needed.

Catheter Malfunction

Complete obstruction of the catheter can be caused by fibrin deposition in the lumen or on the tip of the catheter. Because device malfunction can precede or accompany catheter-related thrombosis, thrombosis should be excluded in every case by ultrasonography.

Catheter malfunction should be managed according to the local cancer centre guidelines based on prospective trial data. Routine intraluminal instillation of thrombolytic agents should be considered (e.g. alteplase, urokinase, streptokinase), which leads to success in 59%–95% of cases, depending on the treatment type and clinical situation. Anticoagulant therapy can be initiated either after or during thrombolytic procedures. Catheter removal should be considered if its effectiveness is not restored.

Declaration of Interest:

Dr Volkov has reported no conflicts of interest.

Dr Moiseenko has reported no conflicts of interest.

Further Reading

- Baskin JL, Reiss U, Wilimas JA, et al. Thrombolytic therapy for central venous catheter occlusion. *Haematologica* 2012; 97:641–650.
- Kamphuisen PW, Lee AY. Catheter-related thrombosis: lifeline or a pain in the neck? *Hematology Am Soc Hematol Educ Program* 2012; 2012:638–644.
- Kucher N. Clinical practice. Deep-vein thrombosis of the upper extremities. *N Engl J Med* 2011; 364: 861–869.
- Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 49:1–45.
- O’Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2011; 52:e162–e193.

- Schiffer CA, Mangu PB, Wade JC, et al. Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2013; 31:1357–1370.
- Sousa B, Furlanetto J, Hutka M, et al. Central venous access in oncology: ESMO Clinical Practice Guidelines. *Ann Oncol* 2015; 26(suppl 5):v152–v168.

Septic Shock

F. Morgillo

E. Martinelli

T. Troiani

Faculty of Medicine, Second University of Naples, Naples, Italy

Definition

Sepsis is a systemic inflammatory response syndrome (SIRS) that is characterised by widespread tissue injury, often due to severe infection. Pathogens or microbial-associated molecules (pathogen-associated molecular patterns) cause tissue damage and inflammatory reactions. Organ dysfunction results from the direct cytotoxic effects of inflammatory mediators and microbial toxins, as well as from dysregulation of the microcirculation and macrocirculation, oxygen transport and tissue oxygenation.

Septic shock is diagnosed when:

- There is evidence of infection (fever, chills, hypothermia, tachypnoea, hyperglycaemia, leukocytosis, left shift of neutrophils or neutropaenia) AND
- There are signs of organ dysfunction or a decrease in organ perfusion (lactic acidosis, oliguria [<30 ml/h or <0.5 ml/kg/h], mental alteration, hypotension [<90 mmHg or decrease of >40 mmHg]), which is persistent despite adequate fluid substitution and exclusion of other reasons for hypotension.

Management of Septic Shock

Early Management

Early goal-directed therapy targets (Figure 1):

- Airway and breathing stabilisation, and perfusion to the peripheral tissues:

- Central venous (superior vena cava) oxyhaemoglobin saturation (ScvO₂) ≥70% (when central access is available), or mixed venous oxyhaemoglobin saturation (SvO₂) ≥65% (if a pulmonary artery catheter is being used);
- Mean arterial pressure (MAP) ≥65 mmHg;
- Urine output ≥0.5 ml/kg/h;
- Static or dynamic predictors of fluid responsiveness, e.g. central venous pressure (CVP) 8–12 mmHg.

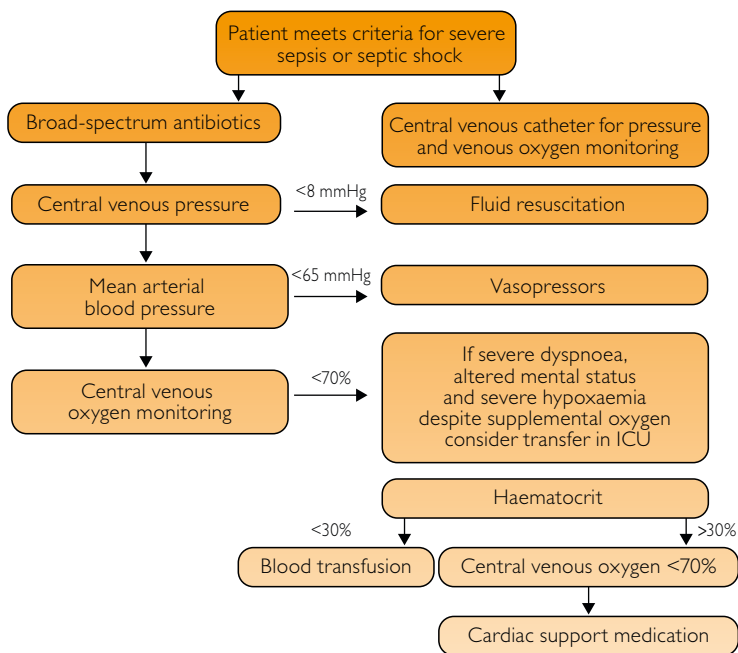


Figure 1 Treatment algorithm for septic shock.

ICU, intensive care unit.

- Diagnosis of the infectious source, by physical examination, vitals, blood analysis and multiple sampling for cultures and Gram stains, and definition of a three-drug combination against Gram-positive and Gram-negative bacteria and fungi (Table 1).

Management of Resistant Septic Shock

- Vasopressor and inotropic agents to keep/reach goals:
 - ScvO₂ ≥70% (when central access is available) or SvO₂ ≥65% (if a pulmonary artery catheter is being used);
 - MAP ≥65 mmHg;
 - Urine output ≥0.5 ml/kg/h.
- Static or dynamic predictors of fluid responsiveness, e.g. CVP 8–12 mmHg.

Management of Refractory Septic Shock

- Low-dose corticosteroids
- Transfer to intensive care unit (ICU).

Table 1 Typical Pathogens During Bacterial Sepsis in Cancer Patients

Origin	Frequent pathogens
Unknown	Coagulase-negative staphylococci, <i>Escherichia coli</i> , <i>Enterococcus</i> species
Lung	<i>Pseudomonas aeruginosa</i> , Pneumococci, Alpha-haemolytic streptococci, <i>Acinetobacter</i> species
Abdomen	<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Clostridium</i> species, <i>Enterococcus</i> species, <i>Klebsiella</i> species
Urogenital	<i>Escherichia coli</i> , <i>Klebsiella</i> species, <i>Pseudomonas aeruginosa</i>
Soft tissue	<i>Staphylococcus aureus</i> , Alpha-haemolytic streptococci
Central venous catheter	Coagulase-negative staphylococci, <i>Corynebacteriae</i> , <i>Propionibacterium</i> species, <i>Candida albicans</i> , <i>Candida tropicalis</i>

Antimicrobial Therapy

Diagnosis and Evaluation

Prompt and effective treatment of the active infection (Table 1) is essential for the successful treatment of severe sepsis and septic shock.

- Meticulous physical assessment of common sites of infection (mouth, pharynx, respiratory tract, skin and soft tissue, perineal area, urinary and gastrointestinal tract, and exit sites of peripheral or venous catheters) should be done immediately.

- A complete blood analysis profile (complete blood count, biochemistry, coagulation times, electrolytes, arterial gases) should be done immediately.
- Samples for cultures and stains for bacteria and fungi (from urine, stool, drainage sites, sputum, blood [if a central venous catheter is in place, collect the cultures from each lumen as well as from a peripheral vein], and cerebrospinal fluid if suspicion of a central nervous system [CNS] infection) should be taken as soon as possible. Cultures, especially from blood, should be done ideally after onset of fever or chills, and before the first dose of antibiotics.
- Potentially infected foreign bodies (e.g. vascular access devices) should be removed when possible and sent for culture, and abscesses should undergo percutaneous or surgical drainage.
- Investigation of suspected pneumonia should include chest radiography (if negative, early computed tomography) and pleural effusion aspiration and evaluation. If intra-abdominal sepsis is suspected, an initial ultrasound or computed tomography should be performed urgently.

Choice of Antimicrobial Therapy

Intravenous antibiotic therapy should be initiated within the first 6 hours, after obtaining appropriate cultures, as early initiation of antibiotic therapy is associated with lower mortality.

The choice of antibiotics can be complex and should consider the patient's history (e.g. recent antibiotics received), comorbidities, clinical context (e.g. community- or hospital-acquired), Gram stain data, and local resistance patterns.

When the potential pathogen or infection source is not immediately obvious, a broad-spectrum antibiotic coverage directed against both Gram-positive and Gram-negative bacteria is favoured. Few guidelines exist for the initial selection of empirical antibiotics in severe sepsis or septic shock.

- An initial treatment with meropenem, or with imipenem/cilastatin, or with piperacillin/tazobactam, is recommended. Treatment with a third- or fourth-generation cephalosporin, such as ceftazidime, is an alternative option.

- In neutropaenic patients with septic shock and severe sepsis, combination treatment with an aminoglycoside may be considered, together with an anti-fungal agent such as amphotericin B (in case of renal impairment, administer liposomal amphotericin B).

Additional coverage for patients at risk of specific pathogens

- Patients with suspected pneumonia by *Pneumocystis carinii* should receive trimethoprim-sulfamethoxazole.
- Anaerobic coverage (metronidazole, clindamycin, and chloramphenicol) should be considered in patients with abdominal abscesses or acute abdominal pain suggestive of typhlitis.
- Aminoglycoside administration (i.e. tobramycin or amikacin) is adapted to the neutropaenic patient, also if a *Pseudomonas aeruginosa* or Gram-negative sepsis is suspected.
- If interstitial pneumonia is observed in a transplanted patient or in a patient being chronically treated with corticosteroids, ganciclovir is also added.

Regardless of the antibiotic regimen selected, patients should be observed closely for toxicity, evidence of response, and the development of nosocomial superinfection. The duration of therapy is typically 7 to 10 days, although longer courses may be appropriate in patients who have a slow clinical response, an undrainable focus of infection, or immunological deficiencies. In patients who are neutropaenic, antibiotic treatment should continue until the neutropaenia has resolved or the planned antibiotic course is complete, whichever is longer.

Treatment of Cardiovascular Insufficiency

Fluid Resuscitation

In patients with sepsis, intravascular hypovolaemia is typical and may be severe, requiring rapid fluid resuscitation.

Aggressive and early goal-directed treatment aiming at restoration of cardiovascular function is crucial, and is indicated as an initial therapy for severe sepsis or septic shock, unless there is co-existing clinical or radiographic

evidence of heart failure. To restore adequate cardiac filling pressures and to maintain adequate organ perfusion (goal: MAP 65 mmHg, CVP 8–12 mmHg, pulmonary wedge pressure 12–15 mmHg, urinary output 0.5 ml/kg/h and central venous or mixed venous oxygen saturation 70%), crystalloid fluids are recommended as the initial fluids of choice in severe sepsis and septic shock (e.g. normal saline, Ringer's lactate).

Vasopressors

If a sufficient MAP (>65 mmHg) cannot be achieved by volume substitution in a reasonable time frame, treatment with vasopressors is indicated. The drug of choice to elevate the vasotonus is norepinephrine at a dose of 0.1–1.3 µg/kg/min.

Although, in few small studies, vasopressin (0.01–0.04 U/min) increased urinary output and creatinine clearance compared to norepinephrine, this effect did not translate to a reduction in 28-day mortality, and there is currently poor evidence to support the use of vasopressin in septic shock (Russell, 2011).

In case of sepsis-related myocardial depression leading to low cardiac output despite adequate volume substitution, vasopressor treatment with dobutamine should be initiated at doses ranging from 2 µg/kg/min to 28 µg/kg/min.

Oxygen Support

Supplemental oxygen should be supplied to all patients with sepsis, and oxygenation should be monitored continuously with pulse oximetry (O₂ saturation of 90%).

When indicated, transfer the patient early to the ICU for placement of an endotracheal tube and mechanical ventilation. Indications include severe dyspnoea (respiratory rate >40 breaths per minute, use of accessory muscles), altered mental status and severe hypoxaemia despite supplemental oxygen.

Intubation and mechanical ventilation may be required to support the increased work of breathing that typically accompanies sepsis, or for airway protection since encephalopathy and a depressed level of consciousness frequently complicate sepsis.

Nutrition

Enteral nutrition is preferred over parenteral nutrition unless contraindicated or impossible, as it is associated with a lower rate of infection. Enteral caloric intake should be calculated according to the phase of sepsis: during the initial phase of sepsis, the supply of >20–25 kcal/kg ideal bodyweight (IBW) was associated with inferior outcome in one observational study (Krishnan et al, 2003). During recovery, 25–30 kcal/kg IBW should be provided.

Hyperglycaemia

Hyperglycaemia in patients requiring intensive care is associated with an inferior outcome. However, intensive insulin therapy aiming at a blood glucose level of 4.4–6.6 mmol/l (80–120 mg/dl) is not recommended. Maintenance of blood glucose levels at least ≤ 9.9 mmol/l (≤ 180 mg/dl) is preferable.

Treatment with Corticosteroids

Replacement of impaired adrenal reserve and anti-inflammatory properties is a rationale for studying corticosteroids as an adjunctive to sepsis therapy. Low-dose corticoid treatment (200–300 mg intravenous hydrocortisone every 6 hours or by continuous infusion every day plus 50 μ g fludrocortisone orally) may be considered in patients with insufficient restoration of blood pressure levels despite adequate fluid resuscitation and vasopressor treatment.

Treatment with Coagulation Inhibitors

In sepsis, the coagulation cascade is frequently activated at early time points. As thrombocytopenia and an increased risk of bleeding are frequently present in patients with cancer and chemotherapy, attempts to positively influence coagulation in patients with neutropenia have to be exerted carefully.

Patients without contraindications to heparin use (thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral haemorrhage, etc.) should

receive deep venous thrombosis prophylaxis, preferably with low molecular weight heparin at the recommended dose. In patients with disseminated intravascular coagulation (DIC) and sepsis, the administration of antithrombin may be considered.

Cytokines and Haematopoietic Growth Factors

The known effect of granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF) in increasing the number of circulating granulocytes is the rationale for their role as additional therapy to antibiotics in febrile patients with chemotherapy-induced neutropaenia, because they effectively reduce the time to neutrophil recovery and of hospitalisation duration.

Transfusion Management in Sepsis

Platelets or packed red blood cell transfusion is recommended in neutropaenic patients with septic shock. However, the cut-off for substitution is often set to higher values (platelets 20 000/ μ l instead of 10 000/ μ l, and <9 g/dl haemoglobin level) to optimise tissue oxygenation.

Declaration of Interest:

Dr Morgillo has reported no conflicts of interest.

Dr Martinelli has reported no conflicts of interest.

Dr Troiani has reported no conflicts of interest.

Further Reading

Krishnan JA, Parce PB, Martinez A, et al. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. *Chest* 2003; 124:297–305.

National Collaborating Centre for Cancer (UK). Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. London: National Institute for Health and Care Excellence (UK); 2012 Sep. PubMed PMID: 26065059.

Penack O, Becker C, Buchheidt D, et al. Management of sepsis in neutropenic patients: 2014 updated guidelines from the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO). *Ann Hematol* 2014; 93:1083–1095.

- Rolston KV. Neutropenic fever and sepsis: evaluation and management. *Cancer Treat Res* 2014; 161:181–202.
- Russell JA. Bench-to-bedside review: Vasopressin in the management of septic shock. *Crit Care* 2011; 15:226.
- Vazquez-Grande G, Kumar A. Optimizing antimicrobial therapy of sepsis and septic shock: focus on antibiotic combination therapy. *Semin Respir Crit Care Med* 2015; 36:154–166.

Extravasation of Chemotherapy

6

M. Unseld

C. Thallinger

*Department of Internal Medicine I, Section of Oncology,
Medical University of Vienna, Austria*

Introduction

Paravasation or extravasation (from Latin, *vas*: vessel) describes the process of inadvertent, accidental escape of a substance from a vessel into the adjacent tissue. It is mainly caused by the injection of a cytotoxic agent into the surrounding tissue, or secondarily by leakage of involved blood vessels.

Mostly depending on the chemical properties of the agent, extravasation is a potentially serious complication of anticancer drug administration.

Immediate standard treatment procedures are indispensable to avoid functional impairments and to ensure scheduled treatment adherence. A combination of non-pharmacological approaches, specific agents and – if unavoidable – surgical intervention is applied to improve the outcome of extravasation. Despite standardised management of extravasation injuries, priority should be given to preventive measures.

Differential Diagnosis and Grading

Extravasation injuries may appear rapidly but can also develop over time. All manifestations have to be evaluated carefully; thrombophlebitis, hypersensitivity or photosensitisation must be excluded by differential diagnosis. Some chemotherapeutic drugs (e.g. cisplatin, dacarbazine, epirubicin) are prone to cause local reactions, which resemble an extravasation and thus should not be confused with true extravasation.

Clinical signs of local irritative reactions without extravasation are predominantly erythema, urticaria and/or local itching along the accessed vein. A new flare-up of skin toxicity (redness, swelling, inflammation and blistering) at the site of a previous extravasation, following correctly administered chemotherapy, may occur as a recall phenomenon. The exact pathophysiological mechanism of the recall phenomenon is unknown, but drug hypersensitivity reaction has been suggested as a potential factor.

Epidemiology

Extravasation is responsible for 0.1%–6.5% of adverse effects following antineoplastic treatment. Incidence data for extravasation vary greatly according to the literature; thus ranges between 0.01% and 11% are reported for paediatric and adult patients. Most of these injuries can be prevented with appropriate precautions. The overall incidence is described as declining, due to improvements in the quality of instruction, management training, infusion procedures, adjustment of intravenous application to oral or subcutaneous formulations, and early recognition. However, extensive studies on extravasation incidence are still lacking, with the suspicion of a large number of non-reported cases.

Risk Factors – Intravenous Infusion

Careful examination for risk factors is a prerequisite to prevent extravasation. The presence of multiple risk factors identifies high-risk patients (Table 1).

Individual Associated Risk Factors

Patient related

The vein situation of the patient has to be considered as one of the most important risk factors. Elderly/young patients or patients with narrow, mobile or fragile veins, as well as veins following manifold puncturing, are more prone to extravasation.

Recommendations not to puncture the elbow flexure are difficult to put into practice, as these anatomical sites often offer the veins with the

largest luminal diameter, and are therefore likely to be chosen in routine practice. Careful handling of such locations by the staff is therefore indispensable.

Table 1 Risk Factors for Extravasation of Peripheral Intravenous Drug Application.

Adapted from: de Wit M, Ortner P, Lipp HP, et al. Management of cytotoxic extravasation – ASORS expert opinion for diagnosis, prevention and treatment. Onkologie 2013; 36:127–135; Pérez Fidalgo JA, García Fabregat L, Cervantes A, et al; ESMO Guidelines Working Group. Management of chemotherapy extravasation: ESMO-EONS Clinical Practice Guidelines. Ann Oncol 2012; 23(Suppl 7):vii167–vii173. By permission of Oxford University Press.

Individual associated	
Patient related	Staff related
Vein situation	Vein puncture technique
Cardiovascular disorder	Low patient information
Decreased lymphatic drainage	Insufficient monitoring
Elderly patients	Time pressure
Procedure associated	
Workflow related	Substance related
Injection site	Chemical properties
Infusion volume	Volume of extravasation
Duration of infusion	Duration of exposure
Catheter gauge	Frequency

Extravasation has been shown to be associated with cardiovascular disorders such as increased venous pressure or right cardiac insufficiency, impairment by decreased lymphatic drainage (e.g. as a result of lymph node dissection or irradiation), motoric agitation and hypaesthesia due to neuropathy. The patient’s mental status or difficulties in understanding have to be considered, as well.

Staff related

Trained staff are a prerequisite for chemotherapeutic application. Lack of time and concomitant insufficient monitoring are often associated with extravasation injury. Veins, especially upon handling of cytotoxic agents with necrotising capacity, ought not to be punctured by inexperienced trainees. Multiple puncturing must be avoided in all cases, due to leakage of the vessel system upon needle injury. Patients must be informed precisely about the application procedure.

Procedure associated

Substance related: The chemical properties of the specific drug (e.g. pH value, osmolarity, mechanism of action) are to a large extent responsible for the severity of the injury. Volume, concentration, duration and frequency of infusions may increase the risk and therefore should be applied carefully considering the chemotherapy protocol.

Workflow related: Preparation of chemotherapeutic agents must be performed under standardised conditions. Catheter gauge size and material must be appropriate in relation to the vein diameter. The forearm should be preferred as the safest location, above the back of the hand to the elbow flexure being the least safe. Readjustments should be avoided and catheters must be properly fixed. Following cannulation, blood aspiration should be visible, and a flush with 10 ml physiological saline should be given to examine for signs of extravasation. Preferably, a transparent catheter dressing should be used to reveal skin swelling or redness at an early stage. If multiple drugs are administered, particular attention must be paid to catheter placement at the beginning of the administration of each agent.

Central Venous Systems

In high-risk patients, the earliest possible placement of a central venous access device (CVAD) must be considered. A peripherally inserted central catheter (PICC) or central venous catheter (CVC) placement allows safe administration of cytotoxic drugs, but is time-consuming and may lead to complications of the procedure itself. Port-A-Caths (PAC) are implanted ports visible under the skin, which can remain in place for a long period. Complications of drug instillation via central venous devices are rare, and radiological control ensures proper location of the implant. As extravasation normally causes more severe damage in central venous systems, the procedure for PAC use has to be well taught to personnel dealing with such devices. Central venous device infections are possibly severe and may become systemic. Sterile handling is therefore indispensable, and is the most important precaution in the handling of such devices (Table 2).

Table 2 Safety Precautions for Use of Port-A-Cath (PAC) Devices

PAC instructions for use	
1.	Inspection of PAC system and adjacent skin (normal, redness, swelling)
2.	Position patient to encompass the PAC with fingers
3.	Sterile disinfection of puncture location (residence time: 3 minutes)
4.	Meanwhile, prepare PAC needle and equipment
5.	Vertical puncturing in centre of PAC under sterile conditions
6.	Aspiration and blood draw, if required
7.	Flush with 10 ml isotonic solution without resistance
8.	Proper fixation of PAC needle
9.	Infusion of specific agent
10.	At the end of infusion: flush with 20 ml isotonic solution
11.	Seal PAC with heparin solution in case of thromboembolic risk factors
12.	Dispose of needle and clean with sterile isoniazid-saturated swab
13.	Bandage adequately

Substances

Agents have been classified according to the tissue reaction they cause in case of extravasation (Table 3). Based on their ability to damage surrounding tissue, antineoplastic substances are divided in three categories: non-vesicants, irritants and vesicants. Non-vesicants are known to induce temporary skin alterations such as oedema without signs of inflammation or necrosis. Non-vesicant agents, however, which are extravasated in high concentration/volume, should be considered as irritants. Irritants are known to cause pain at the injection site and along the vein. Furthermore, they may also induce inflammation at the respective site of extravasation. Vesicants, on the other hand, have the potential to cause severe tissue damage, including blistering, ulceration and necrosis. According to their mechanism of action, they can be subclassified into DNA-binding and non-DNA-binding substances. DNA-binding agents lead to generation of cell DNA–medication complexes, which propagate tissue damage through endocytosis by adjacent cells. Non-DNA-binding agents are metabolised and neutralised more easily in the tissue, resulting in less skin toxicity.

For some agents, only single case reports define their irritant or vesicant properties. In those cases, agents should be allocated into the group associated with largest potential damage.

Table 3 List of Antineoplastic Agents According to Their Irritant or Vesicant Potential (Alphabetic).

Adapted from: de Wit M, Ortner P, Lipp HP, et al. Management of cytotoxic extravasation – ASORS expert opinion for diagnosis, prevention and treatment. *Onkologie* 2013; 36:127–135; Pérez Fidalgo JA, García Fabregat L, Cervantes A, et al; ESMO Guidelines Working Group. Management of chemotherapy extravasation: ESMO-EONS Clinical Practice Guidelines. *Ann Oncol* 2012; 23(Suppl 7): vii167–vii173. By permission of Oxford University Press.

Non-vesicants	Irritants	Vesicants
Aflibercept	Carboplatin	Amsacrine
Antibodies	Carmustine	Bendamustine*
Arsenic trioxide	Cisplatin	Cabazitaxel
Asparaginase	Dacarbazine	Dactinomycin
Bleomycin	Etoposide	Daunorubicin*
Bortezomib	Fluorouracil	Docetaxel
Cladribine	Ifosfamide	Doxorubicin*
Clofarabine	Irinotecan	Epirubicin*
Cyclophosphamide	Liposomal daunorubicin	Idarubicin*
Cytarabine	Liposomal doxorubicin	Mechlorethamine*
Eribulin	Melphalan	Mitomycin C
Etoposide phosphate	Oxaliplatin	Mitoxantrone
Gemcitabine	Streptozocin	Paclitaxel
Fludarabine	Topotecan	Trabectedin
Interferons		Treosulfan
Interleukin-2		Vinblastine
Methotrexate		Vincristine
Mifamurtide		Vindesine
Pemetrexed		Vinflunine
Pentostatin		Vinorelbine
Raltitrexed		
Temsirolimus		
Thiothepa		

*DNA-binding compounds

Management

During the last decades, management of extravasation with different treatment modalities has been performed mostly on an empirical basis. The literature addressing extravasation management is limited. Classical randomised studies in human subjects to evaluate extravasation treatment modalities are unworkable, due to ethical reasons. Most of the studies found in the literature are thus carried out in murine models.

Even though small extravasation lesions may heal spontaneously, larger lesions – especially due to vesicant agents – can be dramatic and result in tissue necrosis, followed by surgical debridement and potential deformation of the affected body region.

Treatment should be initiated immediately. General treatment strategies include stopping the infusion without removing the needle, and aspiration of extravasated volume without pressure. The affected limb should be placed in an elevated position.

Depending on the substance, cold or warm dry compresses should be applied within the first 48 hours. Dry warm compresses (44–50°C) increase the blood flow and the distribution and elimination of the drug. Warm compresses in combination with hyaluronidase are recommended for vinca alkaloid extravasation.

In contrast, dry cold compresses (0°C) will cause vasoconstriction, with a consequent decrease in the diffusion velocity of the extravasated substance within the tissue, thus minimising the area of tissue damage. Cold compresses should be used for liposomal daunorubicin, liposomal doxorubicin, amsacrine, cisplatin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mitomycin C and mitoxantrone.

Regarding frequently applied corticosteroids, their use either topically or subcutaneously in the treatment of extravasation has not been validated by controlled clinical studies.

As extravasation can cause pain, oral analgesics such as ibuprofen, diclofenac sodium or metamizole can be helpful.

An extravasation kit containing general treatment instructions and documentation forms as well as treatment equipment (dimethylsulphoxide [DMSO] 99%, hyaluronidase, hot–cold pack) should always be available for immediate use when antineoplastic agents are administered.

Antidotes

Dexrazoxane

Since 2007, dexrazoxane has been approved for the treatment of anthracycline extravasation. Dexrazoxane readily passes into cells and forms a strong iron chelator that displaces iron from anthracycline. Additionally, dexrazoxane is a catalytic inhibitor of DNA topoisomerase II, which is generally recognised as the principal molecular target for anthracycline anti-tumour action. Clinical trials demonstrated that dexrazoxane administered intravenously (i.v.) in a large vein, in a remote area from the extravasation process, may prevent severe tissue damage following anthracycline extravasation. The first infusion (dose 1000 mg/m²) should be started before 6 hours following extravasation, and subsequent infusions should be applied after 24 and 48 hours (dose 500 mg/m² each). The dexrazoxane dose should be reduced to 50% in patients with creatinine clearance values <40 ml/min. Importantly, major concerns about the systemic use of dexrazoxane are the side effect profile and the remarkable financial burden.

Based on recent data, DMSO 99% (see below) plus cooling can be used as an appropriate alternative treatment strategy to dexrazoxane for anthracycline extravasation due to similar efficacy rates. Unfortunately, neither comparative nor prospective studies evaluating dexrazoxane versus DMSO 99% are available so far.

DMSO

DMSO is an appropriate treatment option for the extravasation of amsacrine, cisplatin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mitomycin C and mitoxantrone. DMSO is an organic solvent, which acts as a potent radical scavenger by speeding up penetration of the extravasated drug into the adjacent tissue, thus leading to local dilution of the substance. After extravasation, DMSO 99% should be dabbed softly over the affected skin area every 4–6 hours for the first 24 hours, then twice daily. The standard treatment duration is about 1–2 weeks, or perhaps longer in some rare and severe cases. Importantly, DMSO can cause erythema and itching, which in turn can camouflage the success of extravasation treatment.

Hyaluronidase

Hyaluronidase is used in combination with dry warm compresses for vinca alkaloid extravasation. Its use aims to improve the exchange of liquids between tissue and vascular system. Hyaluronidase should be applied immediately by multiple, radiating subcutaneous injections in and around the area of extravasation; 1–10 vials containing 150 USP units are usually required, although 1 vial is the amount most often used.

Surgical intervention

Conservative treatment approaches to ulcers due to tissue damage following extravasation are often ineffective. Thus, the treatment of ulcers often requires surgical debridement with wide, three-dimensional excision of the affected tissue.


The optimal timing of surgical intervention remains contentious. There are no standard recommendations for surgical interventions after paravasation of an antineoplastic agent. However, early involvement of a plastic surgeon in the management of difficult extravasation cases is recommended.

Documentation and Follow-up

Accurate and complete documentation of the extravasation is mandatory and should be done closely (every 24 hours) in the first days after the occurrence. Importantly, some vesicant agents can induce blisters and ulcers after several days, which makes extended close follow-up necessary. Any changes should be reported. In case of improvement, weekly visits are recommended until complete resolution of symptoms. Using a template (Figure 1) can facilitate documentation. Photographic documentation can be helpful for the follow-up visits and further treatment procedures.

Date of extravasation		Time of extravasation	
Substance	Concentration [mg]	Extravasation volume [ml]	
1.			
2.			
3.			

Puncture site			
peripheral venous access <input type="checkbox"/>	left arm <input type="checkbox"/>	right arm <input type="checkbox"/>	
	back of hand <input type="checkbox"/>	wrist <input type="checkbox"/>	forearm <input type="checkbox"/> elbow <input type="checkbox"/>
central venous access <input type="checkbox"/>	which:		where:



Multiple puncture attempts have been performed before extravasation	
yes <input type="checkbox"/>	no <input type="checkbox"/>
if yes, where: proximal <input type="checkbox"/> medial/lateral <input type="checkbox"/> distal <input type="checkbox"/>	

Extravasation was recognised by (name)	
during application <input type="checkbox"/>	following application <input type="checkbox"/>
..... hours following application <input type="checkbox"/> days following application <input type="checkbox"/>

Performed procedures		
aspiration of agent yes <input type="checkbox"/> no <input type="checkbox"/>	conservative procedures:	surgical procedures:
others:		

Risk factors		
upper venous congestion <input type="checkbox"/>	lymphoedema <input type="checkbox"/>	haematoma <input type="checkbox"/>
other		

Symptoms					
pain <input type="checkbox"/>	oedema <input type="checkbox"/>	blisters <input type="checkbox"/>	discoloration <input type="checkbox"/>	ulceration <input type="checkbox"/>	necrosis <input type="checkbox"/>
Size:					

Time point of assessment			
day of extravasation <input type="checkbox"/>	I. control <input type="checkbox"/>	II. control <input type="checkbox"/>	III. control <input type="checkbox"/>
Notes:			
Next visit:			

Department	Date	Signature/Pager
------------	------	-----------------

Figure 1 Extravasation documentation sheet.

Declaration of Interest:

Dr Unseld has reported no conflicts of interest.

Dr Thallinger has reported no conflicts of interest.

Further Reading

- Bertelli G, Gozza A, Forno GB, et al. Topical dimethylsulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective clinical study. *J Clin Oncol* 1995; 13:2851–2855.
- Boulanger J, Ducharme A, Dufour A, et al; Comité de l'évolution des pratiques en oncologie (CEPO). Management of the extravasation of anti-neoplastic agents. *Support Care Cancer* 2015; 23:1459–1471.
- Bronner AK, Hood AF. Cutaneous complications of chemotherapeutic agents. *J Am Acad Dermatol* 1983; 9:645–663.
- Camidge R. Oxaliplatin-induced radiation recall: timing not a problem. *Clin Oncol (R Coll Radiol)* 2001; 13:236.
- Conde-Estévez D, Mateu-de Antonio J. Treatment of anthracycline extravasations using dexrazoxane. *Clin Transl Oncol* 2014; 16:11–17.
- de Wit M, Ortner P, Lipp HP, et al. Management of cytotoxic extravasation – ASORS expert opinion for diagnosis, prevention and treatment. *Onkologie* 2013; 36:127–135.
- Goutos I. Neuropathic mechanisms in the pathophysiology of burns pruritus: redefining directions for therapy and research. *J Burn Care Res* 2013; 34:82–93.
- Mader I, Fürst-Weger PR, Mader RM, et al. *Extravasation of Cytotoxic Agents; Compendium for Prevention and Management*, 2nd edition. New York: Springer Verlag, 2009.
- Pérez Fidalgo JA, García Fabregat L, Cervantes A, et al; ESMO Guidelines Working Group. Management of chemotherapy extravasation: ESMO-EONS Clinical Practice Guidelines. *Ann Oncol* 2012; 23(Suppl 7):vii167–vii173.
- Reynolds PM, MacLaren R, Mueller SW, et al. Management of extravasation injuries: a focused evaluation of noncytotoxic medications. *Pharmacotherapy* 2014; 34:617–632.
- Walser EM. Venous access ports: indications, implantation technique, follow-up, and complications. *Cardiovasc Intervent Radiol* 2012; 35:751–764.
- Wickham R, Engelking C, Sauerland C, Corbi D. Vesicant extravasation part II: Evidence-based management and continuing controversies. *Oncol Nurs Forum* 2006; 33:1143–1150.

II - Neurological complications



Spinal Cord Compression

7

E.B. Köksoy

Y. Ürün

Ankara University School of Medicine,

Department of Medical Oncology, Ankara, Turkey

Introduction

Spinal cord compression (SCC) is an oncological emergency that early diagnosis and intervention may prevent, and presents with debilitating neurological sequelae including paraplegia and incontinence. SCC is the second most common neurological complication in cancer patients after brain metastases, and affects approximately 5% of cancer patients. Although lung, prostate and breast cancer are leading causes of SCC, patients with prostate and breast cancer and multiple myeloma have increased risk of developing SCC. Even if SCC mostly occurs in patients with pre-existing cancer, it is the initial manifestation of cancer in 20% of patients, especially in lung cancer, cancer of unknown primary origin, myeloma and non-Hodgkin's lymphoma.

The mechanism of the compression is multifactorial and has complex processes. Haematogenous vertebral corpus metastasis is the most common mechanism in adults. Epidural venous plexus obstruction may lead to vasogenic oedema of the white matter, which occurs in early stages, and is associated with increased inflammatory reactions that result in hypoxic injury of the spinal cord. Vascular endothelial growth factor (VEGF) release is induced by relative hypoxia and venous stasis. VEGF increases vascular permeability and interstitial oedema, creating a vicious cycle. While early decompression increases the likelihood of recovery, prolonged compression may cause irreversible spinal cord damage and debilitating sequelae.

Clinical Manifestations

Though multiple vertebral metastases are common, more than half of SCC arise from the thoracic spine (60%), followed by lumbosacral (30%) and cervical spine (10%). The presenting symptom is usually pain, which is observed in 83%–95% of patients. In later phases of SCC, local pain may gain a radicular pattern. Referred pain can also be seen. Pain may be aggravated by movement, straining and coughing.

Muscle weakness is a common sign of motor deficits and is observed in 60%–86% of patients. Unfortunately, two-thirds of patients are not ambulatory at the time of diagnosis, which is the most important predictor of the ability to walk and of survival after treatment. Compared with muscle weakness, sensory loss is less common but may be observed in 40%–90% of patients. Numbness and paraesthesia may also occur in patients with SCC. Bladder and bowel dysfunction and ataxia can occur in later phases of SCC.

Evaluation of SCC

A high level of suspicion and assessment for SCC is crucial for early diagnosis, to prevent debilitating results in cases of new onset of back or neck pain with cancer. Physical examination and history are initial steps. Conventional plain radiography is frequently used, but, because of the high rate of false-negative results and low sensitivity and specificity, it is not recommended for initial evaluation and screening.

Magnetic resonance imaging (MRI) is the gold standard method for SCC diagnosis and should be performed immediately. Both the sensitivity and specificity of MRI are >90%, and its accuracy is approximately 95%. Additionally, MRI has an important role in treatment decisions. Additional imaging modalities such as myelography, bone scan, computed tomography (CT) and positron emission tomography (PET) are less useful for evaluating SCC.

Differential Diagnosis

Benign musculoskeletal diseases (muscle spasm, spinal stenosis, and intervertebral disc diseases), infectious diseases (spinal epidural abscess), radiation myelopathy and metastatic disease with vertebral metastases

without SCC should be considered in differential diagnosis. Additionally, brain metastasis may lead to similar presentations and should be ruled out.

Management

The main goal of treatment is to maintain and improve neurological functions and survival. Although SCC is a common and devastating problem, limited data from randomised controlled trials (RCTs) are available. Glucocorticoids (GCs), radiotherapy (external beam radiation therapy [EBRT] and stereotactic body radiation therapy [SBRT; also known as stereotactic radiosurgery, SRS]), and surgery are widely used for decompression. Patients' pre-treatment neurological status is the most important prognostic factor. Rapidity of symptom onset is also associated with treatment outcome. Likewise, patients with chemo- or radiosensitive tumours, such as small-cell carcinoma, lymphoma or germ cell tumours, may have favourable treatment outcomes. Therefore, patient selection for the most appropriate treatment has a crucial role. Systemic chemotherapy also plays a role in the case of chemosensitive tumours. An algorithm for the management of SCC is shown in Figure 1.

Glucocorticoids

GCs are the first-line treatment for most patients. GCs reduce inflammation and vasogenic oedema, and also may show antitumoural effects in several types of tumour, including lymphoma, leukaemia, breast cancer and prostate cancer. However, there is no consensus on the optimum loading and maintenance doses of GCs.

“High-dose” corticosteroid treatment (96 mg intravenous [i.v.] dexamethasone, followed by 24 mg qid for 3 days, and then tapered over 10 days) is recommended for patients with paraparesis or paraplegia. For patients with pain but minimal neurological dysfunction, “low-dose” treatment (10 mg dexamethasone i.v. bolus, followed by 16 mg daily) is recommended. High-dose or long-term use of GCs may be associated with several toxicities, which can be classified into:

- Cardiovascular: hypertension, atherosclerosis, elevation of serum lipoproteins, arrhythmias

- Gastrointestinal: gastritis, peptic ulcer disease, steatohepatitis, pancreatitis, visceral perforation
- Endocrine: diabetes mellitus, hypothalamic-pituitary-adrenal insufficiency, amenorrhoea, infertility
- Renal: hypokalaemia, fluid retention
- Infectious: opportunistic and typical infections
- Neuropsychiatric: euphoria, depression, mania, psychosis, akathisia, pseudotumour cerebri
- Bone: avascular necrosis, osteoporosis
- Muscular: myopathy
- Ocular: posterior subcapsular cataract, exophthalmos, elevated intraocular pressure
- Dermatological: skin thinning, petechia/purpura, cushingoid appearance, alopecia, acne, striae, hypertrichosis, hirsutism.

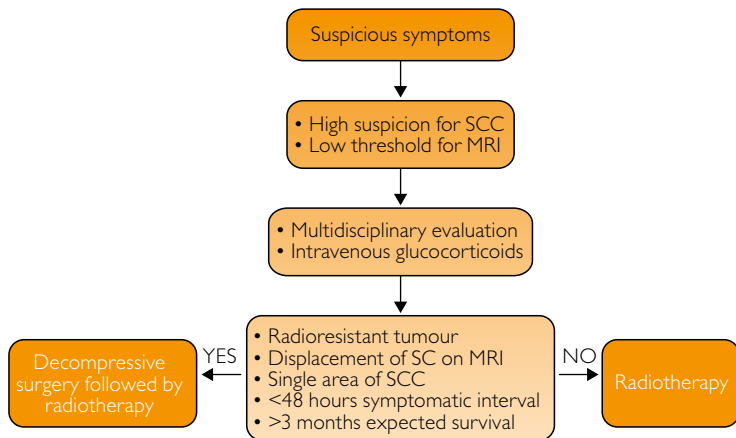


Figure 1 Algorithm for the management of SCC.

Adapted from: Cole JS, Patchell RA. Metastatic epidural spinal cord compression. *Lancet Neurol* 2008; 7:459–466; Loblaw DA, Mitera G, Ford M, Laperriere NJ. A 2011 updated systematic review and clinical practice guideline for the management of malignant extradural spinal cord compression. *Int J Radiat Oncol Biol Phys* 2012; 84:312–317.

MRI, Magnetic resonance imaging; SC, spinal cord; SCC, spinal cord compression.

Radiotherapy

Radiotherapy (RT) with or without surgery is the recommended treatment for SCC. No RCTs have compared different fractionations and doses, but, according to retrospective analysis, different RT schedules had similar functional outcomes. Nonetheless, long-course RT may be associated with less long-term toxicities, and is recommended for patients with a favourable expected survival longer than six months. However, while the rate of being ambulant after RT is approximately 90%, only one quarter of non-ambulant patients regain ambulation. Patients with in-field recurrence should be evaluated for re-irradiation. In relatively radioresistant tumours, such as renal cell carcinoma and melanoma, SBRT may be much more effective than EBRT.

Surgery

Decompressive surgery followed by RT may have better outcomes than RT alone in selected patients, such as patients with radioresistant primary tumours, displacement of spinal cord on MRI, a single area of cord compression, loss of motor function less than 48 hours, or estimated survival longer than three months.

Chemotherapy

Due to its unpredictable and slow response, the role of chemotherapy is limited in the acute management of SCC. Nevertheless, chemosensitive tumours, like Hodgkin's lymphoma, non-Hodgkin's lymphoma, neuroblastoma, germ cell neoplasm and breast cancer, may be treated with a combination of RT and systemic chemotherapy. Hormonal treatment may also play an important role in the management of hormone-sensitive breast and prostate cancers.

Declaration of Interest:

Dr Köksoy has reported no conflicts of interest.

Dr Ürün has reported no conflicts of interest.

Further Reading

- Chen B, Xiao S, Tong X, et al. Comparison of the therapeutic efficacy of surgery with or without adjuvant radiotherapy versus radiotherapy alone for metastatic spinal cord compression: a meta-analysis. *World Neurosurg* 2015; 83:1066–1073.
- Cole JS, Patchell RA. Metastatic epidural spinal cord compression. *Lancet Neurol* 2008; 7:459–466.
- George R, Jeba J, Ramkumar G, et al. Interventions for the treatment of metastatic extradural spinal cord compression in adults. *Cochrane Database Syst Rev* 2015; CD006716.
- Graham PH, Capp A, Delaney G, et al. A pilot randomised comparison of dexamethasone 96 mg vs 16 mg per day for malignant spinal-cord compression treated by radiotherapy: TROG 01.05 Superdex study. *Clin Oncol (R Coll Radiol)* 2006; 18:70–76.
- Helweg-Larsen S, Sørensen PS, Kreiner S. Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. *Int J Radiat Oncol Biol Phys* 2000; 46:1163–1169.
- Loblaw DA, Mitera G, Ford M, Laperriere NJ. A 2011 updated systematic review and clinical practice guideline for the management of malignant extradural spinal cord compression. *Int J Radiat Oncol Biol Phys* 2012; 84:312–317.
- Maranzano E, Trippa F, Casale M, et al. Reirradiation of metastatic spinal cord compression: definitive results of two randomized trials. *Radiother Oncol* 2011; 98:234–237.
- Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet* 2005; 366:643–648.
- Rades D, Lange M, Veninga T, et al. Final results of a prospective study comparing the local control of short-course and long-course radiotherapy for metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys* 2011; 79:524–530.
- Rades D, Stalpers LJ, Veninga T, et al. Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. *J Clin Oncol* 2005; 23:3366–3375.

Complications of Brain Metastases

L. de Mattos-Arruda^{1,2,3}

M. Preusser⁴

¹*Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, UK*

²*Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain*

³*Universitat Autònoma de Barcelona, Barcelona, Spain*

⁴*Department of Medicine I and Comprehensive Cancer Center CNS Unit, Medical University of Vienna, Vienna, Austria*

Introduction

Brain metastases are the most common type of intracranial tumour in adults. Brain metastases occur in 20% to 40% of advanced stage cancers, and lung cancer, breast cancer and melanoma are the primary tumours that most commonly give rise to metastases to the brain. Notably, the incidence of brain metastases has increased in the last few years as a consequence of superior imaging methods and improved control of primary cancers.

The development of brain metastases constitutes an important clinical challenge associated with poor prognosis and reduced quality of life; thus, an understanding of its complications, namely intracranial hypertension, seizure, haemorrhage and neurocognitive decline, can bring value to the management of patients. In this chapter we will briefly review the complications of brain metastases and their management.

Evaluation and Treatment of Brain Metastases

Signs and symptoms associated with brain metastases are usually related to the location of the lesion(s), increased intracranial pressure or haemorrhage.

About 80% of brain metastases occur in the cerebral hemispheres, 15% occur in the cerebellum, and 5% in the brainstem. The most frequent signs and symptoms comprise headache and seizure, followed by nausea and vomiting, and cognitive and/or motor dysfunction. Intracranial hypertension may be associated with morning headache, nausea and vomiting and papilloedema.

The diagnostic method of choice for brain metastases is magnetic resonance imaging (MRI), due to its higher sensitivity and specificity as compared to other imaging modalities.

The standard treatments for patients with brain metastases are radiotherapy-based approaches (i.e. whole brain radiotherapy [WBRT] or stereotactic radiosurgery) or surgical resection. In selected cases, systemic therapy, including targeted agents, should also be considered. Some chemotherapies and targeted agents that cross the blood–brain/blood–tumour barrier, such as BRAF inhibitors (vemurafenib, dabrafenib) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors (ipilimumab) in melanoma, human epidermal growth factor receptor-2 (HER2) tyrosine kinase inhibitors (lapatinib) in breast cancer, and epidermal growth factor receptor (EGFR) inhibitors (gefitinib, erlotinib) in lung cancer, have shown evidence for clinically relevant activity against brain metastases. WBRT continues to be a standard of care for patients with multiple metastatic lesions (>4 lesions). For limited brain metastatic disease (1 to 3 lesions or low disease volume), surgical resection with or without adjuvant radiotherapy may be considered.

Important Complications of Brain Metastases

Increased Intracranial Pressure

Brain metastases commonly lead to increased intracranial pressure, which is typically associated with headache, nausea/vomiting or focal neurological signs. In many cases, significant peritumoural brain oedema can be detected on MRI, especially on FLAIR or T2-weighted imaging sequences. Symptomatic brain oedema is usually treated with dexamethasone. Commonly, the initial daily dexamethasone dose is 12 to 16 mg. Owing to the significant and manifold adverse effects of dexamethasone,

the steroid dose should be rapidly reduced and tapered to individual need (“as much as needed, as little as possible”). Dexamethasone may be combined with osmotic drugs such as mannitol or glycerol. Interestingly, the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab has been shown to have considerable anti-oedematous properties, and may help to control brain oedema in selected patients with brain metastases.

Acute increase of intracranial pressure associated with brain metastases may necessitate decompressive neurosurgery, especially when there is a single space-occupying lesion in a non-eloquent brain area. In patients with obstructive hydrocephalus, a cerebrospinal fluid (CSF) shunt may be considered.

Seizures

Up to 70% of patients with brain metastases experience epileptic seizures during their disease course. However, prophylactic antiepileptic treatment is, in general, not recommended. At development of seizure, anticonvulsive therapy should follow general guidelines for treatment of epilepsy. Antiepileptic monotherapy has been shown to be associated with better tolerability and compliance than combination therapy, and should be initially preferred. However, persisting seizures may necessitate a multidrug regimen. Of note, some anticonvulsants such as phenobarbital, phenytoin and carbamazepine induce hepatic cytochrome P450-mediated metabolism, and as a consequence may interfere with the metabolism of systemic antineoplastic agents, thus potentially increasing the risk for adverse effects. Therefore, non-enzyme-inducing anticonvulsants such as levetiracetam are preferentially used.

Intracranial Haemorrhage

In clinical routine, detection of asymptomatic intratumoural haemorrhages on MR images of brain metastases are not an uncommon finding, and do not per se require special treatment. It is, however, unclear whether such asymptomatic bleeds predispose to larger haemorrhages, and whether drugs that interfere with blood clotting, such as anticoagulants or antiangiogenic therapies (e.g. bevacizumab), should be withheld in such patients.

Symptomatic intracranial haemorrhage is a relatively rare but potentially life-threatening complication in patients with brain metastases. Insufficient data are available on the incidence of this complication, but it seems that the risk correlates with the primary tumour type. Increased risk for intracranial haemorrhage has been described for patients with brain metastases of melanoma and hepatocellular carcinoma. Of note, treatment with bevacizumab has been shown not to be associated with an excess risk of intracranial haemorrhages in brain tumour patients including those with brain metastases.

In patients presenting with acute signs of intracranial pressure, neuroimaging (computed tomography [CT] and/or MRI) should be performed to diagnose or rule out intracranial bleeding. Treatment for confirmed symptomatic intracranial haemorrhage needs to be rapidly initiated, and includes symptomatic therapy (analgesics, anti-emetics, stabilisation of vital signs), prophylactic anticonvulsant therapy, anti-oedematous therapy (dexamethasone), correction of any identifiable coagulopathy (e.g. fresh frozen plasma, vitamin K, protamine, or platelet transfusions) and neurosurgical intervention.

Neurocognitive Impairment

Cognitive decline, especially of memory function, is common in patients with brain metastases and significantly affects quality of life. The aetiology of neurocognitive decline may be multifactorial and related to treatment-associated (radiotherapy, chemotherapy) damage of the brain parenchyma, tumour growth with destruction of brain tissue, and comorbidities. WBRT is generally believed to contribute considerably to neurocognitive decline in patients with brain metastases, mainly due to damage to the hippocampus.

There are no treatment strategies with proven efficacy for patients with established cognitive deficits, although symptom-focused treatment of anxiety and depression and cognitive rehabilitation programmes (neurocognitive training) may offer some help. Medical therapies tested in dementia patients, such as donepezil, have not been adequately studied in patients with brain metastases. In general, neurocognitive decline should be prevented by avoiding WBRT, or replacing classic WBRT by

advanced radiation techniques such as hippocampal-avoidance WBRT, if possible. Some studies are emerging on drug-mediated neuroprotection using memantine or renin–angiotensin–aldosterone system blockers.

Leptomeningeal Carcinomatosis

Leptomeningeal carcinomatosis (LC) represents a rare but often dreadful complication of advanced cancers. It refers to the multifocal seeding of the leptomeninges by malignant cells. LC may occur concomitantly with brain metastasis in 50% to 80% of patients.

Signs and symptoms such as headache, nuchal rigidity, motor weakness, cranial nerve palsies and photophobia indicate meninges involvement and should lead to rapid work-up and treatment. LC diagnosis relies on clinical symptomatology, detection of malignant cells in the CSF by CSF cytology (spinal tap) and MRI.

The treatment goal is to improve the neurological status of the patient and to prolong survival. Treatment options include radiation therapy (WBRT, craniospinal radiation, localised radiotherapy of tumour nodules), administration of systemic or intrathecal chemotherapy or palliative therapy. Unfortunately, virtually no data from clinical trials are available to provide treatment guidelines with a high level of evidence, and treatment decisions should be made on an individual basis, preferably in the context of a multidisciplinary tumour board. Symptom-oriented therapy is indicated in most patients at some point, and includes analgesic, anti-oedematous and anticonvulsive therapy. The same principal considerations apply to patients with LC as to patients with brain metastases, as discussed above.

Future Strategies

Brain metastases are a very common problem in clinical oncology and are associated with high morbidity. Most clinical oncologists are challenged with the symptomatic treatment and management of complications in patients with brain metastases on a regular basis. Unfortunately, only very few studies have been conducted on this issue, and consequently there is a grave lack of data and evidence-based treatment guidelines.

Future efforts should be directed to improve the knowledge on prophylaxis and symptomatic treatment of complications in brain metastases.

Declaration of Interest:

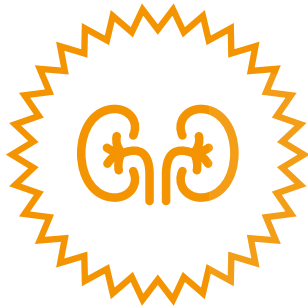
Dr de Mattos-Arruda has reported no conflicts of interest.

Professor Preusser has declared research grants from: Roche, GlaxoSmithKline, Boehringer Ingelheim; honoraria from: Roche, GlaxoSmithKline, Bristol-Myers Squibb, Mundipharma; and travel grants from: Roche, Bristol-Myers Squibb.

Further Reading

- Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol* 2004; 22:2865–2872.
- Berghoff AS, Bartsch R, Wöhrer A, et al. Predictive molecular markers in metastases to the central nervous system: recent advances and future avenues. *Acta Neuropathol* 2014; 128:879–891.
- Dye NB, Gondi V, Mehta MP. Strategies for preservation of memory function in patients with brain metastases. *Chin Clin Oncol* 2015; 4:24.
- Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep* 2012; 14:48–54.
- Preusser M, Capper D, Ilhan-Mutlu A, et al. Brain metastases: pathobiology and emerging targeted therapies. *Acta Neuropathol* 2012; 123:205–222.
- Schouten LJ, Rutten J, Huvneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* 2002; 94:2698–2705.
- Tabouret E, Chinot O, Metellus P, et al. Recent trends in epidemiology of brain metastases: an overview. *Anticancer Res* 2012; 32:4655–4662.

III - Renal and urological complications



Renal Failure and Urological Emergencies in Cancer Patients

9

M. Mediano

I. Duran

Virgen del Rocio University Hospital, Seville, Spain

Introduction

An oncological emergency is defined as an acute condition that is caused by cancer or its treatment, requiring rapid intervention to avoid death or severe damage.

Urological emergencies are those that arise from the genitourinary tract, including urinary tract obstruction and non-infectious cystitis. Acute renal failure (ARF) is another relevant emergency in cancer patients, which overlaps with urological emergencies, and will be also covered in this chapter.

Urological Emergencies

Urinary Tract Obstruction

Definition. Urinary tract obstruction (UO) is defined as the complete interruption of urine natural flow. This complication may occur iatrogenically, or as a result of the underlying cancer. It concerns patients with primary tumours in the pelvis (such as gynaecological or urological malignant neoplasms), but may also result from metastatic disease from any primary cancer to the pelvic area. According to the location, UO is classified as low or high, and the two types will be presented separately.

Low UO

Mechanisms and causes. Low UO is due to obstruction of urine output at the level of the urethra, prostate or bladder. It can be related to urethral

strictures, benign prostatic hyperplasia, prostatitis, prostate cancer, or to iatrogenic causes, such as Foley catheter obstruction, previous extensive pelvic surgery, or the use of anticholinergics or opioid drugs.

Presentation. The pivotal symptom is the inability to urinate, although in some patients it presents as incontinence due to overflow of a full bladder.

Diagnosis. At physical examination, the patient presents with suprapubic tenderness. Ultrasound (US) is used to confirm the diagnosis, if not clinically clear.

Treatment. Urinary Foley catheter placement, or use of a suprapubic tube if there is a tight urethral stricture.

Upper UO

Mechanisms and causes. Stones and cancer growth are the two most frequent causes of upper UO. Ureter flow may be compromised in one or both sides, due to neoplasms such as lymphoma, prostate, bladder, cervical or colon cancer.

Presentation. If there is bilateral upper UO or involvement of a solitary kidney, or poor renal function, the signs and symptoms will be those of uraemia. Otherwise, upper UO will present as abnormal renal function in routine blood work with no symptoms.

Diagnosis. Upon suspicion, imaging tests must be performed to confirm and localise. Ultrasound followed by computed tomography (CT) without contrast, or magnetic resonance imaging (MRI), are carried out in some cases.

Treatment. If the cause is not reversible in the short term and/or there are severe symptoms and/or renal failure, diversion of the urinary tract is indicated. Two methods are available:

- 1) Placement of percutaneous nephrostomy tubes,
- 2) Addition of indwelling ureteral stents through cystoscopy.

These devices need to be changed every 3–6 months.

Reversible causes such as distal ureter stones can be treated medically (by administering tamsulosin 0.4 mg qd).

Non-infectious Cystitis

Definition. Cystitis encompasses a number of symptoms consistent with bladder irritation, which include urinary urgency, dysuria and frequency. There are multiple causes of cystitis, which is the most prevalent infection in the general population. The non-infectious aetiologies of cystitis in cancer patients will be discussed here.

Radiation-induced cystitis (RIC)

Mechanism and causes. External beam radiation (EBR) and brachytherapy, used to treat different pelvic neoplasms such as cervix, prostate and bladder cancer, can cause incidental harm to the bladder mucosa. This damage occurs in three stages (acute, chronic and late), ranging from 4 to 6 weeks, 6 months to a year, and up to 10 years after radiation treatment, respectively.

Presentation. Symptoms, based on the underlying mechanism of RIC previously mentioned, may present from weeks to several years after treatment, and include haematuria, burning, frequency, urgency and incontinence.

Diagnosis. The diagnosis is based on clinical suspicion, and confirmation can be obtained through cystoscopy when considered. Urine culture and/or cytology are recommended to rule out other causes.

Treatment. The first measure is placement of a urinary catheter with irrigation until the elimination of clots, followed by continuous normal saline bladder irrigation. If unsuccessful, cystoscopy and/or imaging of the upper genitourinary tract are indicated.

Systemic and intravesical medical treatments can also be used in refractory cases, although their evidence is weak. The former includes sodium pentosan polysulphate and epsilon aminocaproic acid, and the latter alum and formalin. Treatment with hyperbaric oxygen has shown favourable short-term results in recurrent RIC, although the long-term efficacy is unknown. Surgery is considered when all conservative measures fail.

Chemotherapy-induced cystitis (CIC)

Mechanism and causes. Alkylating agents from the oxazaphosphorine class, such as cyclophosphamide, ifosfamide, trofosfamide and sufosfamide, are related to urinary tract toxicity, including haemorrhagic cystitis. The damage is caused by a metabolite with no antitumour effect, named acrolein and excreted in the urine.

Presentation. Symptoms include haematuria, burning, frequency, urgency and incontinence, and appear within hours after chemotherapy treatment.

Diagnosis. The diagnosis is based on clinical suspicion, and confirmation may be obtained through cystoscopy when considered. Urine culture and/or cytology are recommended to rule out other causes.

Treatment. Prevention is critical in this potentially avoidable type of cystitis, and consists in vigorous intravenous hydration to reduce the urine concentration of metabolites, along with concurrent administration of sodium 2-mercaptoethane sulphonate (MESNA) to detoxify acrolein. If CIC develops, the same principles of therapy as for general haemorrhagic cystitis apply.

Acute Renal Failure

Definition. Acute renal failure (ARF) is defined as a sudden decrease in glomerular filtration rate, leading to an acute rise in blood urea nitrogen (BUN) and serum creatinine (Cr) levels. It is a serious complication of many malignancies, which causes important morbidity and mortality. In critically ill patients with cancer, ARF usually occurs in the context of multiple organ dysfunction, and is associated with mortality rates ranging from 72% to 85%.

Mechanisms and causes. Three different mechanisms (pre-renal, intrinsic and post-renal) have been described to explain ARF.

1. Pre-renal failure: Pre-renal failure is caused by the reduction in blood renal perfusion and the response of the kidney to a decreased effective circulating volume. Response to hypoperfusion is characterised by a fast and reversible rise in serum Cr and BUN, with the renal parenchyma usually remaining intact. Cancer patients appear particularly susceptible

to this mechanism of ARF, due to their high comorbidities and the multiple medical interventions they are exposed to. Pre-renal failure can appear in association with dehydration related to mucositis, bleeding or third spacing. Non-steroidal anti-inflammatory drugs (NSAIDs) can precipitate pre-renal azotaemia in a context of poor hydration or extra-renal fluid losses. Sepsis can also alter the haemodynamics of the kidney, and induce pre-renal ARF if the cause is not reversed in a timely manner.

2. *Intrinsic failure:* An unresolved acute pre-renal failure can evolve towards damage of the renal parenchyma, in what is called acute tubular necrosis (ATN). This damage can also be provoked by other causes, such as nephrotoxic compounds or intravascular haemolysis. When ATN is established, there is renal vasoconstriction and decrease of glomerular blood flow, along with tubular cell injury and obstruction that may cause medullary ischaemia.

Example: Nephrotoxic compounds: There are multiple agents that cause damage to the kidneys through direct tubular toxicity, such as radiological dyes, specific antibiotics, NSAIDs and some others. Among the anticancer agents, cisplatin is probably the most extensively studied nephrotoxic. The most widely used protective measure is saline infusion to induce solute diuresis. Cisplatin is usually administered in divided doses for 5 days. The maximum dose should not exceed 120 mg/m² body surface area, and renal dysfunction may require a dosage reduction. Repeated administration up to a cumulative dose of 850 mg of cisplatin is associated with a 9% reduction in glomerular filtration rate over a 5-year period, compared to a 40% reduction in patients given more than 850 mg (Arany et al, 2003). Contrast agents may also produce intrinsic renal failure.

3. *Post-renal failure:* ARF in this case is a result of an obstruction located within the kidneys (crystals) or downstream of the kidneys. Signs and symptoms vary with the site and the rapidity of obstruction. Diagnosis and management are described in the urinary obstruction section above.

Presentation. Symptoms related to ARF will differ based on the underlying cause and mechanism.

Diagnosis. The diagnosis is based on laboratory results, with a decrease in glomerular filtration rate, and a rise in BUN and serum Cr levels.

Treatment. Treatment is established according to the underlying cause (see Table 1).

Table 1 Acute Renal Failure Causes

Pre-renal failure	<ol style="list-style-type: none">1. Sepsis2. Extracellular dehydration (diarrhoea, mucositis, vomiting)3. Drugs (e.g. NSAIDs)
Intrinsic failure	<ol style="list-style-type: none">1. Acute tubular necrosis (shock, severe sepsis)2. Nephrotoxic agents (contrast agents, aminoglycosides, ifosfamide, cisplatin)3. Disseminated intravascular coagulation4. Intravascular haemolysis5. Acute interstitial nephritis6. Pyelonephritis7. Cancer infiltration (e.g. metastasis)8. Thrombotic micro-angiopathy9. Glomerulonephritis amyloidosis (e.g. renal carcinoma)10. Membranous glomerulonephritis (pulmonary, breast or gastric carcinoma)
Post-renal failure	<ol style="list-style-type: none">1. Intra-renal obstruction (e.g. urate crystals, methotrexate)2. Extra-renal obstruction (retroperitoneal fibrosis, ureteral , bladder or urethra outlet obstruction)

NSAIDs, Non-steroidal anti-inflammatory drugs.

Declaration of Interest:

Dr Mediano has reported no conflicts of interest.

Dr Duran has reported no conflicts of interest.

Further Reading

Arany I, Safirstein RL. Cisplatin nephrotoxicity. *Semin Nephrol* 2003; 23:460–464.
Bosscher MR, van Leeuwen BL, Hoekstra HJ. Surgical emergencies in oncology. *Cancer Treat Rev* 2014; 40:1028–1036.

Cervantes A, Chirivella I. Oncological emergencies. *Ann Oncol* 2004; 15(suppl 4):iv299–306.

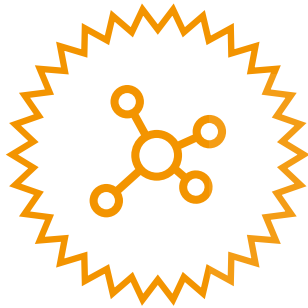
Manso Sánchez, LM. Urgencias oncológicas, “Hospital Universitario 12 de Octubre”. Madrid: Ediciones Ergón, 2014. [In Spanish]

NCCN guidelines for supportive care. Available at: <http://www.nccn.org/profes->

sionals/physician_gls/f_guidelines.asp#supportive

Yeung S, Escalante C. Oncologic emergencies. In: Holland, JF, Frei E III, Bast RC Jr, et al (Editors). *Cancer Medicine*, 6th edition. Hamilton: BC Decker Inc 2003:2659–2680.

IV - Metabolic complications



Hypercalcaemia

M. Strijbos¹

K. Punie²

¹Medical Oncology, AZ Klina, Iridium Cancer Network, Antwerp, Belgium

²Medical Oncology, Leuven University Hospitals, Leuven, Belgium

Definition

Hypercalcaemia is defined as elevated calcium (Ca^{2+}) levels in the blood. Normal albumin-corrected serum calcium levels are 8–10 mg/dl or 2.0–2.5 mmol/l, but reference values may differ slightly between laboratories. Hypercalcaemia is a frequent metabolic complication of both solid cancers and haematological malignancies, with a reported incidence of 20%–30% (Stewart 2005). Patients suffering from breast cancer, multiple myeloma, small cell lung cancer and renal cell carcinoma appear to be most at risk for developing hypercalcaemia. Patients with hypercalcaemia of malignancy often have a poor prognosis.

Aetiology

Osteolytic Metastasis

Bone destruction by osteolytic metastasis is the main cause of hypercalcaemia of malignancy. It is caused primarily by osteoclast activation as a result of tumoural secretion of parathyroid hormone-related protein (PTHrP). PTHrP causes hypercalcaemia through an increase in expression of receptor activator of nuclear factor kappa-B ligand (RANKL) in bone, which consequently causes osteoclast activation by binding to RANK, present on their surface (Ratcliffe et al 1992).

1.25-Dihydroxyvitamin D

Elevated levels of 1.25-dihydroxyvitamin D (1.25-D) is the most frequent cause of hypercalcaemia in lymphoma, acting by increasing

intestinal calcium absorption. This has been hypothesised to be related to an increase of 1-alpha hydroxylase activity in tumour cells, causing accelerated transition from 25-hydroxyvitamin D (25-D) to 1.25-D. In physiological conditions, increased serum calcium causes suppression of parathyroid hormone (PTH), and thereby decreases conversion to 1.25-D. In lymphoma and myeloma, malignant lymphocytes are able to produce PTH-independent 1.25-D from 25-D, causing hypercalcaemia.

Parathyroid Hormone

Secretion of PTH by tumour cells other than parathyroid carcinoma is extremely rare. Reports have been published on ovarian carcinoma, small cell and squamous cell lung carcinoma.

Differential Diagnosis

It should be kept in mind that, although numerous diseases can cause hypercalcaemia (Table 1), the most frequent among these are hyperparathyroidism and malignancy.

Table 1 Differential Diagnosis of Hypercalcaemia.

Modified from: Rottey S, Van Belle S. Hypercalcaemia. In: Kosmidis PA, Schrijvers D, André F, Rottey S (Editors). *ESMO Handbook of Oncological Emergencies*. Oxon: Taylor and Francis, 2005; 68–76.

Cancer	<ul style="list-style-type: none"> ■ PTHrP-related (osteolytic metastasis) ■ Other circulating factors
Endocrine and metabolic disease	<ul style="list-style-type: none"> ■ Familial hypocalcaemic hypercalcaemia ■ Exogenous thyroid hormone administration ■ Primary hyperparathyroidism ■ Addison's disease ■ Immobilisation
Infection and granulomatosis	<ul style="list-style-type: none"> ■ Tuberculosis ■ HIV ■ Sarcoidosis ■ Berylliosis ■ Coccidioidomycosis
Diet and drugs	<ul style="list-style-type: none"> ■ Exogenous vitamin D ■ Exogenous vitamin A ■ Lithium ■ Calcium supplements ■ Milk-alkali syndrome ■ Thiazide and diuretics

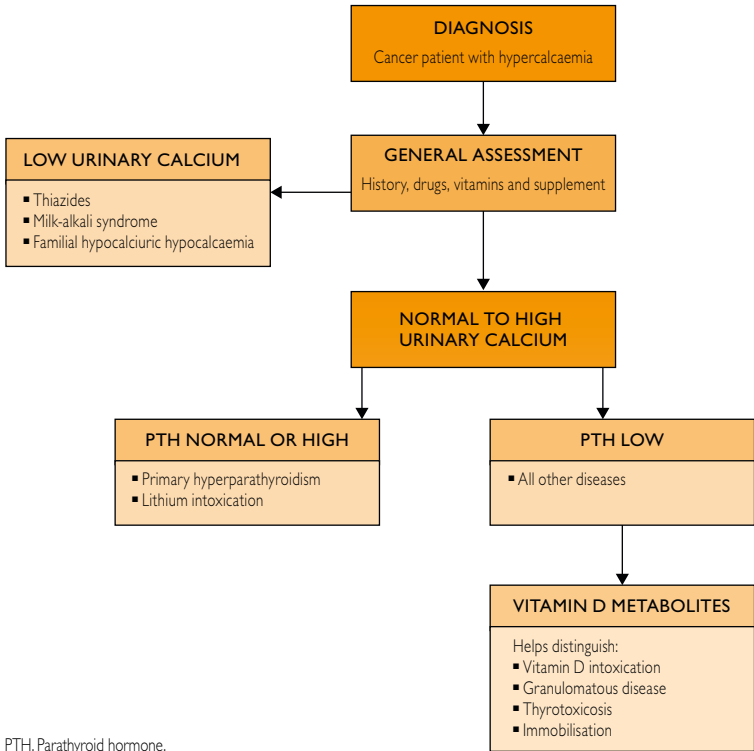
HIV, Human immunodeficiency virus; PTHrP, parathyroid hormone-related protein.

Evaluation

A standardised approach to the diagnosis of hypercalcaemia usually helps to elucidate the cause quickly (Figure 1).

- Early manifestations of hypercalcaemia can be very insidious, including fatigue, muscle weakness, depression, vague abdominal pain, constipation and anorexia. They can be easily mistaken for manifestations of the underlying malignant disease.
- Besides non-specific gastrointestinal manifestations, hypercalcaemia can sporadically cause pancreatitis and a predisposition to peptic ulcers.
- Renal complications can be subdivided into acute and chronic complications. An acute rise in calcium level in the blood causes renal vasoconstriction and natriuresis-induced volume contraction, leading to a reversible fall in glomerular filtration. Long-lasting hypercalcaemia induces concentrating defects, leading to nephrogenic diabetes insipidus (Rose & Post 2001). Also, renal tubular acidosis, nephrolithiasis and chronic renal insufficiency are observed.
- The degree of neuropsychiatric disturbances varies with calcium concentrations, starting with slight cognitive dysfunction and anxiety with moderate hypercalcaemia, and evolving into hallucinations, psychosis, somnolence and coma with high calcaemia.
- Cardiovascular complications have a tendency towards hypertension and accelerated calcium deposition in endothelial structures.
- Urinary calcium excretion is usually high normal or elevated. In rare cases this parameter is low (in milk-alkali syndrome, use of thiazide diuretics and familial hypocalciuric hypercalcaemia).
- Phosphataemia is usually low in humoural hypercalcaemia of malignancy and hyperparathyroidism, but is often elevated in metastatic bone disease.
- Serum PTH levels: in case of primary hyperparathyroidism and lithium intoxication, intact PTH is expected to be inappropriately normal or high. All other causes of hypercalcaemia are associated with low (suppressed) PTH.

- Vitamin D metabolites can be determined if no malignancy is obvious and if neither PTH nor PTHrP are elevated.



PTH, Parathyroid hormone.

Figure 1 Approach to hypercalcaemia.

Modified from: Rottey S, Van Belle S. Hypercalcaemia. In: Kosmidis PA, Schrijvers D, André F, Rottey S (Editors). ESMO Handbook of Oncological Emergencies. Oxon: Taylor and Francis, 2005; 68–76.

Treatment

The ultimate treatment of hypercalcaemia of malignancy is curing the malignancy. More often than not, this is not feasible since most patients already have metastatic disease at the time of appearance of hypercalcaemia.

Increasing Urinary Calcium Excretion

Intravenous saline induces volume expansion, inhibiting sodium reabsorption in the proximal tubule. As proximal calcium reabsorption is a passive process, dependent on the gradient established by sodium reabsorption, calciuria increases. Theoretically, blocking the sodium/potassium/chlorine (Na/K/Cl) carrier in Henle's loop by using diuretics (e.g. furosemide [frusemide]) could enhance calciuria. However, in vivo, this calciuretic effect is counteracted by volume contraction induced by the diuretic. It should be stressed that the above-mentioned measures are seldom enough to render patients normocalcaemic (20% of patients with a calcaemia >12 mg/dl become normocalcaemic after a single course of therapy), but adequate hydration is a cornerstone in the treatment.

Inhibition of Bone Resorption

Bisphosphonates

Bisphosphonates are non-hydrolysable analogues of inorganic pyrophosphate. Their mechanism of action is adsorption to the surface of bone hydroxyapatite, thus inhibiting calcium release by interfering with the metabolic activity of the osteoclast. As these agents are relatively non-toxic (adverse events: pyrexia, hypophosphataemia and mild gastrointestinal distress) and more potent than other drugs inhibiting bone resorption, they have become one of the essential measures in the treatment of cancer-induced hypercalcaemia. It should be remembered that their maximum effect occurs only after 2–4 days, necessitating other treatment measures with swifter action.

Pamidronate was, until recently, the agent of choice, taking into account its augmented potency and its longer action period (response often sustained for 2–4 weeks). The maximum calcium response occurs at 90 mg intravenously. The minimum dosage interval is weekly, but in practice this is every 2–4 weeks. A less favourable response is seen in patients with PTHrP-induced hypercalcaemia, who respond better to gallium citrate.

Zoledronate has become the treatment of choice for cancer-induced hypercalcaemia because of its still higher potency (88% and 70% of the patients achieve normocalcaemia after single-dose treatment with

zoledronate and pamidronate, respectively), and significantly shorter infusion period (15–30 minutes). Furthermore, the duration of calcium control increases to 1–1.5 months. Renal toxicity and osteonecrosis have been reported (Wong et al, 2012).

Denosumab

The monoclonal antibody denosumab blocks RANKL, which plays a pivotal role in osteoclast activation. It is approved for hypercalcaemia refractory to bisphosphonates. The compound has little toxicity (osteonecrosis), and is safe to administer in patients with decreased renal function. Denosumab administered at 120 mg subcutaneously on days 1, 8, 15 and 29, and then every 4 weeks, to patients with refractory hypercalcaemia resulted in normocalcaemia in 64% of patients (Hu et al, 2014).

Calcitonin

Calcitonin decreases bone resorption and also increases the urinary clearance of calcium. It should be administered intramuscularly or subcutaneously every 12 hours. Calcitonin is a relatively weak compound (lowering of calcaemia by 1–2 mg/dl), but its main advantage is that it acts rapidly (within 6 hours). However, its effect is limited to the first 24 hours. Apart from gastrointestinal discomfort and hypersensitivity, it has limited side effects. Hence, it is the ideal treatment of choice immediately after the diagnosis, to bridge the time of action of other agents (e.g. bisphosphonates).

Calcium Removal/Chelation

Sodium EDTA (ethylenediaminetetraacetic acid) and intravenous phosphate can form complexes with ionised calcium, after which these are cleared from circulation. They act immediately, but are toxic: they are replaced by the above-mentioned agents.

Dialysis is the ultimate rescue treatment in patients with uncontrollable or severe hypercalcaemia. It can be considered when hypercalcaemia is accompanied by renal failure.

Corticosteroids

Corticosteroids inhibit osteoclast-mediated bone resorption in vitro and decrease gastrointestinal calcium uptake. These drugs should only be prescribed in patients with malignancies susceptible to steroids (e.g. myeloma, lymphoma, leukaemia and occasionally breast cancer). Doses of methylprednisolone range from 15–30 mg/day in breast cancer to 40–100 mg/day in haematological diseases.

The treatment decision tree (Figure 1) is a proposal to initiate adequate treatment rapidly in cancer patients, and is tailored to the clinical situation.

Declaration of Interest:

Dr Strijbos has reported no conflicts of interest.

Dr Punie has reported no conflicts of interest.

Further Reading

- Carano A, Teitelbaum SL, Konsek JD, et al. Bisphosphonates directly inhibit the bone resorption activity of isolated avian osteoclasts in vitro. *J Clin Invest* 1990; 85:456–461.
- Gardner EC Jr, Hersh T. Primary hyperparathyroidism and the gastrointestinal tract. *South Med J* 1981; 74:197–199.
- Gurney H, Grill V, Martin TJ. Parathyroid hormone-related protein and response to pamidronate in tumour-induced hypercalcaemia. *Lancet* 1993; 341:1611–1613.
- Heath H 3rd. Clinical spectrum of primary hyperparathyroidism: evolution with changes in medical practice and technology. *J Bone Miner Res* 1991; 6(Suppl 2):S63–S70.
- Hu MI, Glezerman IG, Leboulleux S, et al. Denosumab for treatment of hypercalcaemia of malignancy. *J Clin Endocrinol Metab* 2014; 99:3144–3152.
- Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcaemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001; 19:558–567.
- Quinn JM, Matsumura Y, Tarin D, et al. Cellular and hormonal mechanisms associated with malignant bone resorption. *Lab Invest* 1994; 71:465–471.
- Ratcliffe WA, Hutchesson AC, Bundred NJ, Ratcliffe JG. Role of assays for parathyroid-hormone-related protein in investigation of hypercalcaemia. *Lancet* 1992; 339:164–167.

- Raue F. Epidemiological aspects of hypercalcemia of malignancy. *Recent Results Cancer Res* 1994; 137:99–106.
- Rose BD, Post TW. *Clinical Physiology of Acid-Base and Electrolyte Disorders*, 5th edition. New York: McGraw-Hill, 2001; 754.
- Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med* 2005; 352:373–379.
- Warrell RP Jr. Metabolic emergencies. In: DeVita V, Hellman S, Rosenberg SA (Editors). *Cancer: Principles and Practice of Oncology*. Philadelphia: Lippincott-Raven, 1997; 2486–2493.
- Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. *Cochrane Database Syst Rev* 2012; 2:CD003474.
- Wysolmerski JJ, Broadus AE. Hypercalcemia of malignancy: the central role of parathyroid hormone-related protein. *Annu Rev Med* 1994; 45:189–200.

Tumour Lysis Syndrome

11

K. Punie¹

M. Strijbos²

¹*Medical Oncology, Leuven University Hospitals, Leuven, Belgium*

²*Medical Oncology, AZ Klina, Iridium Cancer Network, Antwerp, Belgium*

Introduction

Tumour lysis syndrome (TLS) is a potentially deadly complication of tumours or their treatment. It is an acute metabolic syndrome caused by the release of nucleic acids, proteins and intracellular metabolites of lysed cancer cells in the bloodstream. When the excretory capacity of the kidneys is exceeded, hyperuricaemia, hyperkalaemia and hyperphosphataemia develop. Due to the hyperuricaemia, the secretion of uric acid in the distal tubules and collecting ducts rises significantly, which gives rise to an acid pH. Under these circumstances, the formation of urate crystals induces intraluminal tubular obstruction and acute renal dysfunction. Hyperphosphataemia gives rise to hypocalcaemia by complexation into calcium phosphate crystals in the soft tissue and renal tract.

TLS is mostly encountered in the treatment of highly proliferative leukaemia or lymphoma, and is much less frequent in less proliferative haematological malignancies and solid tumours. However, reports of tumour lysis exist in nearly every tumour type. TLS is, for example, more frequent in solid tumours than in Hodgkin's disease or multiple myeloma. In the vast majority of the cases described in the literature, it is the initiation of systemic treatment with cytostatic drugs (often in combination with steroids) which gives rise to the onset of acute TLS. However, there are also multiple descriptions of spontaneous TLS in haematological and solid malignancies. Rarely, TLS is seen after a local treatment (surgery, radiation therapy, chemoembolisation, radiofrequency ablation) or even after a biopsy (described in thymoma). There are a few reports of TLS after treatment with tyrosine kinase inhibitors, and even after the start

of an antihormonal or immune treatment. In studies where dinaciclib, a cyclin-dependent kinase inhibitor, is administered for chronic lymphocytic leukaemia, TLS is described as a dose-limiting toxicity. Next to the general preventive measurements, stepping up dose or prior cytoreduction with alternative antitumour therapy are strategies to overcome this issue, which could be encountered in the future with other agents.

Table 1 Cairo-Bishop Definition of Clinical and Laboratory TLS.

Reprinted with permission of John Wiley & Sons Ltd., from: Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004; 127:3–11; permission conveyed through Copyright Clearance Center Inc.

Metabolic abnormality	Criteria for classification of LTLS	Criteria for classification of CTLS
Hyperuricaemia	<ul style="list-style-type: none"> ■ sUA >8.0 mg/dl (or 25% increase from baseline) in adults ■ sUA >ULN in children 	N/A
Hyperphosphataemia	<ul style="list-style-type: none"> ■ Phosphorus >4.5 mg/dl (or 25% increase from baseline) in adults ■ Phosphorus >6.5 mg/dl in children 	N/A
Hyperkalaemia	<ul style="list-style-type: none"> ■ Potassium >6.0 mmol/l (or 25% increase from baseline) in adults and children 	<ul style="list-style-type: none"> ■ Cardiac arrhythmia or sudden death, probably or definitely caused by hyperkalaemia
Hypocalcaemia	<ul style="list-style-type: none"> ■ Corrected calcium <7.0 mg/dl, OR ■ Ionised calcium <1.12 mg/dl, OR ■ 25% decrease from baseline in adults and children 	<ul style="list-style-type: none"> ■ Cardiac arrhythmia, sudden death, seizure, neuromuscular irritability*, hypotension or heart failure due to hypocalcaemia
Acute kidney injury	N/A	<ul style="list-style-type: none"> ■ Increase in serum creatinine level of 0.3 mg/dl, OR ■ Serum creatinine >1.5x ULN in absence of baseline value, OR ■ Presence of oliguria (urine output <0.5 ml/kg/h for ≥6 h)

CTLS, Clinical tumour lysis syndrome; LTLS, laboratory tumour lysis syndrome; N/A, not applicable; sUA, serum uric acid levels; TLS, tumour lysis syndrome; ULN, upper limit of normal.

*E.g. Tetany, paraesthesias, muscle twitching, carpopedal spasm, Trousseau's/Chvostek's sign, laryngospasm, bronchospasm.

Cairo and Bishop (2004) described a diagnostic classification and made a distinction between laboratory and clinical TLS (Table 1). Laboratory TLS (LTLS) is defined as either a 25% change or serum levels above or below specified values for two or more serum values of uric acid, potassium, phosphate and calcium, within three days before or seven days after the initiation of chemotherapy in the case of adequate hydration and hypouricaemic agents. Clinical TLS assumes LTLS and significant clinical toxicity, which requires clinical intervention. It is defined as the presence of LTLS in combination with acute kidney injury, cardiac arrhythmia/sudden death or seizures.

Signs and Symptoms

Clinical TLS is a relatively rare event, affecting around 3%–6% of patients with haematological malignancies. However, around one-third of affected patients require renal replacement therapy, and the overall mortality rate of clinical TLS is up to 15%, even in the rasburicase era. LTLS is more frequent, with reported frequencies in haematological malignancies of 10%–15%, but an association between LTLS and increased mortality has never been shown.

Clinical manifestations may include nausea, vomiting, somnolence, haematuria, flank pain, oliguria/anuria, oedema and fluid overload with hypertension, azotaemia, acidosis, congestive heart failure, muscle cramps, tetany, syncope, seizures and sudden death. They most commonly present within 12–72 hours after the administration of the cytotoxic therapy.

Risk Stratification

For adequate risk stratification, not only the type of malignant disease, but also host and treatment factors as well as pre-existing spontaneous TLS are important (Table 2). Potent novel agents can induce TLS even in the context of lower risk diseases. Cairo et al (2010) provided recommendations for risk stratification of the different tumour types which are applied in most guidelines (Table 3).

Table 2 Predisposing Factors for TLS

High-grade tumours, rapid cell-turnover
High tumour burden
Sensitivity to treatment/activity of treatment
Leukocytes >50 000/ μ l
Baseline LDH >1000 U/l
Baseline elevation of serum uric acid, phosphate or potassium
Hypovolaemia
Baseline renal dysfunction
Hydronephrosis/urinary tract obstruction
Use of nephrotoxic drugs
Increased age
Use of drugs that increase uric acid levels

LDH, Lactate dehydrogenase; TLS, tumour lysis syndrome.

Table 3 Risk Classification of Tumour Types.

Adapted with permission of John Wiley & Sons Ltd., from: Cairo MS, Coiffier B, Reiter A, et al. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol* 2010; 149:578–586; permission conveyed through Copyright Clearance Center Inc.

High risk	ALL with leukocytes >100 000/ μ l or LDH >2x ULN
	AML with leukocytes >100 000/ μ l
	Burkitt leukaemia
	Burkitt/ALL with LDH >2x ULN or Stage III-IV
	Other high-grade lymphomas* with LDH >ULN and bulky disease (>10 cm diameter)
Intermediate risk	Any tumour type with intermediate risk and baseline renal dysfunction, uric acid, phosphate or potassium >ULN, renal involvement or contraindication to allopurinol
	AML with leukocytes 25 000–100 000/ μ l or LDH >2 x ULN
	ALL with leukocytes <100 000/ μ l and LDH <2x ULN
	Chronic myelomonocytic/plasma cell leukaemia
	CLL (targeted and/or biological therapies or WBC >50 000/ μ l)
	Burkitt lymphoma/ALL with LDH <2x ULN and Stage I-II
	Other high-grade lymphomas* with LDH > ULN and non-bulky disease
	Any leukaemia or lymphoma with renal dysfunction or renal involvement
Low risk	Bulky solid tumours, sensitive to chemotherapy (e.g. neuroblastoma, germ-cell tumours, SCLC)
	Hodgkin's lymphoma
	CLL (therapy only using alkylating agents)
	Chronic myeloid leukaemia (chronic phase)
	Indolent non-Hodgkin's lymphoma**
	Multiple myeloma
	AML with leukocytes <25 000/ μ l and LDH <2x ULN
Anaplastic large-cell lymphoma	
Other high-grade lymphomas* without LDH elevation	
Other solid tumours (even in pre-existing renal dysfunction or renal involvement)	

ALL, Acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; LDH, lactate dehydrogenase; SCLC, small-cell lung cancer; ULN, upper limit of normal; WBC, white blood count.

*Diffuse large B-cell, peripheral T-cell, transformed, blastoid variant mantle cell. **Small lymphocytic, follicular, marginal zone B-cell, mucosa-associated lymphoid tissue (MALT), non-blastoid variant mantle cell, cutaneous T-cell.

Prevention

Risk stratification, adequate hydration and monitoring for signs and symptoms of TLS are warranted for all risk categories. In intermediate-risk patients, the preventive use of allopurinol is advised. There is evidence for preventive treatment with rasburicase in the high-risk category (Table 4). Avoidance of drugs that increase uric acid levels is useful in all risk categories. It seems clear that any form of prophylaxis is not likely to be useful after remission induction.

Table 4 Prevention of TLS for Different Risk Categories

Low risk	Adequate hydration
	Urine output goals listed
	Monitor for signs and symptoms of TLS
	Low threshold for intravenous fluids
	Consider allopurinol on individual basis
Intermediate risk	Aggressive hydration + allopurinol prophylaxis (or febuxostat) up to 7 days
	Urine output goals listed
	Monitor for signs and symptoms of TLS (starting 8 h after treatment initiation, laboratory tests every 8–12 h)
High risk	Aggressive hydration + rasburicase prophylaxis
	Urine output goals listed
	Monitor for signs and symptoms of TLS (starting 4–6 h after treatment initiation, laboratory tests every 6–8 h)
	Consider “preventive” admission to intensive care unit, especially in case of pre-existing cardiac or renal dysfunction

TLS, Tumour lysis syndrome.

Hydration (Figure 1)

Prophylactic hydration is the most effective preventive therapy for TLS. By inducing a high urine output, the likelihood of uric acid or calcium phosphate precipitation in the tubules is reduced. Patients with intermediate to high risk should receive 2–3 L/m² intravenous (i.v.) crystalloids daily (200 ml/kg/day in infants <10 kg), consisting of 1/4 normal saline/5% dextrose. Urine output should be maintained within the range of 80–100 ml/m²/h (4–6 ml/kg/h in infants <10 kg). Alkalinisation of urine with sodium bicarbonate has historically been a general recommendation for prevention and treatment of TLS, as the excretion of urate is more effective in alkaline urine. However, the solubility of xanthine and hypo-

xanthine significantly decreases at these pH values, which may give rise to xanthine crystallisation and nephropathy, especially after treatment with xanthine oxidase inhibitors. Urine alkalisation also exposes patients to higher risk of calcium phosphate precipitation. Urinary alkalisation is therefore not recommended in the prevention or treatment of TLS.

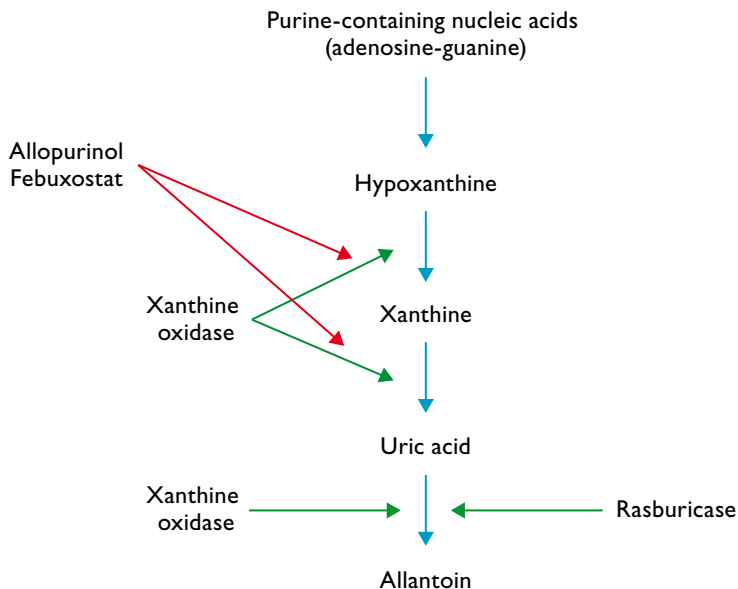


Figure 1 Uric acid-lowering agents.

Reprinted with permission of the American Society of Hematology, from: Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood* 2001; 97:2998–3003; permission conveyed through Copyright Clearance Center Inc.

Xanthine Oxidase Inhibitors

Allopurinol inhibits xanthine oxidase by its analogy to hypoxanthine. As a result, the formation of new uric acid is inhibited. It takes several days before the maximal effect of this therapy is reached. Allopurinol is not effective against already-formed uric acid. Around 5% of treated patients experience treatment-related toxicity, mainly liver disturbances, rash and

hypersensitivity syndrome. The main metabolite, oxypurinol, has a long half-life and undergoes renal excretion. The advised dose in adults is 200–400 mg/m² daily divided in 1–3 oral doses, with a maximum dose of 800 mg daily. Treatment is generally initiated 24–48 hours before the start of chemotherapy, if possible. It is continued for up to 3–7 days after the last day of chemotherapy, or until normalisation of the metabolic disturbances of TLS. In the vast majority of intermediate-risk patients with haematological malignancies, allopurinol started 48 hours prior to treatment onset is able to prevent serum creatinine increase. Dose reduction of 50% or more is needed in case of baseline or treatment-emergent renal dysfunction, but there are reports of insufficient efficacy in cases of reduced doses. There are multiple significant drug–drug interactions described. The i.v. formulation is not available in Europe.

Febuxostat is a novel selective xanthine oxidase inhibitor that has been developed for the treatment of chronic hyperuricaemia in gout. Febuxostat induces a more selective and potent inhibition of xanthine oxidase activity. In a recent randomised phase III pivotal trial in patients with haematological malignancies, febuxostat achieved significantly superior serum uric acid control in comparison to allopurinol, with comparable renal function preservation and safety profile (Spina et al, 2015). The onset of the uric acid-lowering effect was clearly more rapid, which makes it an interesting compound in patients at high risk of TLS in urgent need of chemotherapy when rasburicase is unavailable. Febuxostat can also be considered in patients at intermediate risk of TLS in case of intolerance to allopurinol, or with additional risk factors such as mild to moderate baseline renal dysfunction. The results of this trial led to approval by the European Medicines Agency of febuxostat for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy with haematological malignancies at intermediate to high risk of TLS.

Due to the inhibition of xanthine oxidase by allopurinol or febuxostat, hypoxanthine and xanthine concentrations rise, but the solubility and renal elimination of xanthine is much greater than the elimination of uric acid. However, xanthine nephropathy is described rarely after effective prevention of acute TLS with xanthine oxidase inhibitors.

Rasburicase

Rasburicase is a recombinant urate oxidase that is responsible for the enzymatic conversion of uric acid to allantoin, which is 5–10 times more soluble than uric acid. Rasburicase can, in contrast to xanthine oxidase inhibitors, break down urate deposits. It is clearly faster and more effective than allopurinol in controlling serum uric acid levels in children and adults at risk for TLS. There is one multicentre randomised controlled phase III study that shows statistically significant reduction in the incidence of laboratory TLS compared with allopurinol (Cortes et al, 2010). However, there is only non-randomised level III evidence for patient-oriented outcomes. The initially advised dose in preventive settings was 0.15–0.20 mg/kg i.v. once daily during five days. Several studies investigated the effectiveness of single and even flat doses of rasburicase. There exists a meta-analysis of these dose-reduction studies, showing non-inferior efficacy for a single standard dose of 6 mg for the prevention of TLS. In the absence of established clinical or LTLS, even a single fixed dose of 3 mg rasburicase was shown to be effective to prevent TLS in the majority of high-risk adults (Coutsouvelis et al, 2013). Close monitoring is warranted as, in these trials, repeated doses were needed in up to 20% of patients. There is insufficient evidence for single fixed-dose rasburicase for TLS prophylaxis in the paediatric population.

The antitumour treatment has to start 4–24 hours after the first administration of rasburicase. No dose adjustments are necessary for renal or hepatic dysfunction. The main toxicities are hypersensitivity syndrome, headache and gastrointestinal complaints. There are no known drug interactions, but potentially fatal haemolysis and methaemoglobinaemia result when patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are treated with rasburicase. Therefore, this condition is an absolute contraindication, and when it is suspected an urgent enzyme measurement assay can be helpful. Rasburicase interferes with uric acid measurements by enzymatic degradation of urate in the blood tube. Falsely low results seem to be less frequent when sent to the laboratory on ice. This cold handling is probably not necessary if testing is performed without delay. The use of allopurinol is contraindicated when rasburicase is used in the treatment or prevention of TLS, as it can reduce the effectiveness of this treatment.

Treatment

A high level of suspicion, rapid recognition and prompt treatment are critical in the effective treatment of this dangerous oncological emergency. Antitumour therapy should be delayed if possible in patients at high risk for the development of TLS, until prophylactic measures are initiated. Once laboratory or clinical TLS is diagnosed, nephrotoxic- and uric acid-increasing drugs should be avoided, and the dose of the medications should be adjusted to the renal dysfunction if needed.

Adequate hydration is the core element of effective treatment, and consists of up to 3 L/m² i.v. crystalloids daily, to maintain a urine output of >100 ml/m²/h (or >4 ml/kg/h in infants). Prior to aggressive hydration, urinary tract obstruction should be excluded. The initial fluids should be free of potassium and phosphate. Frequent monitoring of urine output and serum electrolytes is necessary. Diuretics (mannitol or loop diuretics) can be used to augment urine output when it is not reached with adequate hydration alone, but only if there is clear fluid overload and in the absence of obstructive uropathy, as furosemide may promote tubular uric acid formation and increase potassium excretion, with higher risk of calcium phosphate precipitation.

Electrolyte disturbances due to TLS are treated in a similar way as in other conditions that induce these metabolic derangements. Hypocalcaemia is treated with short i.v. calcium gluconate only if symptomatic, because of the risk of calcium phosphate precipitation in the renal parenchyma.

Severe hyperkalaemia (>7 mmol/l), intractable hyperphosphataemia and hypocalcaemia, a calcium–phosphate product >70 mg²/dl², severe oliguria or anuria in the absence of hypovolaemia, and significant fluid overload with haemodynamic repercussions are all indications for urgent renal replacement therapy by haemodialysis or haemofiltration. In patients who are haemodynamically compromised, continuous renal replacement therapy can be useful.

For the treatment of hyperuricaemia in established laboratory or clinical TLS, rasburicase is the drug of choice, at a dose of 0.2 mg/kg daily given as a 30-minute infusion. Allopurinol is indicated for treatment

only in case of G6PD deficiency or in known rasburicase hypersensitivity. Febuxostat could be considered in specific cases. The duration of treatment is determined by the clinical response, but uric acid-lowering therapy is usually given for 3–7 days

Declaration of Interest:

Dr Punie has reported no conflicts of interest.

Dr Strijbos has reported no conflicts of interest.

Further Reading

- Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol* 2004; 127:3–11.
- Cairo MS, Coiffier B, Reiter A, et al. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol* 2010; 149:578–586.
- Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol* 2008; 26:2767–2778.
- Cortes J, Moore JO, Maziarz RT, et al. Control of plasma uric acid in adults at risk for tumor lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone – results of a multicentre phase III study. *J Clin Oncol* 2010; 28:4207–4213.
- Coutsouvelis J, Wiseman M, Hui L, et al. Effectiveness of a single fixed dose of rasburicase 3 mg in the management of tumour lysis syndrome. *Br J Clin Pharmacol* 2013; 75:550–553.
- Dinnel J, Moore BL, Skiver BM, Bose P. Rasburicase in the management of tumor lysis: an evidence-based review of its place in therapy. *Core Evid* 2015; 10:23–38.
- Feng X, Dong K, Pham D, et al. Efficacy and cost of single-dose rasburicase in prevention and treatment of adult tumour lysis syndrome: a meta-analysis. *J Clin Pharm Ther* 2013; 38:301–308.
- Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med* 2011; 364:1844–1854.
- Jones GL, Will A, Jackson GH, et al. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. *Br J Haematol* 2015; 169:661–671.

- Pession A, Masetti R, Gaidano G, et al. Risk evaluation, prophylaxis, and treatment of tumor lysis syndrome: consensus of an Italian expert panel. *Adv Ther* 2011; 28:684–697.
- Spina M, Nagy Z, Ribera JM, et al. FLORENCE: a randomized, double-blind, phase III pivotal study of febuxostat versus allopurinol for the prevention of tumor lysis syndrome (TLS) in patients with hematologic malignancies at intermediate to high TLS risk. *Ann Oncol* 2015; 26:2155–2161.

Other Endocrine and Metabolic Complications of Advanced Cancer

M. Magalhães

J. Febra

A. Araújo

Service of Medical Oncology, Centro Hospitalar do Porto - Unit for Multidisciplinary Research in Biomedicine, Institute of Biomedical Sciences Abel Salazar, University of Porto, Porto, Portugal

Metabolic emergencies and other endocrine abnormalities are common in patients with cancer, either by disease progression itself or by chemotherapy-induced toxicities. They include renal insufficiency, tumour lysis syndrome, hypercalcaemia, hyponatraemia and other electrolyte imbalances.

It is important for the oncologist to be aware of these complications and understand their pathogenesis and treatment, because they are potentially life-threatening and can be prevented or reversed by prompt action.

Hyponatraemia and the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

Hyponatraemia is generally defined as a serum sodium level of less than 135 mEq/l, and is considered severe when the serum sodium level is below 125 mEq/l. Table 1 lists its multiple potential causes.

Hyponatraemia with an increase in total-body surface and water content, manifested as peripheral oedema and/or ascites, is the most common electrolyte abnormality in cancer patients. This situation can occur

in two settings: oedematous states and true volume depletion (mainly associated with salt losses). Severe liver disease secondary to infiltration by tumour, drug toxicity, infection or veno-occlusive disease, malignant ascites (with fluid sequestration in the peritoneal cavity), tumoural venous obstruction, or congestive heart failure all produce a decrease in effective circulating blood volume, which leads to water and sodium retention. Decreased tissue perfusion is a potent stimulus to antidiuretic hormone (ADH) release. This response is mediated by baroreceptors in the systemic circulation, which sense a decrease in effective circulating blood volume and stimulate ADH-mediated water retention.

Table 1 Causes of Hyponatraemia.

Republished with permission of the American College of Physicians, from: Mange K, Matsuura D, Cizman B, et al. Language guiding therapy: the case of dehydration versus volume depletion. *Ann Intern Med* 1997; 127:848–853; permission conveyed through Copyright Clearance Center Inc.

Hyponatraemia subtypes	Possible causes of hyponatraemia
Hypervolaemic hyponatraemia (both sodium and water content increase)	<ul style="list-style-type: none"> ■ Cirrhosis of the liver ■ Congestive heart failure ■ Nephrotic syndrome ■ Massive oedema of any cause
Euvolaemic hyponatraemia (there is volume expansion in the body, no oedema, but hyponatraemia occurs)	<ul style="list-style-type: none"> ■ Severe pain or nausea ■ In the setting of trauma or other damage to the brain ■ SIADH (and its many causes) ■ Hypothyroidism ■ Glucocorticoid (steroid) deficiency
Hypovolaemic hyponatraemia (hypovolaemia, extracellular volume loss, is due to total body sodium loss)	<ul style="list-style-type: none"> ■ Any cause of hypovolaemia: prolonged vomiting, decreased oral intake, severe diarrhoea, acute bleeding or third-space fluid accumulation ■ Diuretics use ■ Addison's disease and congenital adrenal hyperplasia (combined glucocorticoid and mineralocorticoid deficiency)
Miscellaneous causes	<ul style="list-style-type: none"> ■ Factitious hyponatraemia (due to massive increases in blood triglyceride levels, immunoglobulin extreme elevation, as in multiple myeloma, and very high blood glucose level) ■ Hypothyroidism and adrenal insufficiency ■ Beer potomania and other malnourished states, where poor dietary protein intake leads to inadequate urine solute formation, thereby impeding the kidney's ability to excrete free water ■ Primary polydipsia

SIADH, Syndrome of inappropriate antidiuretic hormone secretion.

Persistent ADH release and water retention can also be seen in a variety of disorders that are not associated with hypovolaemia (Table 2). Patients with SIADH appear clinically euvolaemic, without overt signs of hypovolaemia as documented by blood pressure and pulse. They have no oedema; nonetheless, there is a modest expansion of the intravascular volume, and this is reflected in low blood urea nitrogen (BUN), low serum uric acid

Table 2 Causes of SIADH.

Adapted with permission from Massachusetts Medical Society, from: Ellison DH, Berl T. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; 356:2064–2072. Copyright © 2007 Massachusetts Medical Society.

Central nervous system-related causes	<ul style="list-style-type: none"> ■ Infections (meningitis, encephalitis, brain abscess, rocky mountain spotted fever, HIV) ■ Mass/bleed (trauma, subarachnoid haemorrhage, subdural haematoma, cavernous sinus thrombosis) ■ Hydrocephalus ■ Guillain-Barré syndrome ■ Multiple sclerosis
Cancer-related causes	<ul style="list-style-type: none"> ■ Carcinomas: <ul style="list-style-type: none"> • lung cancers, mesotheliomas • gastrointestinal cancers • genitourinary cancers ■ Lymphomas ■ Sarcomas (Ewing's sarcoma)
Pulmonary causes	<ul style="list-style-type: none"> ■ Infection (pneumonia, lung abscess) ■ Asthma ■ Cystic fibrosis
Drug-induced causes	<ul style="list-style-type: none"> ■ Amitriptyline ■ Anticancer drugs (ifosfamide, cyclophosphamide, vincristine, vinblastine, melphalan) ■ Carbamazepine, oxcarbazepine, valproic acid ■ Chlorpropamide ■ Ciprofloxacin, moxifloxacin ■ Clofibrate ■ Phenothiazine ■ Morphine ■ Selective serotonin reuptake inhibitors ■ 3,4-Methylenedioxymethamphetamine (MDMA), also called ecstasy ■ Oxytocin
Other causes	<ul style="list-style-type: none"> ■ Transient causes (endurance exercise, general anaesthesia) ■ Hereditary causes ■ Sarcoidosis

HIV, Human immunodeficiency virus; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

level, and urine that, despite being inappropriately concentrated, shows large amounts of sodium. In this situation, hyponatraemia is not only the result of water retention, but also, as volume expansion occurs, of a progressive increase in urinary sodium excretion. Thus, the pathogenesis of hyponatraemia in SIADH involves both water retention and sodium loss. The severity and rapidity of hyponatraemia development depend on the volume and how rapidly fluids are given to these patients.

Small-cell lung carcinoma is the malignancy most commonly associated with SIADH. In these patients, abnormal ADH levels and subclinical defects in water excretion are more common than overt spontaneous significant hyponatraemia, and often resolve after treatment of the malignancy.

SIADH due to high-dose intravenous (i.v.) cyclophosphamide is a particular problem, since these patients also receive vigorous hydration to prevent haemorrhagic cystitis. As a result, water retention and potentially fatal hyponatraemia may develop. This complication has been primarily described with cyclophosphamide doses in the range of 30 to 50 mg/kg or 600 mg/m² used to treat malignancy, and as a myeloablative therapy before bone marrow transplantation. Although less common, hyponatraemia can also occur with lower doses (10–15 mg/kg) given to treat autoimmune diseases.

Hyponatraemia has also been described in patients receiving combination chemotherapy, especially when cisplatin is given together with larger volumes of hypotonic fluids to prevent nephrotoxicity.

Chemotherapy-induced nausea probably plays a significant role in patients receiving this agent, since nausea is an important stimulus to ADH release. Chemotherapy-induced emesis has been shown to produce rapid and significant increases in plasma ADH levels, independent of changes in osmolality or blood pressure. The fall in plasma sodium concentration in this setting can be minimised by using isotonic saline and furosemide to maintain a high urine output. With the emergence of new and more powerful antiemetic agents, this complication is now less frequently seen.

Signs and symptoms

The signs and symptoms of hyponatraemia are primarily neurological and related to the severity and the rapidity with which hyponatraemia develops. The symptoms are directly attributable to neurological dysfunction induced by cerebral oedema. Anorexia, nausea and malaise are the earliest findings, which may be followed by headache, confusion, lethargy, obtundation, seizures and coma. Hyponatraemia-induced cerebral oedema occurs primarily with a rapid (1–3 days) reduction in the plasma sodium concentration. Patients with chronic hyponatraemia undergo adaptive changes that protect against brain swelling, and they may present with serum sodium levels of 115–120 mEq/l and few symptoms. Severe life-threatening symptoms are seen almost uniformly when the serum sodium concentration falls below 105 mEq/l.

Diagnosis

To diagnose hyponatraemia we need a blood serum test showing a low sodium concentration. To diagnose SIADH we need a euvolaemic hyponatraemia <134 mEq/l, and plasma osmolality (P_{Osm}) <275 mOsm/kg or ($P_{\text{Osm}} - \text{serum } [\text{urea}]_{\text{mmol/l}} <280$ mOsm/kg), urine osmolality >100 mOsm/kg of water during hypotonicity, and urine sodium concentration >40 mEq/l with normal dietary salt intake.

Treatment

The treatment of hyponatraemia and SIADH depends on the underlying cause and, when possible, the treatment of the underlying cause will resolve the issue. In patients with oedema and evidence of fluid retention, treatment consists of restriction of both salt and water. Administration of saline to these patients, in an attempt to correct hyponatraemia, results only in worsening of their oedema and/or ascites. Conversely, in patients with true extracellular fluid volume depletion, administration of saline suppresses non-osmotic ADH release, which leads to increased renal free water excretion and correction of hyponatraemia. If hypokalaemia is also present, correction of potassium deficits will hasten the correction of the hyponatraemia. Water restriction is the mainstay of therapy for patients with SIADH and asymptomatic hyponatraemia. Severe, symptomatic

hyponatraemia in these patients often requires the administration of hypertonic saline (with or without furosemide). Furosemide, alone or together with saline tablets, can be used for the outpatient management of SIADH.

The optimal rate of correction of hyponatraemia is the subject of considerable debate. It is clear that severe, symptomatic hyponatraemia, especially if acute, can lead to cerebral oedema, permanent neurological damage or death. Conversely, rapid correction of chronic hyponatraemia can lead to development of the osmotic demyelination syndrome. The current recommendation in asymptomatic patients is that hyponatraemia should be corrected at a rate not higher than 0.5 mEq/l/h (10 to 12 mEq in the first 24 hours). More rapid therapy (1.5 to 2 mEq/h) is indicated in symptomatic patients with acute hyponatraemia during the first few hours, but the total correction should be no more than 12 to 15 mEq in the first 24 hours.

Lactic Acidosis

Lactic acidosis is a frequent cause of life-threatening metabolic acidosis and is characterised by lactate levels >5 mmol/l and serum pH <7.35 . It often occurs in association with hypoperfusion and severe tissue hypoxia, as seen in patients with shock, sepsis, low cardiac output states and very severe anaemia. Lactic acidosis without evidence of tissue hypoperfusion, and in the absence of other conditions predisposing to lactic acidosis (drugs such as metformin, and alcoholism or diabetes mellitus), has also been described in patients with malignancy. The majority of these patients have had acute rapidly progressive haematological neoplasms, and the aetiology has been attributed to tumour overproduction of lactate under anaerobic circumstances. On some occasions, lactic acidosis has been associated with extensive liver involvement by tumour in patients with non-haematological malignancies. In these instances, lactic acidosis has been attributed to reduced hepatic clearance of lactate. There are several reports of lactic acidosis being diagnosed at the time of presentation of a lymphoma or leukaemia, with reappearance of the metabolic disorder coinciding with recurrence of the malignancy. Lactate levels parallel the disease activity, and starting chemotherapy often leads to a prompt resolution of lactic acidosis.

The diagnosis of lactic acidosis relies on detecting a metabolic acidosis with an increased anion gap, and on the documentation of an elevated lactate level (>4 mEq/l). However, it should be kept in mind that lactic acidosis can also be present with an anion gap in the normal range. In the initial stage of lactic acidosis, decreasing serum bicarbonate and a widening anion gap are more reliable indicators of the presence of this metabolic disorder. Chemotherapy to treat the underlying haematological malignancy is the only effective treatment for this type of lactic acidosis, and long-term survival is related to tumour responsiveness.

Hypoglycaemia

Glucose homeostasis is normally maintained by appropriate hormonal regulation of gluconeogenesis and glycogenolysis in patients who have adequate caloric intake. Tumour-induced hypoglycaemia may be caused by secretion of insulin or of an insulin-like substance, increased glucose utilisation by the tumour, or alterations in the regulatory mechanisms for glucose homeostasis. When there is a rapid reduction in the glucose levels of a healthy person, counter-regulatory mechanisms should increase the secretion of adrenocorticotrophic hormone, glucocorticoids, growth hormone and glucagon. In patients with tumour-induced hypoglycaemia, however, the fall in glucose is usually not rapid enough to produce an increase in these hormone levels.

Cancer patients have reduced rates of hepatic gluconeogenesis, reduced glycogen breakdown following epinephrine or glucagon, and decreased stores of hepatic glycogen. These data suggest that impaired glucose homeostasis may contribute to tumour-induced hypoglycaemia. In the past, increased glucose utilisation by the tumour was thought to be one of the causes of hypoglycaemia. In this situation, however, increased glycogen breakdown and gluconeogenesis should compensate for increased glycolysis. Therefore, the most common causes of hypoglycaemia (exogenous insulin use, oral diabetic agents, adrenal failure, pituitary insufficiency, ethanol abuse and malnutrition) should be excluded before making the assumption that the metabolic abnormality is due to the cancer.

Most cancer patients with hypoglycaemia complain of excessive fatigue, weakness, dizziness and confusion. Hypoglycaemic symptoms tend to

occur after fasting in the early morning or late afternoon. Seizures may result if the blood sugar remains depressed below 40 mg/dl.

Fasting and late-afternoon glucose levels are most helpful in making the diagnosis. Patients with insulinomas have increased insulin levels with fasting glucose levels below 50 mg/dl, while patients with non-islet-cell tumours have normal to low levels of insulin during the periods of hypoglycaemia. If technically feasible, insulin-like plasma factors should be measured by bioassays or radioreceptor technique.

Hypoglycaemia can be rapidly corrected with i.v. injections of high-dose dextrose. Insulinomas can frequently be treated by surgery (enucleation, subtotal or total pancreatectomy). Patients with an inoperable insulinoma can be managed with somatostatin analogues or chemotherapy. If effective antitumour therapy is available for non-islet-cell tumours associated with hypoglycaemia, the metabolic abnormalities should resolve with tumour regression. Corticosteroids may occasionally provide temporary relief. Some patients have also benefited from intermittent subcutaneous or long-acting intramuscular glucagon injections.

Complication of Forced Diuresis

Vigorous hydration, to induce a brisk diuresis, is used to prevent nephrotoxicity from cisplatin and high-dose methotrexate, to prevent and manage the complications of the acute tumour lysis syndrome, and to prevent or ameliorate haemorrhagic cystitis due to high-dose cyclophosphamide and ifosfamide chemotherapy. Although, in general, it is well tolerated, complications can occur. Fluid retention is common in cancer patients with oedema or ascites. In these situations, vigorous hydration can overcome the limited excretory function of the kidneys, with resulting fluid overload and hyponatraemia. Mannitol, also given in an attempt to induce diuresis, is retained in patients with renal insufficiency and can lead to hyperosmolality, hyponatraemia and pulmonary oedema. In the setting of sodium and water retention, diuretics must be used to balance fluid intake, and i.v. fluids should not be given blindly without close attention to fluid balance.

Sodium bicarbonate is routinely administered in patients receiving high-dose methotrexate and in patients at risk of acute tumour lysis syndrome. Renal involvement by lymphoma and acute renal dysfunction secondary to methotrexate nephrotoxicity, or as a result of acute uric acid nephropathy or calcium phosphate precipitation, can also be present. Continuing bicarbonate administration in this situation may lead to metabolic alkalosis, which will aggravate the neurological complications of hypocalcaemia and may lead to seizures. Therefore, this potential complication should be kept in mind and bicarbonate should be administered cautiously in these patients.

Acute hyponatraemia may be seen in patients receiving large amounts of i.v. fluids and who at the same time have high ADH levels as a result of chemotherapy-induced emesis, high-dose cyclophosphamide or vincristine, or tumour production. In these cases, administration of saline in conjunction with furosemide may allow for a continuing diuresis while treating or preventing the development of hyponatraemia.

Declaration of Interest:

Dr Magalhães has reported no conflicts of interest.

Dr Febra has reported no conflicts of interest.

Dr Araújo has attended advisory boards for AstraZeneca, Eli Lilly Oncology, Hospira, Merck, Astellas and Bayer. He also declared being a member of the speaker's bureau of Eli Lilly Oncology and Astellas.

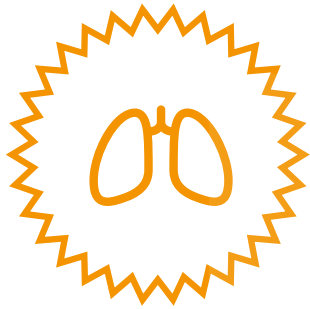
Further Reading

Bodnar TW, Acevedo MJ, Pietropaolo M. Management of non-islet-cell tumor hypoglycemia: a clinical review. *J Clin Endocrinol Metab* 2014; 99:713–722.

Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. *Oncologist* 2012; 17:756–765.

Devita V, Lawrence T, Rosenberg S, et al. *Cancer: Principles & Practice of Oncology*, 9th edition. Philadelphia: Lippincott Williams & Wilkins, 2011; 2147–2148.

V - Respiratory complications



Dyspnoea and Respiratory Failure

P. N. Aguiar, Jr¹

H. Tadokoro¹

R. Andrade de Mello²

¹*Department of Oncology and Haematology, Division of Medical Oncology, Federal University of São Paulo, São Paulo, Brazil*

²*Department of Biomedical Sciences and Medicine, Division of Medical Oncology, University of Algarve, Faro, Portugal; Department of Medicine, Faculty of Medicine, University of Porto, Porto, Portugal; Department of Medical Oncology, Centro Oncológico São Mateus, Ceará Cancer Institute, Fortaleza, Brazil*

Introduction

Dyspnoea is a common need for emergency medical services (in up to 50% of admitted patients with cancer). The European Society for Medical Oncology defines dyspnoea as “a subjective perceived breathlessness, difficult breathing or shortness of breath.” In recent years, there has been much progress in research regarding the complex pathophysiology of dyspnoea, in which both physical and cognitive factors play an important role. Cancer is commonly diagnosed in patients who have significant underlying cardiopulmonary problems, such as chronic obstructive pulmonary disease (COPD) or cardiac insufficiency. Moreover, the progression of cancer, as well as its treatment, are known to be precipitating factors for several pathologies that involve the cardiopulmonary system, such as interstitial, thromboembolic or infectious diseases.

Aetiology

There are several causes of dyspnoea that are generally related to neurophysiological mechanisms, to the dynamics of the airway, and to cardiopulmonary dysfunctions. In cancer patients, dyspnoea can originate from the disease and/or its therapy. A list of possible causes for dyspnoea is presented in Table 1.

Table 1 Causes of Dyspnoea.

Adapted from: Bard M. Dyspnea and respiratory failure. In: Kosmidis PA, Schrijvers D, André F, Rottey S (Editors), *ESMO Handbook of Oncological Emergencies*. Oxon: Taylor and Francis, 2005.

Directly related to cancer	<ul style="list-style-type: none">■ Lung involvement■ Carcinomatous lymphangitis■ Pleural involvement (e.g. effusion)■ Pericardial effusion■ Superior vena cava syndrome■ Atelectasis■ Tracheoesophageal fistula■ Pathological chest wall fracture or invasion
Indirectly related to cancer	<ul style="list-style-type: none">■ Electrolyte abnormalities (e.g. Mg²⁺ depletion)■ Pulmonary embolus■ Paraneoplastic syndrome■ Infection
Related to cancer therapy	<ul style="list-style-type: none">■ Surgery (after lung or thorax wall resection)■ Radiation pneumonitis■ Chemotherapy or TKI-induced pulmonary fibrosis■ Chemotherapy-induced cardiomyopathy■ Immunotherapy-induced pneumonitis
Often not related to cancer	<ul style="list-style-type: none">■ Obstructive disease (COPD or asthma)■ Interstitial lung disease■ Pneumothorax
Cardiac diseases	<ul style="list-style-type: none">■ Congestive heart failure■ Cardiac ischaemia■ Arrhythmias
Other causes	<ul style="list-style-type: none">■ Obesity/deconditioning■ Neuromuscular disorders■ Anxiety■ Cachexia/weakness

COPD, Chronic obstructive pulmonary disease; TKI, tyrosine kinase inhibitor.

Evaluation

History and physical examination are essential elements for the assessment of dyspnoea and its diagnosis in up to two-thirds of cases. It is important to explore the medical, smoking, familial and occupational histories and previous therapies (radiotherapy, chemotherapy, small molecule targeted therapy and, recently, immunotherapy). Physical examination provides a rapid assessment of the patient's respiratory failure status.

Anamnesis of Dyspnoea

Language of Dyspnoea

There are several different expressions that patients use to describe their breathing discomfort, such as “fatigue” or “painful breathing.” Moreover, various physiological and emotional factors are implicated in the management of the respiratory system; the disturbance of any one of them might cause different feelings/types of breathlessness.

Quantification

It is important to highlight that the measurement of oxygen saturation is not always directly correlated with dyspnoea. In a similar manner to pain, breathlessness has to be quantified in order to assess treatment efficacy. Nevertheless, a subjective questionnaire is difficult to create, and even more difficult to validate. Although functional assessments, such as a walking test or the reading aloud of numbers, have been validated, they are not very useful in an emergency context. Some evaluation scales, such as the visual analogue or the Borg scale, can be used to simply and rapidly quantify dyspnoea. Typically, these scales display verbal descriptors (such as “0–no breathlessness” and “10–worst possible breathlessness”); however, these scales are sensitive to subjects' emotional feelings.

History

The anamnesis of dyspnoea should provide a complete history of the symptom and should detail the following:

- The temporal onset – there is not a consensus about the temporal onset of acute or chronic dyspnoea. Generally, acute dyspnoea

develops suddenly or over few days instead of chronic dyspnoea that develops over weeks to months. Nevertheless, it is necessary to understand how long the symptom has been present, as acute dyspnoea is generally less well tolerated than chronic dyspnoea.

- Precipitating events, such as exercise or the thorax position (e.g. orthopnoea, platypnoea).
- Associated symptoms, such as thorax pain, haemoptysis, fever, cough and sputum, are also important to establish the correct diagnosis and adopt a better approach.

Antineoplastic Therapy

Cancer patients are often exposed to a high fraction of inspired oxygen (FiO_2); furthermore, the lungs receive the entire blood supply and therefore experience greater exposure to potentially harmful antineoplastic agents. It is estimated that around 10% of all patients receiving an antineoplastic agent experience lung toxicity. Table 2 lists the most important drugs related to lung toxicity.

Table 2 *The Most Important Drugs Related to Lung Toxicity*

Cytotoxic agents	Targeted agents
Bleomycin	Imatinib/dasatinib
Bortezomib/carfilzomib	Bevacizumab
Carmustine (BCNU)	Everolimus/temsirolimus
Busulfan	Checkpoint inhibitors (e.g. ipilimumab, nivolumab and pembrolizumab)
Cyclophosphamide/ifosfamide	
Cytarabine/fludarabine	
Doxorubicin/mitoxantrone	
Irinotecan/topotecan	
Paclitaxel/docetaxel	
Thalidomide/lenalidomide	

BCNU, Bis-chloroethylnitrosourea (carmustine).

The clinical presentation of pulmonary toxicity is variable and unspecific. Symptoms include cough, dyspnoea, low-grade fever and hypoxaemia. Chills and sputum are rare. Physical examination may reveal bibasilar crackles in a majority of cases. There are several possible radiological findings; however, none are specific for dyspnoea.

The timing of the manifestations is variable; they may be present after the first cycle of treatment, or following treatment completion in a few cases (especially after the use of nitrosoureas and bleomycin). It is of utmost importance to have a high suspicion of pulmonary toxicity and a rapid management strategy.

Clinical Examination

Physical examination of the patient should include the following:

- The respiratory frequency (in 1 minute) and its amplitude is a clinical parameter easily assessed, as well as blood pressure and cardiac frequency. Deep and rapid breathing (Kussmaul breathing) is common in metabolic disorders (acidosis). On the other hand, cyclic breathing with an apnoeic period (Cheyne–Stokes breathing) suggests neurological disease.
- The presence or absence of thorax asymmetry or thorax deformation.
- The predominant phase of the breath in which dyspnoea occurs. Inspiratory dyspnoea suggests an upper airway obstruction that is often a reversible emergency. Expiratory dyspnoea is common in cases of bronchospasm, such as COPD or asthma.
- The presence of added sounds, such as rhonchi, sibilant wheezes or crepitation, should facilitate the diagnosis of infectious diseases.
- The dullness of haemothorax should be present in cases of pleural effusion or atelectasis.
- Signs of cardiac insufficiency (left or right) may allow the differentiation between pulmonary or cardiac breathlessness.

Complementary Investigations

The investigation should consider the cause of dyspnoea as well as the clinical context of the patient and should avoid procedures that may be hazardous for the individual. In the context of very advanced disease, a simple clinical examination and pulse oximetry are almost always sufficient to manage the symptoms. For other patients, it is necessary to conduct testing to identify treatable causes as well as extra-thoracic diseases. The most practical and available tests are listed below:

- *Arterial blood gas analysis with pH and measurement of electrolytes:* metabolic disorders can be assessed as well as the oxygen pressure; however, it is important to consider the chronic status when assessing arterial blood gas. These tests are also important during the follow-up care of the patient.
- *Blood cell count:* anaemia is frequent among cancer patients and is a reversible cause of dyspnoea.
- *Glycaemia:* hyperglycaemia may lead to a metabolic disorder and is often symptomatic; hypoglycaemia may increase the discomfort of the patient and increase the symptom of breathlessness.
- *Electrocardiogram, echocardiography and brain natriuretic peptide serum level:* these tests should help to detect cardiac failure as the cause of dyspnoea.
- *Chest X-ray:* this basic test is very helpful to evaluate several disorders, such as costochondral abnormalities, infectious diseases, pleural effusions, progressive diseases and interstitial diseases.
- *Computed tomography angiography and ventilation/perfusion scintigraphy scan:* these tests should not only confirm embolic events, but also estimate their extent.

Evaluation of Tolerance

In an emergency setting, some signs and symptoms can be rapidly assessed in order to identify patients who are close to respiratory failure. Transfer to an Intensive Care Unit must be considered, according to the

prognosis of the patient and the cause of dyspnoea. Several systems are affected in this situation:

Respiratory

- Use of accessory respiratory muscles (e.g. the intercostals)
- Cyanosis
- Paradoxical respiration (contraction of the abdominal muscles during inspiration, which is a sign of respiratory muscular exhaustion)

Haemodynamic

- Hypotension or shock

Neuropsychic

- Coma

Management of Dyspnoea

The management of dyspnoea must be adapted to the aetiology and must take into account the patient's previous ECOG (Eastern Cooperative Oncology Group) performance status and the stage of the cancer disease.

Oxygen

There is no direct correlation between hypoxaemia and dyspnoea. Nevertheless, oxygen can be administered in an effort to relieve the symptoms. The amount must be titrated to reach an oxygen saturation level of 90%–92%. For patients with chronic hypoventilation (such as patients with COPD), potential respiratory acidosis induction with high doses of oxygen must be monitored using arterial blood gas (pH). Moreover, for patients under suspicion of bleomycin-induced lung injury, it is believed that a high FiO_2 may increase the oxidative damage, so it is important to carefully titrate the oxygen supplementation for these patients (to an oxygen saturation of 89%–93%).

Corticosteroids

Corticosteroids have multiple potential effects for the treatment of dyspnoea. These drugs decrease endobronchial inflammation in cases

of asthma or COPD, and improve lung carcinomatous lymphangitis. Corticosteroids are also necessary in cases of pulmonary toxicity associated with systemic antineoplastic therapy, especially following the administration of immune checkpoint inhibitors when immunosuppressive doses are indicated. Although there is little evidence, corticosteroids can improve some cases of tumoural compression (vena cava syndrome, bronchial or vascular compression). Table 3 shows the equivalent doses of different corticosteroids.

Table 3 *Equivalent Doses Among Different Corticosteroids*

Drug	Equivalent dose
Prednisone	20 mg
Methylprednisolone	16 mg
Hydrocortisone	80 mg
Dexamethasone	3 mg

Bronchodilators

Bronchodilators can be used in cases of bronchospasm of different aetiologies. Nebulisation is the first route of administration for these drugs. Moreover, anticholinergic local therapies have also been reported to decrease sputum production.

Opioids

To provide the best supportive care, the management of dyspnoea patients concentrates on relieving their symptoms and removing or reducing patients' "feelings of breathlessness". Opioids have been reported to decrease exercise-induced dyspnoea and to increase exercise tolerance in COPD or in elderly patients. The mechanisms of action of opioids are not entirely clear, but they can be safely and effectively used for the relief of dyspnoea with a first administration of a low dose of morphine (5 mg subcutaneously or 10 mg extended-release capsules), and a careful titration during the first day of utilisation. In cases of chronic use, it is necessary to alternate drugs to avoid some adverse events associated with opioids, especially constipation.

Anxiolytics

The effectiveness of anxiolytic therapies on dyspnoea relief has not been demonstrated. Theoretically, anxiolytics may improve dyspnoea-related anxiety but, as for opioids, their utilisation must be progressive and titrated, in order to avoid sudden respiratory depression. In the case of refractory dyspnoea, patient sedation can be discussed after obtaining the individual's informed consent. A recent review of the literature revealed that refractory dyspnoea is only the fourth most common reason for palliative sedation, and this practice had no negative effect on patients' survival. Nevertheless, the patient should be involved in the decision-making process for palliative sedation.

Antineoplastic Discontinuation

Some antineoplastic agents, such as bleomycin, gemcitabine, mitomycin, taxanes (rarely), everolimus and immune checkpoint inhibitors, carry the potential risk for pneumonitis through different pathophysiologies. For patients receiving these compounds, significant lung toxicity has to be highly suspected. In cases of adverse events of grade 2 or more (according to the Common Terminology Criteria for Adverse Events–version 4.0), drug discontinuation is justified. An exception is the differentiation syndrome seen in patients with acute promyelocytic leukaemia, treated with a differentiating agent.

Rechallenge

The decision to reintroduce the same antineoplastic agent for a patient who has recovered from drug-induced pneumonitis must be made on a case-by-case basis. It is important to consider the benefit of the drug in the treatment as well as the severity of the pulmonary toxicity. Nevertheless, when the adverse event diagnosis is unequivocal, it is preferable to avoid a rechallenge. For bleomycin-induced or immune checkpoint inhibitor-induced lung injury, re-initiation of these agents is not recommended. Successful rechallenge has been reported with the differentiating agents dasatinib and temsirolimus or everolimus.

Pleural Effusions

The management of pleural effusion may include tissue biopsy, especially in its first episode. Although it has a low sensitivity for cancer diagnosis, in some cases it can be very important in the differential diagnosis when empyema, transudates or haemothorax are present. In a variety of cases, there is a high rate of recurrence; for these patients, an invasive approach, such as pleurodesis, should be considered. This approach involves the instillation of an irritant agent into the pleural space to cause inflammatory changes, which result in bridging fibrosis between the visceral and parietal surfaces. A multidisciplinary care approach is mandatory for malignant pleural effusions.

Pulmonary Rehabilitation

There is no role for pulmonary rehabilitation in an emergency context; however, after recovery from the acute phase, it is very important to consider this option. Pulmonary rehabilitation has several beneficial effects, such as an improvement in exercise tolerance and a decrease in self-reported dyspnoea, especially during physical activities. Pulmonary rehabilitation mainly consists of exercise. Therefore, for patients with a disease that directly decreases cardiopulmonary function or is related to its treatment, pulmonary rehabilitation must be considered as soon as possible.

Declaration of Interest:

Dr Aguiar has reported no conflicts of interest.

Dr Tadokoro has reported no conflicts of interest.

Professor Andrade de Mello has served on advisory boards for Pfizer.

Further Reading

- Correia JL, Coelho SP, Capelas ML, et al. Palliative sedation in terminal cancer patients with refractory uncontrolled symptoms. 2015 ASCO Annual Meeting. Abstract # e20551. Chicago, Illinois. *J Clin Oncol* 2015; 33;15_suppl; e20551.
- Grant S, Aitchison T, Henderson E, et al. A comparison of the reproducibility and the sensitivity to change of visual analogue scales, Borg scales, and Likert scales in normal subjects during submaximal exercise. *Chest* 1999; 116:1208–1217.

- Kloke M, Cherny N. Treatment of dyspnoea in advanced cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol* 2015; 26(Suppl 5):v169–v173.
- Mularski RA, Reinke LF, Carrieri-Kohlman V, et al. An official American Thoracic Society workshop report: assessment and palliative management of dyspnea crisis. *Ann Am Thorac Soc* 2013; 10:S98–S106.
- Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012; 185:435–452.
- Ripamonti C, Fusco F. Respiratory problems in advanced cancer. *Support Care Cancer* 2002; 10:204–216.
- Snyder LS, Hertz MI. Cytotoxic drug-induced lung injury. *Semin Respir Infect* 1988; 3:217–228.
- Stock G, Aguiar Jr PN, Tadokoro H, et al. Cancer screening and epidemiology. In: de Mello RA, Tavares A, Mountzios G (Editors). *International Manual of Oncology Practice*. Basel: Springer, 2015.
- Thomas JR, von Gunten CF. Clinical management of dyspnoea. *Lancet Oncol* 2002; 3:223–228.

Pulmonary Infections in Cancer

14

T. Padua¹

H. Tadokoro¹

R. Andrade de Mello²

¹*Department of Medical Oncology, Federal University of São Paulo, São Paulo, Brazil*

²*Department of Biomedical Sciences and Medicine, Division of Medical Oncology, University of Algarve, Faro, Portugal; Department of Medicine, Faculty of Medicine, University of Porto, Porto, Portugal; Department of Medical Oncology, Centro Oncológico São Mateus, Ceará Cancer Institute, Fortaleza, Brazil*

Introduction

Pulmonary infections are very frequent among cancer patients, mainly during the course of chemotherapy or other immunosuppressive treatments. Several factors contribute to this, such as comorbidities, as well as other individual patient characteristics, chronic corticosteroid therapy, prior chemotherapy and radiotherapy, tumour type and immunosuppression. These infections are generally associated with high morbidity and mortality, and early diagnosis and treatment are therefore essential. This chapter addresses the aetiology, clinical manifestations, diagnosis and treatment of common pulmonary infections in cancer patients.

Aetiology

A wide spectrum of pathogens is known to cause pulmonary infections in cancer patients. Moreover, it is important to identify and evaluate these patients, who may be grouped according to immunosuppression

level and treatment phase. As indicated, each group has a different susceptibility to a subset of pathogens (Table 1).

Table 1 Aetiology of Pulmonary Infections in Cancer Patients

Non-neutropaenic phase
<ul style="list-style-type: none">Same pathogens as those seen in the general publicRisk of multidrug-resistant strains in frequently hospitalised patientsCommunity-acquired respiratory viruses:<ul style="list-style-type: none">Influenza, parainfluenza, respiratory syncytial virus, adenovirus, rhinovirus
Neutropaenic phase
<ul style="list-style-type: none">Gram-negative bacilli and <i>S. aureus</i>: most common cause of bacterial pneumoniaPatients at risk for superinfections with multidrug-resistant organisms:<ul style="list-style-type: none"><i>Acinetobacter</i> species, <i>Citrobacter</i> species, <i>Enterobacter</i> species, <i>Pseudomonas</i> (non-aeruginosa) species, <i>Stenotrophomonas maltophilia</i>, <i>Klebsiella pneumoniae</i>Patients at risk for fungal infections with prolonged (>15 days) and severe (< 100/mm³) neutropenia:<ul style="list-style-type: none"><i>Aspergillus</i>, <i>Zygomycetes</i> and <i>Fusarium</i>: most common pathogens
Impaired humoral immunity
<ul style="list-style-type: none">Patients after allogeneic or autologous stem cell transplantation, diagnosed with multiple myeloma or chronic lymphocytic leukaemia, and after splenectomySusceptible to infections caused by encapsulated organisms:<ul style="list-style-type: none"><i>S. pneumoniae</i> and <i>H. influenzae</i>
Impaired cellular immunity
<ul style="list-style-type: none">Diagnostic of lymphoproliferative diseases, use of chemotherapy with purine analogues (fludarabine, pentostatin, cladribine), use of immunosuppressive agents for graft-versus-host disease (GVHD), or chronic corticosteroid therapy<i>Legionella</i> species: frequent causes of pneumonia<i>Nocardia</i> species and <i>Rhodococcus equi</i>: systemic infection with pulmonary involvementOthers: <i>Listeria monocytogenes</i> and <i>Salmonella</i> speciesMycobacterial infectionsPulmonary viral infections:<ul style="list-style-type: none">Cytomegalovirus (CMV), herpes simplex virus, varicella zoster virus, and human herpesvirus 6 (HHV6)Parasitic infections: <i>Pneumocystis carinii</i>, toxoplasmosis, <i>Strongyloides stercoralis</i>

Clinical Manifestations and Presentations

Cancer patients with pulmonary infections can present with a variety of symptoms and signs, depending on the pathogen involved, immunosuppression level and treatment phase. In non-neutropaenic patients, the presentation may be similar to that in cancer-free patients with acute

fever onset, productive cough and dyspnoea, but may result in a greater number and longer duration of complications. Bacterial pneumonia can progress quickly, resulting in high mortality. In immunocompromised patients the symptoms are usually minimal, due to reduced inflammatory responses, although we must be aware of the rapid course of the infection and the high risk of rapid worsening and development of acute respiratory failure.

Lung cancer patients generally develop an infection because of bronchial airway obstruction by the tumour, leading to post-obstructive pneumonia. In some cases, the infection may progress to abscess and cavity formation. Other risk factors in this population are frequently associated with chronic obstructive pulmonary disease (COPD). Tuberculosis resulting from reactivation of a latent infection is also more frequent, mainly in southern Europe, in patients with head and neck cancer, lung cancer and lymphoproliferative disorders. Aspiration pneumonia is often characterised by impaired swallowing, mainly in patients with brain tumours or head and neck cancers.

Fungal pneumonia, caused mainly by *Aspergillus*, is more frequent in patients with prolonged (>15 days) and severe (<100/mm³) neutropenia, who usually present with fever, dyspnoea, non-productive cough and pleuritic chest pain. In some cases it can be more indolent with just fever and pulmonary infiltrates, resistant to antibiotics.

Pneumocystis pneumonia is characterised by cough, shortness of breath and fever, and progresses rapidly without treatment, leading to death. The most common radiographic appearance is diffuse bilateral symmetrical, mixed interstitial and alveolar infiltrates.

Toxoplasmosis is another possible parasitic infection, which is rare and occurs after haematopoietic stem cell transplantation (HSCT); the hyperinfection syndrome, caused by *Strongyloides stercoralis*, is a serious complication which can occur after allogeneic bone marrow transplantation or HSCT, involving the lungs.

Diagnosis

Early diagnosis is essential to improve outcomes and avoid complications. At first, the exclusion of non-infectious diseases is important. This should be followed by a full history and physical examination, appropriate laboratory tests, and imaging of the lungs. Chest radiography must be the first option; however, chest computed tomographic scanning is a more sensitive technique to detect abnormalities in neutropaenic patients (Table 2). In this population there is often high discrepancy between the discrete clinical and radiological picture and the severity of the pulmonary infections.

Table 2 Diagnostic Aspects of Pulmonary Infections in Cancer Patients

Clinical history	<ul style="list-style-type: none">■ Onset of symptoms■ Previous use of antibiotics■ Presence of neutropaenia and duration■ Previous history of bone marrow transplantation■ Chronic corticosteroid therapy■ Presence of hypoxaemia■ History of travel and exposure■ Comorbidities
Basic laboratory analysis	<ul style="list-style-type: none">■ Haemogram■ Biochemistry assessment: urea, creatinine, Na⁺, K⁺, C-reactive protein (CRP), pro-calcitonin■ Haemocultures■ <i>Legionella</i> and urine <i>Streptococcus</i> analysis
Radiographic appearance	<ul style="list-style-type: none">■ Localised infiltrates, consolidation: pneumonia (bacterial, mycobacterial, fungal)■ Diffuse infiltrates: <i>Pneumocystis carinii</i> pneumonia; viral pneumonia■ Hilar and/or mediastinal adenopathy: tuberculosis and atypical mycobacterial pneumonia; pathogenic fungal pneumonia (histoplasmosis, coccidiosis)■ Cavitation: bacterial pneumonia (Gram-negative bacteria, anaerobes, <i>Legionella</i>, <i>Actinomyces</i>, <i>Nocardia</i>); tuberculosis and atypical mycobacterial pneumonia; septic emboli (bacterial or fungal)■ Pleural effusions: bacterial pneumonia (parapneumonic or empyema); tuberculosis■ Nodules: bacterial pneumonia (<i>Nocardia</i>, <i>Actinomyces</i>, <i>H. influenzae</i>); atypical mycobacterial pneumonia

The identification of a specific pathogen is difficult, particularly in neutropaenic patients. In the early stages, a chest-X ray can be normal, and sputum production absent. Furthermore, whenever possible, a sputum sample must be collected, through induction or bronchoscopy, and microbiological assays and antimicrobial susceptibility can be performed. Other methods include: nasal swabs, urinary antigen tests (*Legionella pneumophila*, *Histoplasma capsulatum* and *Streptococcus pneumoniae*) and polymerase chain reaction (PCR)-based assays (cytomegalovirus [CMV], antigenaemia, cryptococcal antigen, and *Aspergillus* galactomannan antigen). In some cases, invasive procedures (biopsies) are necessary to establish the correct diagnosis.

Treatment

After pulmonary infection has been diagnosed, an appropriate and specific therapy should be initiated immediately. It is also important to determine the necessity of hospitalisation. The following patients are at a high risk for complications and must be hospitalised:

- Patients with newly diagnosed haematological malignancies
- Patients with lymphoproliferative diseases treated with chemotherapy
- Recent haematopoietic cell transplant (HCT) recipients and allogeneic HCT recipients with significant graft-versus-host disease (GVHD)
- Patients with disseminated metastatic cancer
- Patients with severe neutropaenia (<100/ μ l)
- Known colonisation with fungi or resistant bacteria
- Patients undergoing high-dose glucocorticoid or immunosuppression therapy
- Patients with hypotension

Furthermore, the following treatments are specific to each condition, according to the aetiological agent:

Bacterial pneumonia

Neutropaenic patients: Infectious Diseases Society of America (IDSA) / European Society for Medical Oncology (ESMO) treatment guidelines for febrile neutropaenia must be followed along with empirical broad-spectrum antibiotic treatment. If the fever persists, consider additional anti-fungal therapy. It is important to test for all predominant local hospital pathogens. Growth factors should be used very cautiously because of the high risk of respiratory worsening during the rapid recovery from neutropaenia.

Table 3 Recommended Empirical Antibiotics for Community-acquired Pneumonia in Adults.

Adapted with permission of the Infectious Diseases Society of America, from: Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44 Suppl 2:S27–S72; permission conveyed through Copyright Clearance Center Inc.

Outpatient treatment ¹		Inpatient treatment ²		ICU treatment	
Respiratory fluoroquinolone (orally)		Respiratory fluoroquinolone (i.v. or orally)		Antipneumococcal beta-lactam plus:	
Moxifloxacin (400 mg daily)		Moxifloxacin (400 mg daily)		Ceftriaxone (1–2 g daily)	Macrolide
Gemifloxacin (320 mg daily)		Gemifloxacin (320 mg daily)		Cefotaxime (1–2 g 8/8 h)	OR
Levofloxacin (50 mg daily)		Levofloxacin (750 mg daily)		Amp-sulb (1.5–3 g 6/6 h)	Respiratory fluoroquinolone
OR		OR		Risk of <i>Pseudomonas aeruginosa</i>	
Beta-lactam ³ plus macrolide		Beta-lactam (i.v.) plus macrolide		Antipseudomonal beta-lactam plus:	
Amoxicillin (1 g 8/8 h)	Azithromycin (500 mg/day)	Cefotaxime (1–2 g 8/8 h)	Azithromycin 500 mg daily	PIP/TAZ	Ciprofloxacin
Amoxicillin-clavulanate (2 g 12/12 h)	Clarithromycin (500 mg 12/12 h)	Ceftriaxone (1–2 g/day)	Clarithromycin (500 mg 12/12h)	Cefepime	or
		Amp-sulb (1.5–3 g 6/6 h)		Imipenem	Levofloxacin
		Ertapenem (1 g daily)		Meropenem	or
					Azithromycin
				Risk of CA-MRSA	
					Vancomycin
					Linezolid

Amp-sulb, ampicillin-sulbactam; CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; ICU, intensive care unit; i.v., intravenous; PIP/TAZ, piperacillin-tazobactam.

¹Duration of treatment: 5 days

²Duration of treatment: minimum of 5 to 7 days, but should be individualised according with clinical response to treatment and comorbidities. For MRSA pneumonia, duration should be 7 to 21 days.

³Other alternatives: ceftriaxone 1 g twice daily, cefpodoxime 200 mg twice daily, or cefuroxime 500 mg twice daily

Non-neutropaenic patients: treatment guidelines are the same as those for immunocompetent patients (Table 3).

Viral pneumonia

Empirical antiviral therapy (oseltamivir or zanamivir) should be started and continued for five days when the symptoms suggest influenza.

Invasive aspergillosis

Amphotericin B is the drug of choice, just as voriconazole. Itraconazole is the alternative when the cost is an issue. Caspofungin is indicated in patients who are refractory or intolerant to other approved drugs. The duration of therapy can range from 6 weeks to 6 months, and surgical resection should be considered for haematological patients with poor responses to the initial therapy.

Pneumocystis pneumonia

Trimethoprim-sulfamethoxazole (TMP-SMX) 800/160 mg for 14 days is the drug of choice, followed by pentamidine. It is also critical that corticosteroids (prednisone) be part of the treatment.

Cytomegalovirus

Treatment strategies include anti-cytomegalovirus prophylaxis, administration of ganciclovir and intravenous gammaglobulin.

Conclusions

Pulmonary infections represent one of the worse cancer-related comorbidities, mainly for patients who present with poor social status, former or ex-smokers and those with other respiratory disease, such as COPD and pulmonary fibrosis. Taking into account the aggressive systemic treatments, such as dose-dense chemotherapy regimens and/or other highly myelosuppressive drugs, an educational policy and close patient monitoring should be considered. It is important to avoid potential risk factors related to pulmonary infections in cancer patients, and establish the treatment schedule on time. The appropriate antibiotic treatment,

supportive care approaches and a multidisciplinary health care provider platform are very important to optimise the patient care.

Declaration of Interest:

Dr Padua has reported no conflicts of interest.

Dr Tadokoro has reported no conflicts of interest.

Professor Andrade de Mello has served on advisory boards for Pfizer.

Further Reading

- de Naurois J, Novitzky-Basso I, Gill MJ, et al. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. *Ann Oncol* 2010; 21:v252–v256.
- Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2011; 52:e56–e93.
- Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44 Suppl 2:S27–S72.
- Rizvi SM, Lim B. Current treatment of febrile neutropenia: tailored, individual based therapy. In: de Mello RA, Tavares A, Mountzios G (Editors). *International Manual of Oncology Practice*. Basel: Springer, 2015.
- Ruckdeschel JC, Greene J, Sommers KE, Fields KK. Respiratory infections in patients with cancer. In: Kufe DW, Pollock RE, Weichselbaum RR, et al (Editors). *Holland-Frei Cancer Medicine*, 6th edition. Hamilton (ON): BC Decker; 2003. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK13540/>. Accessed 19 January 2016.
- Stover DE, Kaner RJ. Pulmonary complications in cancer patients. *CA Cancer J Clin* 1996; 46:303–320.

Haemoptysis and Intractable Hiccups

E. Castañon Alvarez

K. Papadimitriou

C. Rolfo

*Phase I – Early Clinical Trials Unit, Oncology Department,
Antwerp University Hospital and Center for Oncological Research,
Antwerp University, Antwerp, Belgium*

Haemoptysis

Introduction

Haemoptysis is defined as blood expectoration coming directly from the bronchial tree. Blood loss may vary from little spots in the sputum to gross blood without any accompanying sputum. Haemoptysis may be a life-threatening event, since a vital amount of blood may be lost in a matter of seconds. For assessing the risk and seriousness of haemoptysis there are three main prognostic factors: haemoptysis volume, bleeding speed and patients' previous lung functional capacity. Massive haemoptysis is defined as the loss of ≥ 500 ml of expectorated blood over a 24-hour period or a bleeding rate of ≥ 100 ml/h.

Aetiology

Up to 90% of cases of haemoptysis are caused by bleeding of the bronchial arteries, whereas the other 10% come from the pulmonary arteries. Bronchial arteries are under a higher systemic pressure compared to the pulmonary arteries, and are usually hyperplastic and hypertrophic due to lung inflammation or neoplasm. Table 1 summarises the main causes of haemoptysis.

Table 1 Main Causes of Haemoptysis

Bronchial disease
<ul style="list-style-type: none">■ Bronchiectasis■ Tumours (squamous cell lung carcinoma, small-cell lung carcinoma, metastatic melanoma, metastatic colorectal cancer; metastatic breast cancer; bronchial carcinoid)■ Trauma■ Aorto-bronchial fistula
Pulmonary disease
<ul style="list-style-type: none">■ Pneumonia■ Rheumatic/immune pathology
Coagulopathy
<ul style="list-style-type: none">■ Hereditary■ Anticoagulants
Pharmacological
<ul style="list-style-type: none">■ Bevacizumab■ Other antiangiogenic agents■ Cocaine■ Nitrogen dioxide exposure

Evaluation

The first step to be taken when a patient suffers from haemoptysis is to validate the severity of the event. In the case of non-massive haemoptysis, in which the patient's life is not threatened, there is potentially no action needed, while, when a massive haemoptysis occurs, an urgent intervention should be carried out.

In case of a non-massive haemoptysis, an initial evaluation to attempt to localise the source of bleeding should be performed. Laboratory tests should include total blood cell count, renal and liver function, as well as a coagulation profile. Other tests such as sputum culture (including fungal and mycobacterial cultures) or specific antibodies like antinuclear antibodies, antineutrophil cytoplasmic antibodies, antiglomerular basement membrane antibodies or anticardiolipin antibodies should be carried out if clinical symptoms suggest a specific entity. Among the imaging tests, the most important initial study should be a chest radiograph. In the vast majority of the cases, a chest radiograph may lead us to determine the localisation of the bleeding. Other tests such as computed tomography

(CT) scan or bronchoscopy may be performed when the cause of haemoptysis is not really clear.

On the other hand, when a patient presents with a massive haemoptysis, an arterial gasometry should be requested so that we may validate an adequate gas exchange. Coagulation tests are also very helpful, since a hidden coagulation abnormality may be properly corrected. Many of the diagnostic techniques such as bronchoscopy or arteriography are very useful in cases of massive haemoptysis, since they may also be therapeutic.

Treatment

In the case of a mild haemoptysis, treatment should be focused on the underlying cause. When a massive haemoptysis is present, a totally different approach should be taken as soon as possible.

Supportive Care

Blood concentrates should be urgently reserved in case of severe haemoptysis. In case of an elevated prothrombin time, partial thromboplastin time or international normalised ratio, patients may benefit from receiving fresh frozen plasma. Patients treated with antiplatelet agents, as well as those with thrombopaenia, should receive platelet transfusion.

Determination of the site of the bleeding may be challenging but it is strongly recommended for all cases. Clinical examination may help to determine the lung bleeding site. The patient should be placed in a position in which the presumed bleeding lung is in the dependent position. The purpose of this manoeuvre is to protect the non-bleeding lung, since it may be filled with blood.

Specific Strategies

Bronchoscopy

Bronchoscopy may be very useful since it is not only a diagnostic procedure, but also a therapeutic tool. There are different techniques which may be therapeutically applied with a bronchoscope, such as adrenaline or iced saline, or topical coagulant instillation, or even a bronchus

tamponade with a Fogarty balloon catheter of the bronchus close to the bleeding site. Other approaches such as laser therapy or argon plasma coagulation may be an option in certain circumstances.

Arteriography

Arteriography may be successful in localising and treating a bleeding point in $\leq 85\%$ of cases. Embolisation, guided by arteriography, requires the injection of intravenous contrast, in order to localise the arterial circulation involved and identify the bleeding site. Once localised, the insertion of occlusive material into the bleeding vessel itself, or into the proximal vessels that supply the bleeding vessel, may usually resolve the bleeding episode. Up to 20% of patients present a second episode within the first 12 months. If it is an early relapse, a second arteriography may be performed in order to search for new vessels not visualised during the first procedure.

Surgery

Surgery should be considered when all previous measures have failed to treat the bleeding, and in patients with a good previous pulmonary function. Since mortality rates are high (up to 20%), patients should be specifically selected for a surgical procedure. In some cases, such as aortic aneurysm rupture, hydatid cysts or chest trauma, when vessels or bronchus are disrupted, surgery may be the only effective approach and should be considered upfront.

Conclusions

Haemoptysis may be a life-threatening event in cancer patients. An urgent and targeted approach should be carried out. In case of massive haemoptysis, in which a great volume of blood may be lost in a few minutes, supportive care, warranting blood and oxygen supply, should be urgently requested and followed by further supportive measures if indicated. Bronchoscopy may successfully detect a specific bleeding site, and at the same time be used as a therapeutic tool. Arteriography seems as effective as bronchoscopy in terms of localisation and occlusion of a bleeding site. Arteriography is especially useful in cases of non-visible

bleeding sites at bronchoscopy. Surgery, due to its morbidity, should be left as the last approach, except in certain pathologies.

Persistent and Intractable Hiccups

Introduction

Hiccups are defined as spontaneous, uncontrolled and spasmodic contractions of the diaphragmatic muscle. This movement leads to quick inspiration, blocked by a sudden closure of the glottis. Although hiccups are rather common and usually self-limited, sometimes they last for over 48 hours, then being referred to as persistent hiccups, or for over 2 months, then defined as intractable hiccups. Both persistent and intractable hiccups are a reason for great concern and discomfort in patients, leading to significant morbidity and adverse events such as vomiting, fatigue, insomnia, dehydration, weight loss, mental disturbances and an altered quality of life.

Hiccup contraction is usually controlled by a neurological pathway involving a central origin and an afferent pathway mediated by both vagus and phrenic nerves, the sympathetic chain and an efferent neurological limb including both phrenic and intercostal accessory nerves. The role of the central pathways is the least understood element, since they are not well localised and their complexity involves the medulla oblongata, the reticular formation and the hypothalamus.

Aetiology

Any kind of injury, either physical or chemical, in the neurological hiccup reflex pathway may precipitate hiccups. Cancer patients may present several disturbances which may trigger hiccups, such as metabolic abnormalities, medications, infection or the cancer itself. Table 2 summarises the main causes of hiccups in cancer patients.

Table 2 Main Causes of Hiccups

Drugs
<ul style="list-style-type: none">■ Dexamethasone■ Opioids■ Chemotherapy agents (cisplatin, carboplatin, docetaxel, etoposide, gemcitabine, irinotecan, paclitaxel, vinorelbine)
CNS pathology
<ul style="list-style-type: none">■ Encephalitis, meningitis, brain abscess, brainstem lesions
Vagus and phrenic irritation
<ul style="list-style-type: none">■ External auditory canal obstruction or infection■ Laryngitis■ Pharyngitis
Thoracic disorders
<ul style="list-style-type: none">■ Mediastinitis, pneumonia■ Enlarged lymph nodes■ Pleuritis, empyema
Gastrointestinal disturbances
<ul style="list-style-type: none">■ Gastric distension■ Gastric ulcer■ Gastro-oesophageal reflux■ Oesophagitis■ Pancreatitis■ Ascites■ Abdominal abscess
Cardiac disorders
<ul style="list-style-type: none">■ Myocardial infarction■ Pericardial effusion, pericarditis
Metabolic disorders
<ul style="list-style-type: none">■ Hyponatraemia, hypokalaemia, hypocalcaemia, hyperglycaemia
Tumours
<ul style="list-style-type: none">■ Oesophageal cancer■ Gastric cancer■ Colorectal cancer■ Lymphoma■ Pancreatic cancer■ Renal cancer

CNS, Central nervous system.

Evaluation

Persistent and intractable hiccups require a deep evaluation to determine the intrinsic cause, which may lead to proper treatment.

A profound and meticulous medical history should include information on the duration and severity of hiccups. Medical conditions such as concomitant medications or previous surgery, and also alcohol and illicit drug use, should be included. Although ruling out which medication may be causing hiccups can be very challenging (since cancer patients take different potential hiccup-triggering medications such as corticosteroids or benzodiazepines), it is strongly advised to do so, since the withdrawal of a hiccup-precipitating drug may stop this problematic symptom.

Physical examination should include the external auditory canals, since alteration of tympanic membranes by cerumen or infection may irritate the vagus nerve and provoke hiccup contractions. Also, a careful and detailed exploration of head and neck structures, chest wall and abdomen should be carried out to discount any external or internal compression. A deep neurological examination, accompanied by cardiac and lung exploration, should be also performed.

Laboratory tests should include a complete blood count, electrolytes, creatinine and blood urea nitrogen, lipase and amylase, calcium, liver function tests and glucose. Additional tests, such as chest and abdominal radiography or CT scan, should be performed in case of high suspicion of mediastinal or abdominal abnormalities. An electrocardiogram and echocardiogram should be obtained in case of cardiac symptoms suggesting myocardial ischaemia or pericardial effusion. Other tests including upper endoscopy, bronchoscopy, magnetic resonance imaging of the head, or lumbar puncture should be performed, guided by the patient's symptoms.

Cancer patients may present diverse and different causes of hiccups and sometimes a single intervention is not always successful. It is essential to focus on symptoms, to avoid exposing the patient to multiple and invasive diagnostic techniques.

Treatment

Treatment of persistent and intractable hiccups should be of special concern, due to their impact on the cancer patients' quality of life. Whenever the underlying cause is found, such as a specific drug or a potentially treatable disease, it should be tackled directly. However, hiccups may be a multifactorial consequence and thus medical treatment is usually needed.

Although there are many different treatments proven to be effective in handling hiccups, there is no strong evidence to opt for one specific drug. The European Medicines Agency (EMA) has not approved any drug with a clear indication for hiccups. Nevertheless, among all the options available, chlorpromazine remains the only drug approved by the US Food and Drug Administration (FDA) for treating hiccups. A dose of 25–50 mg orally may be used every 6 or 8 hours. When administered intravenously, caution should be taken, since chlorpromazine may produce hypotension. Chlorpromazine diluted in saline solution and administered with the patient in the supine position may avoid this side effect. Chlorpromazine may be a good and safe option when administered in the indicated doses. Nevertheless, dystonic reaction, drowsiness and tardive dyskinesia have been reported rarely with chlorpromazine use. Its administration is contraindicated in cases of elderly patients with dementia, in whom it may increase the risk of death.

Baclofen, a muscle relaxant, is also an option when treating persistent and intractable hiccups. It has been proven that baclofen 5–10 mg administered orally every 8 hours may decrease the severity of hiccups. It has been reported in several cases that use of baclofen may stop persistent and intractable hiccups. The main side effects of baclofen include drowsiness and nausea.

Metoclopramide, usually given as a gastric motility drug, may also be useful to treat hiccups, especially in patients presenting gastric distension of dyspepsia. Metoclopramide is usually given orally at a dose of 10 mg every 6–8 hours. Signs of overdose include tardive dyskinesia, which is normally observed when high and continuous doses of metoclopramide are administered.

Other options to eliminate persistent and intractable hiccups include anticonvulsants such as valproic acid 500–1000 mg daily or gabapentin 300–400 mg every 8 hours. Other drugs such as nifedipine, nefopam, methylphenidate or olanzapine have some proven efficacy in treating persistent hiccups, although the relevant evidence comes mainly from case reports or small case series.

Other approaches such as acupuncture, phrenic nerve blocking or vagus nerve stimulators may be helpful in selected cases, although the lack of evidence is clear.

Conclusion

Hiccups are a worrying symptom, which may alter patients' quality of life and, sometimes, may trigger other serious complications ranging from depression, anxiety or insomnia to persistent vomiting or malnutrition. Eliminating the main cause of hiccups in cancer patients is challenging, since they are usually a result of a multifactorial event. Medical therapy is usually based on metoclopramide, baclofen or chlorpromazine, although other drugs and approaches have proven success. Currently there is not enough data available to assess the optimal treatment.

Declaration of Interest:

Dr Castañón Alvarez has reported no conflicts of interest.

Dr Papadimitriou has reported no conflicts of interest.

Professor Rolfo has declared that he is part of a speakers' bureau for Novartis.

Further Reading

Calsina-Berna A, García-Gómez G, González-Barboteo J, Porta-Sales J. Treatment of chronic hiccups in cancer patients: a systematic review. *J Palliat Med* 2012; 15:1142–1150.

Earwood JS, Thompson TD. Hemoptysis: evaluation and management. *Am Fam Physician* 2015; 91:243–249.

Lordan JL, Gascoigne A, Corris PA. The pulmonary physician in critical care
* Illustrative case 7: Assessment and management of massive haemoptysis. *Thorax* 2003; 58:814–819.

- Perdue C, Lloyd E. Managing persistent hiccups in advanced cancer 2: treatment. *Nurs Times* 2008; 104:20–21.
- Rizzo C, Vitale C, Montagnini M. Management of intractable hiccups: an illustrative case and review. *Am J Hosp Palliat Care* 2014; 31:220–224.
- Simoff MJ, Lally B, Slade MG, et al. Symptom management in patients with lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143(5 Suppl):e455S–e497S.

VI - **Gastrointestinal** complications



Nausea and Vomiting

G. Mountzios¹

M. Petrova²

¹University of Athens School of Medicine, Athens, Greece

²MHAT Nadezhda (Multiprofile Hospital of Active Treatment), Sofia, Bulgaria

Introduction

Nausea and vomiting are two of the greatest fears of patients with cancer. They may be a result of the disease status of the patient but are more frequently associated with anti-cancer treatment. Inadequately controlled chemotherapy and radiation-induced nausea and vomiting can precipitate a number of medical complications that may prove life-threatening, including dehydration, electrolyte imbalance and malnutrition, or cause physical damage, including Mallory–Weiss rupture of the oesophagus. The distressing symptoms of nausea and vomiting have a considerable impact on all aspects of the patients' quality of life, as well as those of their family and caregivers. The distress resulting from these symptoms can escalate over time, and potentially lead to changes in or delay of the chemotherapy regimen, or even to a patient's refusal to continue with the most effective antitumour therapy.

Nausea should be clearly distinguished from vomiting, as it refers to the gastric and/or medullary distress with distaste for food and an urge to vomit, but without necessarily encompassing vomiting. It should be emphasised that a patient who is not vomiting may still experience severe nausea that needs to be comprehensively diagnosed and managed.

Nausea and vomiting associated with chemotherapy can be classified as acute, delayed, anticipatory and breakthrough.

Acute nausea and vomiting are defined as occurring within 24 hours after chemotherapy and can be further subdivided into early-acute (within 12 hours) and late-acute (12–24 hours). Delayed nausea and vomiting

are usually defined as commencing more than 24–48 hours after administration of chemotherapy and may persist for 6–7 days. They commonly occur following the administration of platinum analogues, alkylating agents or anthracyclines. Anticipatory nausea and vomiting occur before, during or after the administration of a subsequent course of treatment if previous emetic control has been inadequate (although before acute chemotherapy, symptoms would be expected to occur). They are conditioned responses linked to visual, gustatory, olfactory and environmental factors associated with previously administered chemotherapy (the “white uniform” syndrome). Breakthrough nausea and vomiting occur despite prophylactic treatment and are usually abrupt, sudden and acute. The specific reasons for breakthrough nausea and vomiting are inadequately understood (often in young patients, and/or women, and/or with history of motion illness), but they represent a medical emergency that needs to be timely diagnosed and treated.

Aetiology

Nausea and vomiting may have various, and often complex, aetiologies:

Treatment-induced

- Chemotherapy: usually within 5 days following treatment (Table 1)
- Analgesics (e.g. opioids)
- Radiotherapy (especially when upper gastrointestinal [GI] tract or mediastinum is involved in the radiation field)
- Selective serotonin reuptake inhibitors (many cancer patients develop depression, and such medications are usually prescribed)
- Postoperative nausea and vomiting (after general anaesthesia)

Metabolic Causes

- Hypercalcaemia
- Renal failure (uraemia)
- Adrenocortical failure
- Hypo- or hyperglycaemia

Table 1 Emetogenicity of Chemotherapy.

Adapted from: Mountzios G. Nausea and vomiting. In: Kosmidis PA, Schrijvers D, André F, Rottey S (Editors), *ESMO Handbook of Oncological Emergencies*. Oxon: Taylor and Francis, 2005; 99–102.

Low or minimally emetogenic	Moderately emetogenic	Highly emetogenic
Bleomycin	Cyclophosphamide <1500 mg/m ²	Cyclophosphamide >1500 mg/m ²
Etoposide	Oral cyclophosphamide	Cisplatin
Gemcitabine	Ifosfamide	Carmustine
Methotrexate	Doxorubicin 20–60 mg/m ²	Epirubicin >90 mg/m ²
Fludarabine	Epirubicin <90 mg/m ²	Doxorubicin >60 mg/m ²
5-Fluorouracil	Idarubicin	
Docetaxel	Oxaliplatin	Mechlorethamine
Paclitaxel	Carboplatin	
Nab-paclitaxel	Irinotecan	
Cabazitaxel		
Vinorelbine	Methotrexate 250–1000 mg/m ²	Methotrexate >1000 mg/m ²
Vinblastine	Mitoxantrone <15 mg/m ²	
Vincristine		
Mitomycin C	Cytarabine >1000 mg/m ²	Dacarbazine
Eribulin		
Pemetrexed		Temozolomide
Topotecan	Crizotinib	Streptozotocin
Ziv-aflibercept	Ceritinib	
Trastuzumab	Olaparib	
Pertuzumab		
Bevacizumab		
Panitumumab		
Temsirolimus		
Sorafenib		
Trametinib		

Gastrointestinal Causes

- Liver metastases or hepatitis
- Biliary duct obstruction
- Pancreatic disorders
- Obstructive bowel disease (peritoneal carcinomatosis, colorectal cancer)
- Functional bowel disease (reduced bowel motility, paralytic ileus)
- Acute abdomen/peritonitis

- Gastric or oesophageal cancer
- Gastritis, gastro-oesophageal reflux disease, ulcer, pyloric stenosis

Neurological Disorders

- Brain metastases with high intracranial pressure
- Medullary or cerebellar dysfunction
- Carcinomatous or infectious meningitis
- Cerebral haemorrhage

Other Causes

- Myocardial infarction, renal failure, viral infections, hypertension crisis

Pathophysiology

Nausea and vomiting occur due to activation of the chemoreceptor trigger zone (vomiting centre) in the medulla oblongata, due to activation or stimulation of the following structures:

- Dopamine D₂ receptors, serotonin 5-HT₃ receptors, opioid receptors, acetylcholine receptors, receptors for substance P
- Vestibular system
- Vagus nerve
- Vagal and enteric nervous system (activation of 5-HT₃ receptors in gastrointestinal mucosa)

Risk factors

Risk factors that predict the severity of nausea and vomiting are:

- Younger age
- Female gender
- Tumour burden
- Rate, route and dosage of chemotherapy administration
- Emetogenic potential of chemotherapy agent
- Anxiety or depression

Obstructive Bowel Disease

In cancer patients, bowel obstruction is often a reason for nausea and vomiting. The obstruction can occur at any level distal to the duodenum. Usually, treatment starts conservatively over a period of 2–5 days (nasogastric tube, adequate intravenous fluid supplementation, diuresis monitoring). If no improvement occurs within 72 hours, surgery should be considered.

In malignant large bowel obstruction, endoscopically placed, self-expanding metal stents may be used as palliation.

Treatment

Check for potential severe complications!

Low blood pressure, inadequate diuresis, creatininaemia, hypokalaemia, metabolic alkalosis, haematemesis.

Look for a cause if vomiting is not chemotherapy-related!

Clinical examination

Abdomen, neurological examination, blood pressure, diuresis.

Blood examination

Liver tests, creatininaemia, calcaemia, potassium levels, sodium levels, chloride levels, blood gas.

Imaging modalities

Ultrasonography, abdominal X-ray.

- If clinical examination suggests neurological disorder: brain computed tomography (CT) scan or magnetic resonance imaging (MRI), lumbar puncture if carcinomatous or infectious meningitis is suspected
- If clinical examination suggests abdominal cause: Gastrografin meal, abdominal CT scan
- Endoscopic examination (gastro-oesophagoscopy, colonoscopy) whenever clinically indicated

Treatment of Chemotherapy-related Vomiting

If moderate vomiting, without complications

- Outpatient management, treatment with serotonin antagonist orally (or intrarectally) and/or metoclopramide and/or corticosteroids
- Avoid drugs that reduce bowel motility (e.g. loperamide, hyoscyamine, anticholinergic agents)
- Check the evolution after 24 hours

If severe or in case of complications

- Consider hospitalisation
- Serotonin antagonists: e.g. granisetron: 3 mg × 1–3/day intravenously (i.v.), or ondansetron: 8 mg × 1–3/day i.v. over at least 10 minutes, 30 minutes before chemotherapy and at regular intervals thereafter (“round the clock” administration). In cases of moderate or highly emetogenic chemotherapy, preferentially palonosetron 0.25 mg i.v. over 30 seconds, beginning 30 minutes before chemotherapy
- Metoclopramide: 2 mg/kg i.v. over at least 15 to 30 minutes before chemotherapy, then repeat 2 more times every 3 hours after initial dose
Warning: check cardiac rhythm with electrocardiogram. Contra-indicated in case of mechanical bowel obstruction; risk of neurological complications when dose and duration of treatment are increased.
- Corticosteroids: prednisolone or methylprednisolone: 1–2 mg/kg/day, or dexamethasone 4 mg × 1–3/day orally or i.v.
- Neurokinin-1 receptor antagonists: for highly emetogenic chemotherapy, consider aprepitant 125 mg orally one hour prior to chemotherapy, and 80 mg orally in the morning of days 2 and 3 after chemotherapy; or fosaprepitant on day 1, 115 mg i.v. as an infusion over 20 to 30 minutes, approximately 30 minutes before chemotherapy. Neurokinin-1 receptor antagonists should be administered in conjunction with a corticosteroid and a 5-HT₃ antagonist. The recommended dosage of dexamethasone is 12 mg orally on day 1, administered

30 minutes before chemotherapy, and 8 mg in the mornings on days 2 to 4. If fosaprepitant is used, the dose of dexamethasone is 8 mg twice daily for days 3–4. A 5-HT₃ antagonist is administered on day 1 only

- In case of resistance: continuous i.v. perfusion of chlorpromazine 25 mg/day, or olanzapine 5–20 mg/day (Jordan K et al, 2015).

Declaration of Interest:

Dr Mountzios has reported no conflicts of interest.

Dr Petrova has reported no conflicts of interest.

Further Reading

Aapro M, Carides A, Rapoport BL, et al. Aprepitant and fosaprepitant: a 10-year review of efficacy and safety. *Oncologist* 2015; 20:450–458.

Gralla RJ. New agents, new treatment, and antiemetic therapy. *Semin Oncol* 2002; 29(1 Suppl 4):119–124.

Jordan K, Jahn F, Aapro M. Recent developments in the prevention of chemotherapy-induced nausea and vomiting (CINV): a comprehensive review. *Ann Oncol* 2015; 26:1081–1090.

Licitra L, Spinazzé S, Roila F. Antiemetic therapy. *Crit Rev Oncol Hematol* 2002; 43:93–101.

Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol* 2010; 21(Suppl 5):v232–v243.

L. Poulsen¹

C. Qvortrup²

¹Department of Oncology, Aalborg University Hospital, Aalborg, Denmark

²Department of Oncology, Odense University Hospital, Odense, Denmark

Definition

Oral mucositis (OM) is an inflammation of the mucosal lining at the oropharynx level, caused by chemotherapeutic agents or radiation therapy. OM manifests as a continuum from erythema to ulcer formation and may be complicated by secondary infections. The symptoms range from mild burning sensation to severe pain demanding opioid treatment. OM is associated with discomfort in swallowing and eating, potentially leading to dehydration, malnutrition and weight loss, thereby to an increased risk of hospitalisation, lower treatment adherence, and an impaired quality of life. Furthermore, in patients with neutropaenia, an intact mucosa is an important barrier to systemic infections.

The frequency of reported OM ranges from 30% up to 100%, depending on both treatment- and patient-related factors, the latter being age, gender, dental status and comorbidity. The great variance in reported OM incidence also reflects a lack of a standardised reporting scale (see below). As described, OM frequency and severity depend on the type of antineoplastic treatment. OM affects almost all patients treated with radiotherapy (RT) for head and neck cancer, the majority (60%–80%) of patients undergoing conditioning regimens for haematopoietic stem cell transplant (HSCT) and a smaller proportion (20%–40%) of patients with solid tumours treated with chemotherapy (ChT), especially regimens containing 5-fluorouracil, cisplatin and melphalan. The targeted agents are also associated with a risk of OM, with frequencies ranging from as low as 5% when used as monotherapy, to above 50% when given in combination with ChT.

Technical Procedures Involved

The diagnosis of OM is based on patient history and clinical examination. Several OM scoring systems have been developed and validated, but until now none has been defined as the gold standard. The World Health Organisation (WHO) mucositis scale is a five-grade scale based on symptoms and objective observations. The National Cancer Institute Common Terminology Criteria (NCI CTC) scale is a similar five-grade scale also based on symptoms and observations. Other grading scales include the Radiation Therapy Oncology Group (RTOG) mucositis scale and the Oral Mucositis Assessment Scale (OMAS); see Table 1. The last two are based primarily on objective measurements, and hence require a more experienced observer.

Table 1 Different Evaluation Schemes for Oral Mucositis (OM)

	WHO ¹	NCI CTC ²	RTOG ³	OMAS ⁴
Grade 0	None	No oral mucositis	No changes	
Grade 1	Soreness +/- erythema	Erythema	Irritation, may experience slight pain	
Grade 2	Erythema, ulcers	Patchy ulcerations or pseudomembrane formation	Patchy mucositis, may experience moderate pain	
Grade 3	Ulcers with extensive erythema	Confluent ulceration, occupying >50% of the mucosal surface	Confluent, fibrinous mucositis, may include severe pain	
Grade 4	Mucositis to the extent that alimentation is not possible	Tissue necrosis	Ulceration, haemorrhage or necrosis	

WHO, World Health Organisation; NCI CTC, National Cancer Institute Common Terminology Criteria; RTOG, Radiation Therapy Oncology Group; OMAS, Oral Mucositis Assessment Scale.

¹The OMAS grading system is based on an assessment guide which grades alterations of voice, swallowing, lips, tongue, saliva, mucous membrane, gingiva, teeth or denture to a final score.

²From WHO Handbook for Reporting Results of Cancer Treatment. Geneva: World Health Organisation, 1979; and adapted from Sonis ST, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer* 2004; 100(9 Suppl):1995–2025; ³From National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. May 28, 2009 (v4.03; June 14, 2010). Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf; ⁴From Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; 31:1341–1346.

⁵From Sonis ST, Eilers JP, Epstein JB, et al. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. *Mucositis Study Group. Cancer* 1999; 85:2103–2113.

Description of the Processes Involved in Their Essential/Critical Steps

Mucositis arises from non-specific ChT- and radiation-induced damage of the mucosal basal cell layer. In the last few years, translational research has made extensive contributions to the detailed understanding of OM development.

A continuum of five biological stages has been suggested by Sonis (2004), and includes initiation, primary damage response, signal amplification, ulceration and healing.

In cases of fractionated treatment, these stages overlap, whereas conditioning regimens before HSCT induce cell damage in a short time-frame.

- **The initiation stage:** direct toxic tissue damage is seen shortly after initiation of therapy as a result of both DNA and non-DNA damage and generation of reactive oxygen species (ROS).
- **Primary damage response:** the processes involved in the “initiation stage” lead to a complex series of events with activation of several transduction pathways that induce transcription factors (e.g. p53 and nuclear factor- κ B), which result in production of pro-inflammatory cytokines (tumour necrosis factor-alpha [TNF- α], interleukin [IL]-1B and IL-6), leading to early damage of connective tissue and endothelium, and ultimately to epithelial basal cell injury and death.
- **Signal amplification:** due to a pro-inflammatory cytokine-positive feedback loop, the tissue damage is enhanced. At these stages there may be some mucosal erythema, but for the most part tissue integrity is preserved and the patients have few symptoms.
- **Ulceration:** at this stage the mucosal barrier is disrupted, resulting in painful lesions. This increases the risk of bacterial invasion, which can not only propagate local tissue damage, but also poses a risk for systemic infections.
- **Healing:** most often mucositis is an acute condition that self-resolves within 2–3 weeks once antineoplastic treatment is withheld.

The time-span associated with the development of OM varies. ChT-associated OM usually peaks at 7–10 days after initiation of treatment and resolves quite quickly within a few days. In contrast, RT-associated OM usually peaks 4–6 weeks after initiating treatment and lasts for weeks after the treatment is completed.

Management of OM

Many different preventive and therapeutic interventions for OM have been tested, but the optimal treatment strategy is still not established. Many of the reported trials have shown conflicting results, most likely as a consequence of the complex mechanisms behind OM and a lack of standardised reporting scales.

The different treatment strategies can be divided into: preventive treatment strategies and general supportive care strategies, primarily pain management.

In general it is important to discuss the different treatment options and potential side effects with the patient and to give thorough instructions for OM management, especially in an outpatient situation. If a patient has developed severe OM during a ChT cycle, it is highly likely that OM will reappear during the next cycle.

Preventive Treatments

Basic oral care

Basic oral care is thought to be important for preserving good oral hygiene in order to reduce the impact of oral microbial flora and hence limit the risk of an opportunistic infection at the damaged mucosa.

However, even though systematic basic oral care interventions are applied worldwide, the evidence that these interventions can be beneficial in preventing OM is weak and arises from a small study. If applied, what exact oral care regimen should be followed? Most oral care protocols include a combination of tooth brushing with a soft toothbrush to avoid gum trauma, flossing, mouth rinsing and the use of sugar-free chewing gum.

Mouthwashes and antimicrobials

Chlorhexidine mouthwash has been used to reduce bacterial and fungal colonisation of the oral cavity. However, conflicting results have been published, and the majority of studies have failed to show the benefit of this intervention. Thus chlorhexidine as an antiseptic mouthwash is not recommended.

Regarding systemic treatments, such as antibiotics, antivirals and antifungals, many trials have been published, but there is a great variability between them in terms of cancer type, antitumour treatment and antimicrobial agent used; moreover they lack a standardised OM assessment. A comprehensive review by Donnelly (2003) including 31 trials failed to provide definitive conclusions regarding recommendations for the use of these agents. Further trials with standardised assessments are needed.

Oral coating agents

Sucralfate (an aluminium salt) and other coating agents are thought to act by applying a protective layer binding to the damaged mucosal proteins and thus protecting nerve endings, thereby reducing pain. However, data published on sucralfate are controversial, and a recent review concluded that there is a clear lack of benefit for this drug in the prevention of both RT- and ChT-induced OM. Thus sucralfate mouthwash is not recommended for prevention of OM.

Cryotherapy

Oral cryotherapy, which is administered as ice chips to the buccal mucosa, causes local vasoconstriction and decreases blood flow to the oral mucosa, thereby inducing a decreased exposure of the oral mucosa to the cytotoxic drugs. Oral cryotherapy has shown consistent benefit in patients receiving either 5-fluorouracil bolus infusion or melphalan in several clinical trials. Other trials have tested the application time with both 30 and 60 minutes, and found no difference in mucositis severity. A meta-analysis of seven trials in patients undergoing HSCT by Wang (2015) has shown reduced severity of OM, length of hospital stay, and duration of total parenteral nutrition (TPN) with use of cryotherapy. The ice chips are typically placed in the mouth for 30 minutes, starting

5 minutes prior to administration of ChT.

Low-level laser therapy

Low-level laser therapy (LLLT) is a non-pharmacological method, in which various metabolic processes are induced via a photochemical reaction by absorption of energy by chromophores. The effect depends on the applied light wavelength, density and the target tissue exposure time.

Evidence supports the use of LLLT (wavelength 650 nm, power 40 mW, and each square metre treated for the required time to a tissue energy dose of 2 J/cm²) for OM prevention in patients undergoing high-dose ChT with HSCT. Furthermore, LLLT (632.8 nm) has been shown to reduce OM in patients undergoing RT with or without concomitant ChT for head and neck cancer.

Growth factors

The only drug in this group approved for treatment of OM is palifermin, which is a recombinant keratinocyte growth factor. Administration of palifermin 60 µ/kg per day for 3 days before conditioning treatment and for 3 days after transplant has been shown to prevent OM in patients with haematological malignancies receiving high-dose ChT and total body irradiation followed by autologous stem cell transplantation.

Anti-inflammatory agents

Benzydamine oral rinse 0.15% is a topical non-steroidal anti-inflammatory drug which has also been shown to have antimicrobial properties. Prophylactic rinse with 15 ml for 2 minutes 4–8 times a day reduces OM by 33% in patients treated with RT up to 50 Gy.

Others

Zinc is known to have an antioxidative effect and is utilised in some processes of wound healing. Small studies have tested zinc supplements for OM and shown a positive effect. However, there remains some concern that antioxidant drugs could be reducing the effect of RT.

General Supportive Care Strategies

Mechanisms of OM-associated pain are complex. Patients usually experience pain accompanied by burning, dryness and loss of taste.

The recommended treatment algorithm consists of local/topical treatment, which may be intensified with mild/moderate systemic agents and in some cases with strong narcotic analgesics.

Tricyclic antidepressants have been used for many years as a treatment option for chronic pain. Doxepin is available in topical formulation and has been positive in pilot studies in terms of reducing pain for up to 4 hours after application (Epstein et al, 2006). Further trials confirming these promising results are needed before routine use can be recommended.

The use of opioids is often necessary in treating severe OM pain. Routes of administration include patient-controlled analgesia pumps and oral and transmucosal, transdermal and parenteral routes. Many trials have been conducted in this setting, but the great ranges in the use of active drug, treatment approaches in the comparator arm, endpoints and pain assessment makes cross-trial comparison extremely difficult.

Topical morphine was evaluated in a small study including 26 head and neck cancer patients in comparison to a mixture of lidocaine, diphenhydramine and magnesium aluminium hydroxide. Patients in the topical morphine group had a shorter duration and lower intensity of pain (Cerchiatti et al, 2002). Oral transmucosal morphine has been tested in cancer pain earlier on, and showed rapid relief of breakthrough pain, but it has been discussed whether OM compromised the absorption. In a pilot study by Darwish et al (2007), where fentanyl buccal tablets were administered to patients with and without OM, the two groups showed similar absorption and pain relief.

Potential Future Developments

Mucositis remains an important clinical issue in the daily management of cancer patients: consequences for the patients' quality of life and therapy outcomes are underestimated. The clinical data on the management of OM remain controversial, the optimal regimen of prophylaxis is still

unknown and further, larger studies are warranted in this field with the aim to improve the treatment of OM caused both by RT, traditional cytotoxic agents as well as targeted agents.

Declaration of Interest:

Dr Poulsen has reported no conflicts of interest.

Dr Qvortrup has reported no conflicts of interest.

Further Reading

- Cerchietti LC, Navigante AH, Bonomi MR, et al. Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma. *Cancer* 2002; 95:2230–2236.
- Darwish M, Kirby M, Robertson P, et al. Absorption of fentanyl from fentanyl buccal tablet in cancer patients with or without oral mucositis: a pilot study. *Clin Drug Invest* 2007; 27:605–611.
- Donnelly JP, Bellm LA, Epstein JB, et al. Antimicrobial therapy to prevent or treat oral mucositis. *Lancet Infect Dis* 2003; 3:405–412.
- Epstein JB, Epstein JD, Epstein MS, et al. Oral doxepin rinse: the analgesic effect and duration of pain reduction in patients with oral mucositis due to cancer therapy. *Anesth Analg* 2006; 103:465–470.
- Lalla RV, Bowen J, Barasch A, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 2014; 120:1453–1461.
- McGuire DB, Altomonte V, Peterson DE, et al. Patterns of mucositis and pain in patients receiving preparative chemotherapy and bone marrow transplantation. *Oncol Nurs Forum* 1993; 20:1493–1502.
- Peterson DE, Boers-Doets CB, Bensadoun RJ, et al. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol* 2015; 26(suppl 5):v139–v151.
- Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer* 2004; 4:277–284.
- Wang L, Gu Z, Zhai R, et al. Efficacy of oral cryotherapy on oral mucositis prevention in patients with hematological malignancies undergoing hematopoietic stem cell transplantation: a meta-analysis of randomized controlled trials. *PLoS One* 2015; 10:e0128763.

Diarrhoea

D. Pérez-Callejo

V. Calvo

*Medical Oncology Service, Hospital Universitario Puerta de Hierro
Majadahonda, Madrid, Spain*

Introduction

Gastrointestinal toxicity due to chemotherapeutic drugs is a common problem in cancer patients. Diarrhoea is diagnosed if a person has at least three unformed stools in 24 hours. Although a practical definition is lacking, diarrhoea is commonly diagnosed when an abnormal increase in daily stool weight (>300 g), water content more than 75%, and frequency, whether or not accompanied by urgency, perianal discomfort, or incontinence, is present as a consequence of an incomplete absorption of electrolytes and water from luminal content. On the basis of its duration, diarrhoea is classified as: acute if <2 weeks, persistent if 2–4 weeks, and chronic if >4 weeks. Diarrhoea is a common and serious adverse event associated with pelvic or abdominal radiation therapy and with different chemotherapy (ChT) regimens and biological agents.

Diarrhoea can be debilitating and, in some cases, life-threatening. Findings include volume depletion, renal insufficiency and electrolyte disorders (such as hypokalaemia, metabolic acidosis), and they depend upon water intake, hyponatraemia or hypernatraemia. Malnutrition, fatigue or sleep disturbance can also be seen. This adverse event can also lead to treatment delays/discontinuation, reduced quality of life, and increased cost of care.

Although the risk factors contributing to direct toxic effects in the gastrointestinal tract are starting to be understood, why diarrhoea happens remains unclear. Maintenance of the secretory, absorptive and propulsive functions of the gastrointestinal tract relies on complex neurological,

hormonal, muscular, immune and enzymatic systems. Dysfunction of different regions of the gastrointestinal tract may cause completely different physiological effects in different patients despite similar symptoms. The severity of diarrhoea is graded according to the National Cancer Institute (NCI) Common Terminology Criteria for adverse events (Table 1).

While ChT-induced diarrhoea has been most commonly described and investigated with the fluoropyrimidines and irinotecan, the different specific pathophysiological mechanisms of diarrhoea induced by targeted therapies are not fully understood. The main causes associated with this adverse event in cancer patients, and their general management considerations, are discussed below.

Table 1 Common Terminology Criteria for Adverse Events (CTCAE v4.03) Grades of Diarrhoea.

Adapted from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline
Grade 3	Increase of ≥7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in stoma output compared to baseline; limiting self-care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Oncological Therapies Associated with Diarrhoea

Fluoropyrimidines (Fluorouracil and Capecitabine)

Fluorouracil (5-FU) is an antimetabolite whose toxic effects are dependent on the schedule and dose, with bolus regimens causing more myelosuppression, stomatitis and grade 3–4 diarrhoea than infused 5-FU. 5-FU prodrugs, such as capecitabine, produce similar effects. The risk of diarrhoea is increased by the addition of leucovorin.

Clinical factors predictive for 5-FU-induced diarrhoea include female gender, increasing age, normal body mass index (BMI), Caucasian

ethnic origin, and diabetes mellitus. Genetic disorders may also contribute to drug-specific toxic effects. 5-FU is normally metabolised to inactive dihydro-5-FU after an intravenous dose; 80% of the drug is metabolised to the inactive dihydro-5-FU by dihydropyrimidine dehydrogenase (DPD) in the liver. Administration of 5-FU to patients with DPD deficiency can lead to life-threatening complications, including severe diarrhoea, mucositis and pancytopenia. DPD deficiency is relatively common among Caucasians (3%–5%).

In the largest cohort of patients receiving 5-FU monotherapy, 110 (16%) of 683 patients had grade 3–4 toxic effects, and, of these, 59 (54%) had grade 3–4 diarrhoea (Schwab et al, 2008).

Capecitabine is an oral fluoropyrimidine which is then converted to 5-FU. Like 5-FU, capecitabine is contraindicated in patients with known DPD deficiency. Administered at standard doses (1000 mg/m² twice daily for 14 of every 21 days), the prevalence of diarrhoea is 30%–40%, with grade 3–4 rates of 10%–20%.

Irinotecan

Irinotecan can cause acute diarrhoea or delayed diarrhoea. Irinotecan is associated with dose-limiting diarrhoea when given either as a 30-minute bolus every 3 weeks or as a continuous infusion over 7 days. Acute diarrhoea is due to inhibition of acetylcholine esterase, which increases cholinergic transmission within minutes of administration and up to 24 hours later, but is easily controlled with atropine. The delayed-onset diarrhoea usually occurs at least 24 hours after drug administration, and can be potentially life-threatening. Delayed diarrhoea associated with irinotecan is unpredictable, non-cumulative and occurs at all dose levels.

An increased risk of severe diarrhoea from irinotecan is seen in patients with Gilbert's syndrome (a common benign genetic liver disorder that produces elevated levels of unconjugated bilirubin in the bloodstream, without severe consequences). Whether dose reduction is indicated in these patients remains unclear.

Docetaxel

Docetaxel usually causes mild diarrhoea. However, cases of severe enteritis and colitis have been reported. Data from phase II and III studies indicate a prevalence of diarrhoea of 24%–25% (regardless of the grade) when docetaxel is administered (Sheperd et al, 2000).

Targeted Therapies

Diarrhoea is one of the most common adverse events recorded following treatment with tyrosine kinase inhibitors (TKIs) (Table 2). With most TKIs, the severity of diarrhoea is dose-dependent and can be managed with a dose reduction.

Diarrhoea might start as early as 2–3 days after initiation of epidermal growth factor receptor (EGFR) inhibitor therapy, such as gefitinib, erlotinib or afatinib. TKI-associated diarrhoea may be related to excess chloride secretion caused by dysregulated EGFR signalling. It has been reported in up to 90% of patients treated with afatinib (Califano et al, 2015).

The mechanism for diarrhoea related to vascular endothelial growth factor receptor (VEGFR) inhibition remains unexplained, but may be related to ischaemic changes causing direct damage to mucosal cells.

During treatment with monoclonal antibodies, such as cetuximab or panitumumab, grade 2 diarrhoea is observed in up to 21% of cases, and grade 3 in about 1%–2%.

Checkpoint inhibitors, immunomodulatory antibodies that are used to enhance the immune system, have a distinct toxicity profile, with colitis as one of the adverse events related to activation of the immune system. In these patients, especially when treated with ipilimumab, corticosteroids are the standard treatment to inhibit T-cell function. When steroids fail, infliximab has been advocated.

Table 2 Incidence of Diarrhoea with Targeted therapies.

Adapted with permission of the European School of Oncology, from: Pessi MA, Zilembo N, Haspinger ER, et al. Targeted therapy-induced diarrhea: A review of the literature. *Crit Rev Oncol Hematol* 2014; 90:165–179; permission conveyed through Copyright Clearance Center Inc.

Molecule	Target	Incidence of diarrhoea (%)	Grade 3–4 (%)
Gefitinib	EGFR	25.9–51.6	0.9–4.9
Erlotinib	EGFR	18–57	3–6
Afatinib	EGFR	87–95	14.4–22
Crizotinib	EML4-ALK	50–60	0
Lapatinib	HER-2	48 in monotherapy 47.4–75 + ChT 60 + Trastuzumab	7 in monotherapy 2.6–14 + ChT 23.4 + Trastuzumab
Trastuzumab	HER-2	7 in monotherapy 1.6–63 + ChT	1.6–56 + ChT
Pertuzumab	HER-2	48.3 in monotherapy 66.8 + ChT	3 in monotherapy 5–7.9 + ChT
Cetuximab	EGFR	13–28 in monotherapy 70–80 + ChT	2 in monotherapy 4–28 + ChT
Panitumumab	EGFR	21 in monotherapy 60–70 + ChT	2 in monotherapy 8–20 + ChT
Imatinib	TK	20–26	1
Regorafenib	TK, including VEGF receptors, TIE2, PDGFR, RET, c-KIT, RAF	34–40	5–8
Pazopanib	TK, including VEGF receptors, c-KIT, PDGFR	52	4
Sunitinib	VEGF	44–55.3	5–7.8
Sorafenib	VEGF	43–55.3	2–7.8
Axitinib	VEGF	55	11
Cabozantinib	TK, including VEGF receptors, RET, MET, TRB, TIE2	64	12
Aflibercept	VEGF	69.2 + ChT	19.3 + ChT
Bevacizumab	VEGF	20	2–6.7
Everolimus	mTOR kinase	30	1–3
Temsirolimus	mTOR kinase	27	1
Ipilimumab	CTLA-4	27–31	5
Vemurafenib	BRAF	5–6	0
Dabrafenib	BRAF	1	0
Selumetinib	MEK	45–50	4
Trametinib	MEK	45–50	4
Vandetanib	TK, EGFR, VEGF, RET	74	10

ChT, Chemotherapy; CTLA-4, cytotoxic T-lymphocyte associated protein 4; EGFR, epidermal growth factor receptor; EML4-ALK, echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase gene; HER-2, human epidermal growth factor receptor-2; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; TIE2, tyrosine kinase with immunoglobulin-like and EGF-like domains 2; TK, tyrosine kinase; VEGF, vascular endothelial growth factor.

Other Causes of Diarrhoea in Cancer Patients

Medications

Magnesium-containing antacids or excessive doses of laxatives can result in diarrhoea.

Radiotherapy-induced Diarrhoea

Radiation injury to the bowel is usually encountered following treatment of cancers of the anus, rectum, cervix, uterus, prostate, urinary bladder or testes, and as part of total body irradiation. Radiotherapy of the abdomen or pelvis damages intestinal mucosa, causing prostaglandin release and bile salt malabsorption. These two factors increase intestinal peristalsis, causing diarrhoea.

Acute intestinal side effects of radiation begin at approximately 10–20 Gy and peak between weeks 3 and 5 of treatment. Several risk factors for toxic effects include diabetes, inflammatory bowel disease, connective tissue disease, human immunodeficiency virus (HIV), being elderly, smoking and having low BMI.

Chronic radiation enteritis is less common. It is usually associated with radiation doses greater than 45 Gy, and it appears after a latency of months to years following the initial exposure. The underlying pathology is a progressive radiation-induced endarteritis that causes intestinal ischaemia.

No existing pharmacological strategies effectively prevent radiotherapy-induced diarrhoea.

Clostridium difficile Diarrhoea

Clostridium difficile (*C. difficile*) diarrhoea occurs when the normal intestinal flora is altered, allowing *C. difficile* to flourish in the intestinal tract and produce a toxin that causes watery diarrhoea. It can be triggered by repeated enemas, prolonged nasogastric tube insertion, gastrointestinal tract surgery and the use of antibiotics, especially ampicillin, clindamycin and cephalosporins. However, it has been reported after ChT in the absence of antibiotic therapy. The most common confirmatory test is an

enzyme immunoassay for *C. difficile* toxins A and B, with results available in 2 to 4 hours. The specificity of the assay is high (93%–100%), but sensitivity ranges from 63%–99%.

Enteral Feeding

Tube feeding, either by nasogastric tube, gastrostomy or jejunostomy, may be associated with the development of diarrhoea. Many potential factors may contribute to the problem and indeed it is often multifactorial. Formula composition may affect the incidence of diarrhoea. Both formula osmolality and rate of delivery may be associated with diarrhoea. Contamination of the enteral formula is often a contributing or causative factor.

Patients selected for tube feeding are often hypoalbuminaemic. Some data suggest that hypoalbuminaemia predisposes patients to diarrhoea by decreasing osmotic pressure and causing oedema in the intestinal mucosa.

Coeliac Plexus Block

Coeliac plexus block is commonly associated with a self-limiting acute diarrhoea. Occasionally, diarrhoea may be persistent. This diarrhoea may be amenable to treatment with atropine.

Patient Assessment

The assessment of a patient with possible treatment-induced diarrhoea should include a detailed medical history, dietary history, medication review, description of stools and a physical examination focused on the identification of dehydration and abnormalities of the abdominal and rectal areas. When appropriate, abdominal radiographs can be carried out to evaluate abdominal obstruction or faecal impaction. Biochemical parameters should be checked for evidence of dehydration, hypokalaemia or renal impairment. If enteric infections are suspected, stool samples should be sent for faecal leukocytes, *C. difficile* toxins A and B, and culture for organisms including *C. difficile*, *Salmonella*, *Escherichia coli*, *Campylobacter* and infectious colitis. When neutropaenic entero-

colitis is suspected, computed tomography imaging of the abdomen should be undertaken.

Management and Treatment

The NCI of the National Institutes of Health (NIH) has published standardised definitions of adverse events, to describe the severity of organ toxicity for patients receiving cancer therapy (see Table 1). The patient's symptoms should be classified as either "uncomplicated" or "complicated", determined by the number of stools per day or the increase in ostomy output compared to baseline, the need for hospitalisation and the effect on self-care activities. This classification will guide treatment approach, being useful for either ChT- or radiotherapy-induced diarrhoea.

Patients with grade 1 or 2 diarrhoea with no other complicating signs or symptoms may be classified as "uncomplicated" and managed conservatively. However, if a patient with grade 1 or 2 diarrhoea has any of the following added risk factors: moderate to severe cramping, grade >1 nausea/vomiting, decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration, this should be classified as "complicated" and may require more aggressive management.

Any patient with grade 3 or 4 diarrhoea should be classified as "complicated", and requires aggressive management.

Uncomplicated Diarrhoea

Initial management of mild to moderate diarrhoea should include dietary modification (e.g. eliminating all lactose-containing products and high-osmolar dietary supplements). The patient should be instructed to record the number of stools and report other serious symptoms (e.g. fever or dizziness on standing).

Loperamide should be started at an initial dose of 4 mg, followed by 2 mg every 4 hours, or after every unformed stool (not to exceed 16 mg/day). Unlike other opioids, loperamide has no analgesic or euphoric effects even at high doses, because of its low systemic circulation and inability to cross the blood–brain barrier. Its most common side effects are related to the impact on bowel motility, including abdominal pain, distension, bloating,

nausea, vomiting and constipation. Loperamide is not recommended for treatment of acute diarrhoea in children younger than three years or in children who are malnourished, moderately to severely dehydrated or have bloody diarrhoea.

If mild to moderate diarrhoea resolves with loperamide, patients should be instructed to continue dietary modification and to gradually add solid foods to their diet. In the case of ChT-induced diarrhoea, patients may discontinue loperamide when they have been diarrhoea-free for at least 12 hours. However, in case of radiotherapy-induced diarrhoea, patients should be instructed to continue taking standard doses of loperamide for the entire duration of radiotherapy.

If mild to moderate diarrhoea persists for more than 24 hours, the dose of loperamide should be increased to 2 mg every 2 hours (with a maximum daily dose of 16 mg), and oral antibiotics may be started as infection prophylaxis. If mild to moderate ChT-induced diarrhoea has not resolved after 24 hours on high-dose treatment, loperamide should be discontinued, and the patient should be started on a second-line antidiarrhoeal agent, such as subcutaneous octreotide (100–150 µg starting dose, with dose escalation as needed) or other second-line agents, such as oral budesonide.

The patient should be seen in the physician's office or outpatient centre for further evaluation, including complete stool and blood work-up. Fluids and electrolytes should be replaced as needed. However, in the case of radiotherapy-induced diarrhoea, it may be appropriate to continue treatment with loperamide, and a complete stool and blood work-up may not be necessary, unless there are signs of dehydration or infection.

Complicated Diarrhoea

Aggressive management of complicated cases usually requires hospital admission and should involve intravenous fluids; octreotide at a starting dose of 100–150 µg subcutaneously three times a day, or intravenously (25 to 50 µg/h) if the patient is severely dehydrated, with dose escalation up to 500 µg until diarrhoea is controlled, and antibiotics should be administered (e.g. fluoroquinolone). These patients should be evaluated with complete blood count, electrolyte profile and a stool work-up.

As with uncomplicated diarrhoea, this may not be appropriate for radiotherapy-induced diarrhoea.

Conclusions

Diarrhoea is a common adverse event associated with a variety of ChT agents, targeted therapies and with abdominal or pelvic radiotherapy. It can be a serious, debilitating, and even life-threatening complication of cancer treatment. Loss of fluids and electrolytes associated with persistent or severe diarrhoea can result in life-threatening dehydration, kidney failure and electrolyte imbalances, and may contribute to cardiovascular morbidity. The risk of infectious complications is increased, which can lead to sepsis in patients with ChT-induced neutropaenia. In addition, ChT-induced diarrhoea can have a serious impact on the patient's quality of life.

Early assessment and management of ChT-, biological therapy- and radiotherapy-induced diarrhoea are crucial, in order to prevent severe complications and preserve the quality of life of these patients.

Declaration of Interest:

Dr Pérez-Callejo has reported no conflicts of interest.

Dr Calvo has reported no conflicts of interest.

Further Reading

- Andreyev J, Ross P, Donnellan C, et al. Guidance on the management of diarrhoea during cancer chemotherapy. *Lancet Oncol* 2014; 15:e447–460.
- Benson AB 3rd, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol* 2004; 22:2918–2926.
- Califano R, Tariq N, Compton S, et al. Expert consensus on the management of adverse events from EGFR tyrosine kinase inhibitors in the UK. *Drugs* 2015; 75:1335–1348.
- Cherny NI. Evaluation and management of treatment-related diarrhea in patients with advanced cancer: a review. *J Pain Symptom Manage* 2008; 36:413–423.
- Li Z, Vaziri H. Treatment of chronic diarrhoea. *Best Pract Res Clin Gastroenterol* 2012; 26:677–687.

- Pessi MA, Zilembo N, Haspinger ER, et al. Targeted therapy-induced diarrhea: A review of the literature. *Crit Rev Oncol Hematol* 2014; 90:165–179.
- Schwab M, Zanger UM, Marx C, et al; German 5-FU Toxicity Study Group. Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: a prospective clinical trial by the German 5-FU Toxicity Study group. *J Clin Oncol* 2008; 26:2131–2138.
- Sharma R, Tobin P, Clarke SJ. Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhoea. *Lancet Oncol* 2005; 6:93–102.
- Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; 18:2095–2103.

Abdominal Infections in Neutropaenic Patients

19

V. Ballová

Národný onkologický ústav, Hemato-oncological Department, Bratislava, Slovakia

Introduction

The gastrointestinal tract is a common site of infection in neutropaenic patients. There are several well-recognised entities which can cause distinct clinical syndromes in neutropaenic patients, including neutropaenic enterocolitis (NEC), *Clostridium difficile*-associated diarrhoea (CDAD), appendicitis, cholecystitis, cholangitis, cytomegalovirus (CMV) colitis and graft-versus-host disease (GVHD). The clinical manifestation of different types of abdominal infection in neutropaenic patients is not specific. The physical findings may be minimal at the time of diagnosis in severely immunocompromised patients, and rapid progression to fulminant septicaemia may precede the development of more typical abdominal signs. A combination of clinical features, radiographic and microbiological findings, serological and sometimes also histopathological results is needed to make a specific diagnosis.

Abdominal infections in neutropaenic patients are life-threatening situations with substantial morbidity and mortality. Neutropaenic patients with fever and abdominal symptoms of any intensity should immediately undergo evaluation, including blood counts, coagulation, biochemistry and radiological evaluation for bowel wall thickening of >4 mm, the hallmark of NEC. Management includes bowel rest, correction of cytopaenia and coagulopathies, as well as administration of broad-spectrum antibiotics and antifungal agents. Surgical interventions are necessary in certain types of abdominal infection or to manage complications such as perforation and haemorrhage.

Definitions

Neutropaenic Enterocolitis (NEC)

NEC or typhlitis (*typhlon* means caecum, from the Greek word *typhlos*, which signifies blind or closed), or ileocaecal syndrome, is a serious complication of neutropaenia. NEC is characterised by segmental ulceration and inflammation with necrosis of the ileum, caecum and ascending colon, which may progress to haemorrhage, perforation, septicaemia and multisystem organ failure.

NEC is the most common intestinal affliction in neutropaenic patients with fever and abdominal pain following intensive chemotherapy. NEC was originally thought to involve only the ileocaecal area, because of the vascular paucity in the caecum. However, a study with computed tomography (CT) imaging showed that NEC was limited to the ileocaecal area in only 28% of cases, and more extensive colonic involvement was present in 75% of cases. Abnormalities in the small bowel were present in 66% of cases (Kirkpatrick & Greenberg 2003).

An important fact is that NEC can occur anywhere in the small or large bowel. The mortality rate associated with NEC is relatively high, 50% or more according to some reports. The most frequent causes of death are uncontrolled bleeding, perforation or irreversible sepsis with multiple organ failure. Early recognition and appropriate medical or surgical management could reduce mortality.

Necrotising Gastritis (NG)

Acute isolated NG is a recently recognised clinical phenomenon comprising acute, isolated, transmural gastric infection in the context of severe neutropaenia. The symptoms include severe epigastric discomfort, vomiting and circulatory collapse with neutropaenia resulting from chemotherapy or immunosuppression. Combination of neutropaenia, mucositis and achlorhydria (caused by proton pump inhibitor treatment) may be predisposing factors. Gastric biopsy can reveal gastric necrosis and identify an infiltrating microorganism. This entity may be considered as a rare form of NEC with isolated stomach involvement, and with propensity for recurrence in some cases. Early recognition, antibiotic therapy and supportive care are crucial.

Clostridium difficile-associated Diarrhoea (CDAD)

CDAD or pseudomembranous colitis is another common complication in neutropaenic patients occurring after chemotherapy, broad-spectrum antibiotic therapy or both. Alteration of the normal gut flora by medication allows colonisation by *C. difficile* and production of toxins, causing severe colonic inflammation, fever, abdominal pain, watery diarrhoea and typical pseudomembranous exudates. CDAD is considered a type of pancolitis; however, the most frequently and severely damaged segments are the sigmoid colon and the rectum. Patients considered suspect are those presenting with watery diarrhoea (three or more stools within 24 hours), mostly previously treated with antibiotics. Detection of *C. difficile* toxins A/B in stool is usually sufficient for diagnosis.

Risk Factors

NEC was originally described in children treated with intensive chemotherapy, including those with leukaemia. Since then, NEC has been reported with increasing frequency among adult patients treated for haematological and also solid tumours in the era of more frequently used dose-dense and high-dose chemotherapy and transplantation. It is now increasingly reported in patients treated for acute leukaemia, lymphoma, solid tumours while on chemotherapy, and in patients with acquired immune deficiency syndrome (AIDS). It may also occur in patients with aplastic anaemia who have not received cytotoxic therapy.

It has become important for clinicians to consider NEC when neutropaenic patients develop abdominal manifestations following certain cytotoxic agents and drug combinations (Table 1).

CDAD or pseudomembranous colitis is a well-known complication of antibiotic therapy. The incidence is increasing mostly because of intensified use of broad-spectrum antibiotics. Pseudomembranous colitis with and without positive assays for *C. difficile* toxins has also been recently described as a cause of severe diarrhoea in neutropaenic patients receiving chemotherapy in the absence of prior or concurrent antibiotic therapy. Use of certain cytotoxic drugs was thought to be directly related to the development of this complication (Table 2).

Table 1 Predisposing Factors for NEC

Drugs most commonly associated with NEC	<ul style="list-style-type: none">■ Cytosine arabinoside■ Etoposide■ Idarubicin■ Daunorubicin■ Vinca alkaloids■ Methotrexate■ Taxanes■ 5-Fluorouracil*■ Capecitabine*■ Cyclophosphamide■ Ifosfamide
Additional predisposing factors	<ul style="list-style-type: none">■ Previous abdominal surgery■ Diverticulosis and diverticulitis■ Tumour bowel infiltration■ Continuous infusion regimen of chemotherapy■ Occurrence of NEC after previous chemotherapy

NEC, Neutropaenic enterocolitis.

*More likely in dihydropyridine dehydrogenase-deficient patients.

Table 2 Risk Factors for CDAD

■ Previous use of antibiotics (prolonged and frequent use)
■ Haematopoietic stem cell transplantation (HSCT)
■ Methotrexate
■ Docetaxel
■ Anthracyclines
■ Platinum-containing drugs
■ Cyclophosphamide
■ Colonisation by vancomycin-resistant enterococcus (VRE) and use of linezolid*

CDAD, *Clostridium difficile*-associated diarrhoea.

*Risk factor associated with death from CDAD after HSCT.

Pathophysiology

On the basis of the pathophysiological data of gastrointestinal complications in neutropaenic patients, it is possible that neutropaenic enterocolitis, pseudomembranous colitis and ischaemic colitis may share a similar pathophysiological basis and probably represent varying degrees of bowel inflammation and necrosis, elicited by cytotoxic drugs (Table 3).

NEC is believed to be associated with chemotherapy-induced intestinal mucosal injury, followed by superinfection and may lead to bacteraemia. The exact pathogenesis is poorly understood and is multifactorial.

Table 3 Contributing Factors for Gastrointestinal Complications in Neutropaenic Patients

	Factor	Effect
NEC	Neutropaenia	<ul style="list-style-type: none"> ■ Reduced immune response against invasion of intestinal microbes ■ Mucosal neutropaenic ulcerations
	Thrombocytopenia and coagulopathy	<ul style="list-style-type: none"> ■ Intramural haemorrhage
	Mucosal injury caused by chemotherapy	<ul style="list-style-type: none"> ■ Loss of mucosal integrity ■ Inflammatory cytokines ■ Increased mucosal permeability ■ Inhibition of mucosal proliferation and healing ■ Bacterial and fungal invasion
	Distension of caecum	<ul style="list-style-type: none"> ■ Compromised arterial vascular supply
	Sepsis and hypotension	<ul style="list-style-type: none"> ■ Mucosal ischaemia
	Antibiotics	<ul style="list-style-type: none"> ■ Bacterial and fungal overgrowth, intestinal dysbiosis
	Steroids	<ul style="list-style-type: none"> ■ Hyperglycaemia, immunosuppression, wound healing delay
CDAD	Broad spectrum antibiotics	<ul style="list-style-type: none"> ■ Alteration of normal intestinal flora ■ Proliferation of toxigenic strains of <i>C. difficile</i> ■ Production of toxins A/B
	Chemotherapy (methotrexate, docetaxel, cyclophosphamide, platinum-containing drugs)	<ul style="list-style-type: none"> ■ Severe inflammatory changes ■ Disruption of colonic epithelium ■ Mucosal necrosis ■ Microbicidal effect on the normal intestinal flora ■ Proliferation of <i>C. difficile</i>

CDAD, *Clostridium difficile*-associated diarrhoea; NEC, neutropaenic enterocolitis.

CDAD results from a disturbance of the normal bacterial flora of the colon, colonisation with *C. difficile* and the release of toxins that cause mucosal inflammation and damage. Concurrent factors causing severe mucosal injury in neutropaenic patients can contribute to a rapid life-threatening course of this complication.

The mechanism of chemotherapy-induced pseudomembranous colitis seems to be explained by development of severe inflammatory changes, disruption of the normal colonic epithelium and mucosal necrosis.

Clinical Manifestations

Clinical symptoms of abdominal infections are not specific, and include fever and abdominal signs occurring during a period of neutropaenia, classically beginning 7–10 days after chemotherapy (Table 4). Even in the presence of sepsis, physical findings may be minimal, and rapid

progression to fulminant septicaemia may precede the development of more pronounced abdominal symptoms. Recovery from neutropaenia can be occasionally associated with clinical worsening, due to recovery of the inflammatory response. Late complications such as perforation, bleeding or abscess formation may occur after recovery from neutropaenia.

Table 4 Manifestations of Abdominal Infections in Neutropaenic Patients

Clinical findings	<ul style="list-style-type: none"> ■ Fever ■ Protracted diarrhoea (watery or bloody) ■ Vague abdominal pain ■ Progressive abdominal distension ■ Nausea and vomiting ■ Intestinal bleeding
Physical findings (may vary depending on severity, location and presence or absence of complications)	<ul style="list-style-type: none"> ■ Abdominal distension ■ Tenderness in right lower abdomen ■ Mass in right lower abdomen ■ Hypoactive bowel sounds ■ Tympanic abdomen
Warning signs suggesting perforation and peritonitis	<ul style="list-style-type: none"> ■ Rebound tenderness ■ Rigidity ■ "Silent" abdomen ■ Hypotension ■ Clinical deterioration despite optimal therapy

Diagnosis

To establish the exact diagnosis in neutropaenic patients with fever and abdominal symptoms continues to be challenging. Only an awareness and suspicion in the minds of physicians in high-risk patients can lead to early diagnosis and effective treatment (Tables 5–9).

Occasionally two or more entities may be concomitantly present in neutropaenic patients, such as NEC and CDAD, proven by stool polymerase chain reaction (PCR) positivity for *C. difficile* toxin in patients with NEC.

Colonoscopy or sigmoidoscopy is usually **contraindicated** in neutropaenic patients, as air inflations and manipulation of the endoscope may result in bleeding and gut perforation. Endoscopic evaluation may also increase the risk of bacterial translocation and exacerbate septicaemia, due to mechanically induced trauma of fragile mucosa. Moreover, pseudomembrane formation requires neutrophil involvement, so that the typical mac-

roscopic and microscopic appearances may be absent or altered in neutropaenic patients. Targeted treatment for *C. difficile* should be promptly initiated in the case of high suspicion of concurrent CDAD, with regard to the high risk of early progression to fulminant toxic megacolon.

Table 5 Pitfalls of Neutropaenia

- Poor localisation of infection
- Often minimal physical signs despite the presence of severe infection
- Non-specific manifestation of abdominal infection
- Rapid progression to fulminant sepsis
- Worsening at the time of recovery from neutropaenia

Table 6 Differential Diagnosis in Neutropaenic Patients with Fever and Abdominal Symptoms

- NEC
- CDAD and colitis
- Acute GVHD
- Appendicitis
- Diverticulitis
- Ischaemic colitis
- Cholecystitis
- Pancreatitis (L-asparaginase-induced, or other causes)
- Vincristine-induced ileus
- CMV colitis

CDAD, *Clostridium difficile*-associated diarrhoea; CMV, cytomegalovirus; GVHD, graft-versus-host disease; NEC, neutropaenic enterocolitis.

Table 7 Diagnostic Criteria for NEC.

Adapted with permission of John Wiley & Sons, from: Gorschlüter M, Mey U, Strehl J, et al. Neutropenic enterocolitis in adults: systematic analysis of evidence quality. *Eur J Haematol* 2005; 75:1–13; permission conveyed through Copyright Clearance Center Inc.

Type of criteria	Findings	Remarks
Major	<ul style="list-style-type: none"> ■ Neutropaenia ■ Bowel wall thickening on US exam or CT scan ■ Fever (minority of patients may be hypothermic) 	<ul style="list-style-type: none"> ■ ANC <500 × 10⁹ cells/l ■ 4 mm (transverse scan) in any bowel segment for at least 30 mm length (longitudinal scan) ■ 38°C axillar temperature or >38.5°C rectal temperature
Minor	<ul style="list-style-type: none"> ■ Abdominal pain ■ Abdominal distension ■ Abdominal cramping ■ Diarrhoea ■ Lower gastrointestinal bleeding 	<ul style="list-style-type: none"> ■ >3 on a visual analogue scale pain score (1–10) ■ Watery or bloody

ANC, Absolute neutrophil count; CT, computed tomography; US, ultrasonography.

Table 8 Recommended Tests in Neutropaenic Patients with Fever and Abdominal Pain

Investigation	Utility
Full blood count	<ul style="list-style-type: none">■ Neutropaenia■ Correction of thrombocytopenia■ Anaemia, suspicion of bleeding
Coagulation studies	<ul style="list-style-type: none">■ Correction of coagulopathy
Chemistry panel	<ul style="list-style-type: none">■ Monitoring of renal and hepatic function■ Correction of electrolyte imbalance
<i>C. difficile</i> toxin or PCR assay	<ul style="list-style-type: none">■ To rule out / confirm CDAD
Blood cultures	<ul style="list-style-type: none">■ Positive in 28%–84% of cases■ Bowel bacteria being most frequently isolated■ Targeted antibiotic treatment
US examination	<ul style="list-style-type: none">■ Daily monitoring of progression/reduction of bowel wall thickening■ Pericolic fluid collection■ Pseudopolypoid changes of caecal mucosa■ To monitor bowel peristalsis■ Feasible also in patients with renal insufficiency
CT abdominal scan	<ul style="list-style-type: none">■ Wall thickening of >4 mm, intestinal pneumatosis, right-sided colon involvement are suggestive of NEC■ Greatest wall thickening (> 12 mm), wall nodularity, always limited to the colon (mostly pancolitis) are suggestive of CDAD■ Least wall thickening, pronounced bowel dilatation and mucosal enhancement in patient after HSCT are suggestive of acute GVHD
Abdominal plain X-ray	<ul style="list-style-type: none">■ Limited role, non-specific findings■ Right lower quadrant soft tissue density or mass■ Fluid-filled caecum, bowel dilatation■ Free air in the intraperitoneal cavity
Chest X-ray or CT chest scan	<ul style="list-style-type: none">■ Pleural effusion■ To rule out/identify pneumonia and pulmonary infiltrates

CDAD, *Clostridium difficile*-associated diarrhoea; CT, computed tomography; GVHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; NEC, neutropaenic enterocolitis; PCR, polymerase chain reaction; US, ultrasonography.

Table 9 CT Bowel Abnormalities in Patients with NEC, CDAD and Acute GVHD.

Adapted from: Kirkpatrick ID, Greenberg HM. Gastrointestinal complications in the neutropenic patient: characterization and differentiation with abdominal CT. *Radiology* 2003; 226:668–674.

CT findings	Neutropaenic enterocolitis	<i>C. difficile</i> colitis	Acute GVHD
Wall thickening	100% Mean 7 mm (4–15 mm)	100% Mean 12 mm (8–20 mm)	86% Mean 5 mm (3–7 mm)
Wall nodularity	2%	36%	0%
Mucosal enhancement	28%	18%	71%
Pneumatosis	21%	0%	0%
Bowel dilatation	38%	14%	86%
Ascites	43%	57%	28%
Localisation	Right-sided colon Both large and small bowel could be involved	Mostly pancolitis Always limited to colon	Any segment of small and large bowel could be involved

CDAD, *Clostridium difficile*-associated diarrhoea; CT, computed tomography; GVHD, graft-versus-host disease; NEC, neutropaenic enterocolitis.

Management

The optimal treatment of patients with NEC is still controversial, due to the lack of prospective or randomised trials addressing management. Consequently most clinicians follow the guidelines for febrile neutropaenia.

Conservative management is recommended initially (Table 10) when criteria for surgical intervention are absent (Table 11). Recovery from neutropaenia is essential for healing of mucosal injury. Persistent bacterial invasion of the bowel mucosa, increasing size of bowel injury, bleeding and possible perforation may result in failure of haematological recovery, and are associated with a high mortality rate. Aggressive and complex conservative therapy initiated without delay is crucial for a favourable outcome.

Table 10 Supportive Measures In Patients with NEC

Measures	
Broad-spectrum antibiotics	<ul style="list-style-type: none"> ■ Monotherapy with carbapenem or piperacillin–tazobactam ■ Combination with aminoglycoside in patients with septic shock and severe sepsis should be considered ■ Prompt initiation of therapy for <i>C. difficile</i> when CDAD cannot be excluded (i.v. metronidazole or oral vancomycin or oral fidaxomicin)
Empirical antifungal therapy	<ul style="list-style-type: none"> ■ Recommended when fever persists after 72–96 hours of potent antibacterial therapy
Granulocyte colony-stimulating factor (G-CSF)	<ul style="list-style-type: none"> ■ Careful consideration of risk and benefit ■ The routine use of G-CSF in neutropaenic patients with sepsis is not recommended (risk of respiratory deterioration with ARDS, due to G-CSF-induced recovery)
Intravenous fluid support	<ul style="list-style-type: none"> ■ Principally crystalloid fluids
Vasopressor (norepinephrine)	<ul style="list-style-type: none"> ■ If a sufficient mean arterial pressure (>65 mmHg) cannot be achieved by aggressive fluid resuscitation
Correction of coagulopathy	<ul style="list-style-type: none"> ■ Platelet transfusions ■ Fresh frozen plasma and cryoprecipitate
Parenteral nutrition	<ul style="list-style-type: none"> ■ In patients with severe form of NEC, CDAD or NG
Bowel rest	<ul style="list-style-type: none"> ■ In patients with severe form of NEC, CDAD or NG
Nasogastric suction	<ul style="list-style-type: none"> ■ Routine use is not recommended ■ Use in selected cases with vomitus and ileus
Omeprazole	<ul style="list-style-type: none"> ■ Routine use has been questioned (risk of migration of Gram-negative bacteria from bowel to respiratory tract, may increase risk of pneumonia) ■ Use in patients with epigastric pain, gastritis, known gastric ulcers, NG
Antidiarrhoeals, anticholinergics	<ul style="list-style-type: none"> ■ Should be avoided

ARDS, Acute respiratory distress syndrome; CDAD, *Clostridium difficile*-associated diarrhoea; i.v., intravenous; NEC, neutropaenic enterocolitis; NG, necrotising gastritis.

Table 11 Criteria for Urgent Surgical Intervention

1. Persistence of gastrointestinal bleeding despite correction of coagulopathy and thrombocytopenia
2. Free air in the intraperitoneal cavity, indicative of bowel perforation
3. Clinical deterioration despite optimal treatment (uncontrolled sepsis based on requirement for large volumes of fluid and vasopressors)
4. Development of intra-abdominal process that requires surgical intervention after recovery from neutropaenia

Conclusion

Abdominal infections remain a major clinical challenge in terms of diagnosis and management. Given the widespread, aggressive use of systemic chemotherapy in the treatment of various malignancies, patients at risk for these potentially lethal complications are increasingly common. Clinicians treating haematological malignancies and also solid tumours with agents causing mucosal injury should consider NEC and other possible abdominal infections in neutropaenic patients with fever and abdominal symptoms. Even with appropriate therapy, the mortality remains high. A high level of clinical suspicion, early recognition and immediate comprehensive conservative therapy are crucial for a favourable outcome.

Declaration of Interest:

Dr Ballová has reported no conflicts of interest.

Further Reading

- Carrion AF, Hosein PJ, Cooper EM, et al. Severe colitis associated with docetaxel use: A report of four cases. *World J Gastrointest Oncol* 2010; 2:390–394.
- Gorschlüter M, Mey U, Strehl J, et al. Neutropenic enterocolitis in adults: systematic analysis of evidence quality. *Eur J Haematol* 2005; 75:1–13.
- Junpaparp P, Buppajarntham S, Madueno FV, Varadi G. Concomitant typhlitis and *Clostridium difficile* colitis developed after first R-CHOP chemotherapy in a non-Hodgkin lymphoma patient. *BMJ Case Rep* 2013. doi: 10.1136/bcr-2013-008894.
- Kirkpatrick ID, Greenberg HM. Gastrointestinal complications in the neutropenic patient: characterization and differentiation with abdominal CT. *Radiology* 2003; 226:668–674.
- Machado NO. Neutropenic enterocolitis: A continuing medical and surgical challenge. *N Am J Med Sci* 2010; 2:293–300.
- Mehdi I, Al Bahrani B. Chemotherapy-induced neutropenic necrotizing enterocolitis: A review. *J Pak Med Assoc* 2012; 62:718–723.
- Nesher L, Rolston KVI. Neutropenic enterocolitis, a growing concern in the era of widespread use of aggressive chemotherapy. *Clin Infect Dis* 2013; 56:711–717.
- Zafrani L, Azoulay E. How to treat severe infections in critically ill neutropenic patients? *BMC Infect Dis* 2014; 14:512.

VII - Immune- haematological emergencies



Anaemia in Cancer

20

T. Troiani

Faculty of Medicine, Second University of Naples, Naples, Italy

Introduction

Anaemia is defined as a reduction of the haemoglobin (Hb) concentration, red cell count or packed cell volume below normal levels. The degree of anaemia can be graded by considering the Hb level according to the anaemia scale provided by the National Cancer Institute (NCI)–Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Table 1).

Anaemia is a frequent syndrome in cancer patients. It has a negative influence on the quality of life (QoL) of cancer patients, as it may contribute to cancer-induced fatigue. Moreover, it is identified as a negative prognostic factor for overall survival in most types of cancer.

Table 1 NCI-CTCAE v4.03 Anaemia Scale.

Adapted from: Common Terminology Criteria for Adverse Events (CTCAE), v4.03. U.S. Department of Health and Human Services.

Grade	NCI (haemoglobin level in g/dl)
Grade 0 (within normal limits)	Within normal limits
Grade 1 (mild)	10.0 – lower limit of normal (LLN)
Grade 2 (moderate)	8.0 – <10.0
Grade 3 (severe)	<8.0
Grade 4 (life-threatening)	Life-threatening
Grade 5 (death)	Death

NCI, National Cancer Institute.

Aetiology

The pathogenesis of cancer-related anaemia is multifactorial, and is usually due to underlying malignancy and/or cancer therapy. Although patients may have several contributing factors for anaemia, the aetiology

of cancer-related anaemia can always be tracked back to the production, destruction or loss of red blood cells (RBCs).

Anaemia of Chronic Disease

The most common cause of anaemia in cancer is the so-called anaemia of chronic disease (ACD), characterised by a normocytic, normochromic and hypo-regenerative anaemia with decreased serum iron and transferrin saturation (<20%), and normal or increased ferritin levels.

Chemotherapy- and/or Radiotherapy-induced Anaemia

Chemotherapeutic agents induce anaemia by directly impairing haematopoiesis in the bone marrow, including disruption of RBC precursor synthesis. Nephrotoxic effects of particular cytotoxic agents can also lead to anaemia through decreased production of erythropoietin by the kidney.

Localised radiotherapy is often associated with only mild anaemia, but radiotherapy to extended fields frequently causes anaemia or aggravates pre-existing anaemia.

Other Cancer-related Causes of Anaemia

Apart from ACD, complications of cancer such as bleeding, haemolysis, splenomegaly, disseminated intravascular coagulation (DIC), bone marrow fibrosis or tumour infiltration, hypervolaemia, infections and cachexia can lead to anaemia in patients with cancer.

Non-cancer-related Causes of Anaemia

Anaemia in cancer may also be caused by factors not directly related to the disease or its treatment. Among these, vitamin B12 deficiency, folate and iron deficiency, thalassaemia, as well as endocrine and renal dysfunction are most frequent.

Evaluation

As discussed previously, anaemia in cancer patients is the result of a combination of causes, some of which may not be directly related to the cancer. The overall goals of evaluation are to characterise the anaemia

and identify any underlying comorbidity that can potentially be corrected prior to initiating treatment.

Initial Assessment

Initial broad characterisation of anaemia involves:

- *Complete blood count (CBC)*, which will reveal if other cytopaenias are present
- *Peripheral blood smear*: This is critical to confirm the size, shape and colour of RBCs
- *Detailed history*: This should include the onset and duration of symptoms, comorbidities, family history, and whether there has been any exposure to antineoplastic drugs and radiation
- *Physical examination*: Anaemia can cause symptoms and signs in many organ systems:
 - **Heart**: The typical cardiovascular symptoms of anaemia comprise fatigue, shortness of breath and palpitations, particularly during and following exercise
 - **Lung**: An increase in the respiratory rate in order to elevate blood oxygenation is a further important compensatory mechanism in anaemia
 - **Kidney**: Renal perfusion decreases with increasing anaemia, and this may result in fluid retention, hypervolaemia, oedema and cardiac decompensation
 - **Gastrointestinal tract**: Clinically, nausea and anorexia and, in advanced anaemia, malabsorption may ensue
 - **Skin**: A cardinal symptom of anaemia is the pallor of mucous membranes, particularly of the mouth and pharynx, the conjunctivae, the lips and nail beds. Other changes of the skin include pale palms, reduced skin elasticity and broken nails
 - **Brain**: Impaired cerebral perfusion may lead to neurological symptoms such as vertigo, dizziness, tinnitus and headache
 - **Genitourinary tract**: Symptoms may extend from menorrhagia, irregular menstrual cycles and amenorrhea, mainly caused by

impaired secretion of sexual hormones, to the loss of libido; impotence in men.

Approaches to Evaluation

There are two initial common approaches to evaluating anaemia: morphological and kinetic. A complete evaluation often utilises both.

The morphological approach is a characterisation of anaemia by the mean corpuscular volume (MCV), or average RBC size, reported in the initial CBC test, and categorised as follows:

- *Microcytic (<80 fl)*: Most commonly caused by iron deficiency; other aetiologies include thalassaemia, ACD and sideroblastic anaemia
- *Macrocytic (>100 fl)*: Most common causes of macrocytosis are medications and alcoholism, both of which are forms of non-megaloblastic anaemia. In megaloblastic anaemia, macrocytosis is most frequently caused by B12/folate deficiency
- *Normocytic (80–100 fl)*: May be due to haemorrhage, haemolysis, bone marrow failure, anaemia of chronic inflammation or renal insufficiency. The key follow-up test is the reticulocyte (immature RBC) count.

The kinetic approach focuses on the underlying mechanism of anaemia, distinguishing between the production, destruction and loss of RBCs. The most basic RBC index is the reticulocyte index (RI), which corrects the reticulocyte count for the degree of anaemia, as measured by the haematocrit (Hct) value. The reticulocyte count reflects the number of reticulocytes per total number of RBCs, and is an indicator of the RBC production capacity by the bone marrow.

After these initial analyses, forthcoming informative diagnostic tests are as follows:

- *Nutritional deficiency*: Low iron and total iron-binding capacity (TIBC) and/or low vitamin B12 or folate levels (commonly tested together with iron studies)
- *Haemorrhage*: Stool guaiac positive, endoscopy findings

- *Haemolysis*: Coombs' test positive, DIC panel positive, low haptoglobin levels, elevated indirect bilirubin, elevated lactate dehydrogenase (LDH)
- *Renal dysfunction*: Glomerular filtration rate <60 ml/min/1.73 m² for ≥ 3 consecutive months, low erythropoietin level.

Treatment

Blood Transfusions

Indications

Transfusion of packed RBCs offers a rapid increase in Hb and Hct levels, and is hence the only intervention option in patients requiring rapid correction of anaemia. Transfusion of 1 unit of packed RBCs has been estimated to result in an increase in Hb level of 1 g/dl in a normal-sized adult. RBC transfusions are recommended when Hb levels are ≤ 8 g/dl. However, the decision to offer packed RBC transfusion should not be made strictly on the basis of whether the Hb level has reached a certain threshold, but should also take into consideration whether or not the patient is symptomatic and if he/she has comorbidities.

In particular, the clinical manifestations of anaemia are associated with its onset, severity and duration. When anaemia onset is acute, symptoms are likely to be more pronounced, whereas physiological adjustments to compensate for the lower oxygen-carrying capacity of the blood can occur with a gradual onset of anaemia. These adaptive measures include heightened cardiac output, increased coronary flow, altered blood viscosity, and changes in oxygen consumption and extraction. For these reasons, the presence of pre-existing cardiovascular, pulmonary or cerebrovascular disease may compromise the ability of a patient to tolerate anaemia.

Limitations

The main limitation of packed RBC transfusion is that, although it leads to an increase in Hb level in almost all patients, this effect is transient and lasts only two weeks, therefore requiring further transfusions. Moreover, there are several risks associated with blood cell transfusions, including:

- *Transfusion-related reactions:* Transfusions lead to febrile reactions in up to 10% of patients, sometimes accompanied by chills, headache and malaise. Leukoreduction has been shown to reduce the incidence of febrile non-haemolytic transfusion reaction. There is no evidence to support routine premedication with acetaminophen or antihistamine to prevent allergic and febrile non-haemolytic transfusion reactions. However, if repeated transfusions are required, leukocyte-reduced blood and the use of premedication may minimise adverse transfusion reactions.
- *Bacterial contamination and viral infections:* The introduction of numerous safety interventions to screen the blood supply for infectious organisms has dramatically decreased the risk of transfusion-transmitted infections.
- *Iron overload:* The condition of transfusion-related iron overload is observed in patients requiring frequent transfusions over several years to manage their anaemia. However, iron overload is unlikely to occur in patients receiving transfusions that are restricted to the limited time period corresponding to chemotherapy treatment (usually <1 year).
- *Congestive heart failure:* Due to the transient improvement in Hb, further transfusions will be required after a few weeks. This leads to varying Hb levels that may impair the physiological compensatory mechanisms to anaemia, e.g. an increase in cardiac output.
- *Venous and arterial thromboembolism:* A recent study conducted in 60 US medical centres between 1995 and 2003 found an increased risk of venous and arterial thromboembolism and mortality associated with packed RBC transfusion (Khorana et al, 2008).

Advantages

RBC transfusions are the only treatment delivering a rapid relief of symptoms in severely anaemic patients. If a patient suffers from dyspnoea or fatigue, the administration of transfusions prior to the start of erythropoietin treatment should be considered. Furthermore, treatment with erythropoietic agents is ineffective in about 30%–40% of cancer

patients. In these patients, RBC transfusions should be used for the correction of anaemia.

Erythropoietic Agents

Erythropoietin (EPO) is an endogenous hormone produced by the kidneys, which, by binding to the erythropoietin receptor on erythroid colony-forming units, regulates erythropoiesis. Since 1985, recombinant human erythropoietin has been available for use in anaemic patients.

Erythropoietin-alpha and subsequently, a few years later, *erythropoietin-beta* were the first EPOs introduced into the clinic. Numerous studies were conducted in patients with haematological malignancies and solid tumours, showing the effectiveness of both EPOs in improving Hb levels and symptoms of anaemia and decreasing the need for RBC transfusions.

Darbepoetin-alpha is a hyperglycosylated derivative of epoetin that stimulates erythropoiesis by the same mechanism as the endogenous hormone. These different glycosylation patterns result in a three-fold longer serum half-life and greater biological activity for darbepoetin compared with its predecessor.

Continuous erythropoiesis receptor activator (CERA) is a new class of third-generation erythropoiesis-stimulating agents (ESAs) with a prolonged serum half-life. In terms of structure, CERA is similar to the previous synthetic EPO drugs, except that it is related to a chemical called polyethylene glycol (PEG), which makes it persist longer in the body. In preclinical studies and studies in healthy subjects, CERA had a lower systemic clearance and an increased elimination half-life compared with conventional ESAs and a superior potency in vivo with respect to the magnitude and duration of response (Macdougall et al, 2006).

With the expiration of patent protection on European epoetin alfa, *bio-similar EPOs* have been approved for prescription in European countries since 2007. Currently, there are several brand-name biosimilar EPOs marketed across Europe by various license holders; however, these products comprise only two of the EPOs produced by two manufacturers: epoetin alfa and epoetin zeta. Clinical trials demonstrated that treatment with the biosimilar epoetin molecules increased and maintained Hb

concentration in patients to a similar extent as the reference product, and that the proportions of patients achieving and maintaining target Hb concentrations were comparable as well.

Indications

ESAs are indicated to treat anaemia in patients with cancer receiving concomitant myelosuppressive chemotherapy. The aim is to prevent RBC transfusions and their possible complications, and to improve health-related QoL by increasing Hb levels. American Society of Clinical Oncology (ASCO) guidelines recommend the use of ESAs, as shown in Table 2.

Table 2 Dose Modifications for Subcutaneous Epoetin Alpha and Beta and Darbepoetin-Alpha

Agent	Erythropoietin	Darbepoetin-alpha
Treatment indications	Hb \leq 10 g/dl OR Hb \leq 12 g/dl AND symptoms of anaemia	Hb \leq 10 g/dl OR Hb \leq 12 g/dl AND symptoms of anaemia
Starting dose	10 000 IU \times 3/week OR 30 000–40 000 IU/week \rightarrow target Hb = 12 g/dl	2.25 μ g/kg once weekly \rightarrow target Hb = 12 g/dl
Dose increase	20 000 IU \times 3/week OR 60 000 IU/week \rightarrow stop if not successful	Increase dose by 50% \rightarrow stop if not successful
Dose reduction	If Hb $>$ 12 g/dl OR If Hb rise $>$ 2 g/dl/4 weeks: decrease dose by 25%–50%	

Hb, haemoglobin.

- In patients treated with chemotherapy and with an Hb level \leq 10 g/dl, treatment with ESAs may be considered to increase Hb to $<$ 12 g/dl or to prevent further decline in Hb.
- Treatment should also be considered at higher Hb levels (\leq 12 g/dl) if the patient suffers from symptoms of anaemia.

The standard dose of epoetin (10 000 IU 3 times a week or 30 000–40 000 IU weekly) should be customised to a target Hb value of 12 g/dl. This means that if no response is noted after 4 weeks, the dose should be increased to 20 000 IU 3 times a week or 60 000 IU weekly; if there is still no response at these dose levels, therapy with EPO should be discontinued. This is also the case if an Hb level $>$ 14 g/dl is reached, but in

these patients EPO treatment should be restarted at a lower dose if the Hb level falls below 12 g/dl again.

The recommended dose for darbepoetin is 2.25 µg/kg/week. Several trials have shown that longer treatment intervals up to 3 weeks may be feasible with higher darbepoetin doses. In cases of no or insufficient response in the initial treatment phase, dose increments of 50% should be used, as in EPO treatment.

Limitations

The most important disadvantages of EPO compared to RBC transfusions are the long time interval until Hb level is improved, and the fact that not all patients respond to treatment. Other risks include:

- *Thromboembolic events:* Increased thromboembolic risks have been associated with ESA treatment of patients with cancer. The risk of thromboembolic events in patients with cancer is increased by several conditions such as prior history of venous thromboembolism (VTE), heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, recent surgery, hormonal agents and prolonged inactivity by hospitalisation. The use of ESAs should be carefully considered in these patients and treatment with low molecular weight heparin or oral anticoagulants may be indicated in selected cases.
- *Hypertension/seizures:* An increased risk for hypertension in cancer patients using ESA has been reported. Moreover an increased incidence of seizures in patients on dialysis during the first 90 days of therapy has been described.
- *Mortality and tumour progression:* The relationship between increased mortality and ESA therapy has been evaluated in several meta-analyses, and no statistically significant effect of ESAs on mortality or progression has been demonstrated so far.
- *Allergic reactions:* Other side effects of ESAs are rare allergic reactions, including dyspnoea, skin rash and urticaria, arthralgia, peripheral oedema, and mild and transient injection site pain.

Advantages

The major advantage of the use of EPO for treating anaemia is an increase of Hb levels and elimination or reduction of RBC transfusion requirements. It has been demonstrated that the need for transfusions can be totally abrogated in only 1 out of 3–4 patients treated with EPO, whereas the Hb level is increased in 50%–70% of patients. Moreover, some studies have shown that the use of ESAs improves QoL and reduces fatigue. In addition to the known benefits, a meta-analysis showed a potential survival benefit and improved tumour response from the use of ESAs in patients with cancer receiving chemotherapy (Bohlius et al, 2006).

Iron Supplementation

In anaemic patients treated with erythropoietic agents, functional iron deficiency is a major predictive factor. Patients suffering from iron deficiency, which is defined as a ferritin level below 30 ng/ml and a transferrin saturation (TSAT) level below 20%, should be offered iron supplementation. Although intravenous (i.v.) iron is preferred, either i.v. or oral iron products alone (without an ESA) are recommended for patients with cancer who develop absolute iron deficiency. A ferritin level between 30 and 100 ng/ml and a concurrent TSAT level between 20% and 50% indicate adequate iron stores, unless the patient is receiving an ESA. Patients receiving ESA therapy with a ferritin level between 30 and 100 ng/ml and a TSAT level between 20% and 50% will develop functional iron deficiency and will likely benefit from i.v. iron.

Conclusion

Anaemia is a common condition in cancer patients. Although anaemia can be easily corrected by administering blood transfusions, these are associated with several side effects and risks, and their impact on Hb level is transient. In 50%–70% of cancer patients, anaemia can be treated more effectively with erythropoietic agents. In most patients, treatment with erythropoietic agents leads to a stable improvement in Hb levels, QoL and functional capacity.

Declaration of Interest:

Dr Troiani has reported no conflicts of interest.

Further Reading

- Aapro M, Österborg A, Gascón P, et al. Prevalence and management of cancer-related anaemia, iron deficiency and the specific role of i.v. iron. *Ann Oncol* 2012; 23:1954–1962.
- Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst* 2006; 98:708–714.
- Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010). U.S. Department of Health and Human Services. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Last accessed 20 January 2016.
- Gilreath JA, Stenehjem DD, Rodgers GM. Diagnosis and treatment of cancer-related anemia. *Am J Hematol* 2014; 89:203–212.
- Glaspy J, Crawford J, Vansteenkiste J, et al. Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes. *Br J Cancer* 2010; 102:301-315.
- Khorana AA, Francis CW, Blumberg N, et al. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. *Arch Intern Med* 2008; 168:2377–2381.
- Macdougall IC, Robson R, Opatrna S, et al. Pharmacokinetics and pharmacodynamics of intravenous and subcutaneous continuous erythropoietin receptor activator (C.E.R.A.) in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2006; 1:1211–1215.
- Ohashi Y, Uemura Y, Fujisaka Y, et al. Meta-analysis of epoetin beta and darbepoetin alfa treatment for chemotherapy-induced anemia and mortality: Individual patient data from Japanese randomized, placebo-controlled trials. *Cancer Sci* 2013; 104:481–485.

Febrile Neutropaenia in Cancer Patients

21

M. Alonso

J. Corral

Medical Oncology Department, University Hospital Virgen del Rocío, Seville, Spain

Aetiology and Epidemiology

Cancer patients are at increased risk for infection, as a consequence of immune function impairment and loss of barrier integrity, related to both their underlying malignancy and the toxic effects of anticancer therapy. The association of neutropaenia and infection continues to be the commonest life-threatening complication of chemotherapy and a major cause of morbidity and mortality in this patient population.

Approximately 10%–50% of patients with solid tumours and >80% of those with haematological malignancies will develop fever associated with neutropaenia during ≥ 1 chemotherapy cycle. The degree and duration of neutropaenia closely correlate with the risk of serious infectious complications. It is important that physicians are keenly aware of the infection risks and the antimicrobial therapies required for the correct management of febrile patients through the neutropaenic period.

Clinically documented infections occur in 20%–30% of febrile episodes; common sites of tissue-based infection include the intestinal tract, lung and skin. However, up to 20% of febrile patients with neutrophil counts below $500/\text{mm}^3$ present bacteraemia, with most episodes occurring in the setting of prolonged or profound neutropaenia (absolute neutrophil count [ANC] <100 neutrophils/ mm^3).

Clinical variations among patients play a critical role in identifying which patients require antibiotics during the risk period of neutropaenia. We can describe fever and neutropaenia as follows:

- **Fever:** defined as a single oral temperature measurement of $\geq 38.3^{\circ}\text{C}$ or a temperature of $\geq 38.0^{\circ}\text{C}$ sustained over a 1-hour period.
- **Neutropaenia:** defined as an ANC of < 500 cells/ mm^3 , or an ANC expected to decrease to < 500 cells/ mm^3 during the next 48 hours.

The major pathogens causing infection in neutropaenic patients are predominantly bacteria and fungi that normally colonise the body surfaces. Viral and parasitic infections are much less common, and usually develop in patients with a greater degree of myelosuppression. Gram-positive microorganisms have emerged as the predominant pathogens, being responsible for up to two-thirds of bacteraemia documented in neutropaenic patients. The two major Gram-positive bacteria accounting for this change are coagulase-negative staphylococci, mainly associated with the widespread use of indwelling intravascular catheters, and viridans streptococci, particularly in patients receiving prophylaxis with quinolones, or with substantial mucosal damage from chemotherapy.

Initial Assessment and Investigations

Predominant sites of infection largely depend upon the location and size of the tumour and the site and nature of medical devices and surgical procedures. However, signs and symptoms of infection may be subtle, due to the diminished inflammatory response associated with myelosuppression, and fever is often the only presenting sign.

Even a meticulous initial evaluation is able to identify the source of infection in only one-third of patients. A detailed history should be taken, including the nature of the chemotherapy given, recent surgical procedures, prior prophylactic antibiotics, concomitant steroid use and presence of allergies. It is also important to check the clinical record for past positive microbiology, in order to guide therapy, in particular the previous existence of antibiotic-resistant organisms or bacteraemia.

Laboratory tests should include a complete blood cell count (CBC) with differential leukocyte count and platelet count, measurement of serum levels of creatinine and blood urea nitrogen, and measurement of electrolytes, hepatic transaminase enzymes and total bilirubin. At least two sets

of blood cultures are recommended, with a set collected simultaneously from each lumen of an existing central venous catheter (CVC), if present, and from a peripheral vein site; two blood culture sets from separate venepunctures should be sent, if no central catheter is present. Culture specimens from other sites of suspected infection should be obtained as clinically indicated.

Radiological diagnostic tests must be applied based on the suspected site of infection: chest X-ray or computed tomography (CT) scan in cases of respiratory signs or symptoms; abdominal ultrasound or CT with or without urine culture or analysis in cases of abdomen abnormalities, etc.

Risk Factors/Risk Groups

Risk assessment should be performed as part of the initial evaluation, allowing the likelihood of serious complications and death during the febrile episode to be determined, and to initiate the empirical treatment.

The Multinational Association of Supportive Care in Cancer (MASCC) has developed an internationally validated numeric risk index scoring system to identify low-risk febrile neutropaenic cancer patients, based on a prospective study that included 1351 patients from 20 institutions in 15 countries (Table 1). A MASCC risk-index score ≥ 21 identified low-risk patients with a positive predictive value of 91%, a specificity of 68%, and a sensitivity of 71%. Patients can be classified into high/low risk by this scoring system.

Low-risk Patients

Low-risk patients are those with neutropaenia expected to resolve within 7 days and no active medical comorbidity, as well as stable and adequate hepatic and renal function. This patient profile has a MASCC score ≥ 21 . These low-risk features are most commonly found among patients with solid tumours, although not exclusively so. In general, any patient who does not strictly fulfil criteria for being at low risk should be treated according to the guidelines for high-risk patients.

Table 1 MASCC Scoring Index.

Adapted with permission of Springer-Verlag, from: Innes H, Lim SL, Hall A, et al. Management of febrile neutropenia in solid tumours and lymphomas using a Multinational Association for Supportive Care in Cancer (MASCC) risk index: feasibility and safety in routine clinical practice. *Support Care Cancer* 2008; 16:485–491; permission conveyed through Copyright Clearance Center Inc.

Characteristic	Score
Burden of illness: no or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP >90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age <60 years	2

Scores ≥ 21 are at low risk of complications. Score < 21 defines high-risk patients

BP; blood pressure; MASCC, Multinational Association of Supportive Care in Cancer

High-risk Patients

Patients are considered to be at high risk for serious complications during fever and neutropaenia, and are recommended to initially receive intravenous (i.v.) empirical antibiotic therapy in the hospital, if they have any of the following criteria:

- MASCC score < 21
- Profound neutropaenia ($ANC \leq 100$ cells/mm³) expected to last > 7 days
- Presence of any comorbid medical problems, including but not limited to:
 - Haemodynamic instability
 - Oral or gastrointestinal mucositis that interferes with swallowing or causes diarrhoea
 - Gastrointestinal symptoms, including abdominal pain, nausea and vomiting
 - Neurological or mental status changes of new onset
 - Intravascular catheter infection, especially catheter tunnel infection
 - New pulmonary infiltrate or hypoxaemia, or underlying chronic lung disease

- Evidence of hepatic insufficiency (defined as aminotransferase levels $>5\times$ normal values) or renal insufficiency (defined as a creatinine clearance <30 ml/min)

It is important to note that the duration of neutropaenia is not included as a criterion for risk in the MASCC assessment scheme, but we think it to be an important determinant. In the initial multivariate analysis that led to the development of the MASCC criteria, longer neutropaenia duration was not found to be a significant risk factor for poor outcome. Patients receiving autologous haematopoietic stem cell transplantation (HSCT) or consolidation therapy for leukaemia may also have prolonged neutropaenic periods, but appear to be at somewhat lower risk for serious infections (Hämäläinen et al, 2008). If these patients attain a MASCC score that predicts low risk, it may be reasonable to prescribe antimicrobial management accordingly.

Treatment

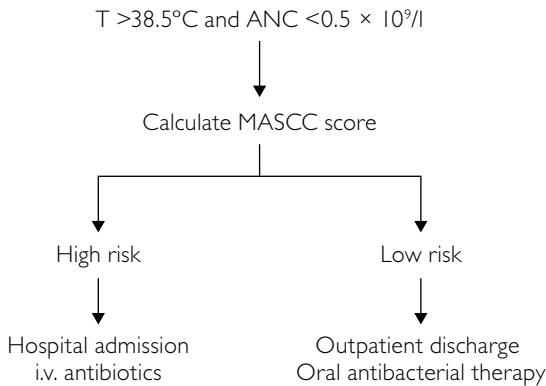
Low-risk Patients

Some patients classified as low risk in their initial evaluation of febrile neutropaenia (FN) can be treated with oral outpatient treatment (Figure 1). In patients who are haemodynamically stable, with no evidence of organ failure, without respiratory failure or local infection (especially those who are carriers of nephrostomies or CVCs), single-agent quinolones are not inferior to combinations (quinolone with amoxicillin plus clavulanic acid), but combinations are preferred given the rise in Gram-positive FN episodes.

Oral quinolone therapy should not be used in patients who have taken a quinolone antibacterial as prophylaxis. Early change to oral combinations in afebrile patients after 48 hours on i.v. therapy is the preferred option for the majority of physicians. It is necessary, in patients who are managed under close clinical and analytical control in outpatient oncology every 48 hours, to check the good progression of the patient and the proper effectiveness of treatment, and to resolve promptly the possible complications that may arise.

The possibility of exclusively oral outpatient management for low-risk FN cases has become increasingly appealing on the grounds of patient

convenience, economy and reduction in the incidence of nosocomial infections, but is unsupported by high-level evidence. Furthermore, only large series have reported outcomes similar to those of patients treated conventionally, but approximately 20% of cases required later re-admission. There is, however, evidence to support an early discharge policy in these low-risk cases once they have become clinically stable, symptomatically better and with evidence of fever lysis after a minimum of 24 hours in hospital.



ANC, Absolute neutrophil count; i.v., intravenous; MASCC, Multinational Association for Supportive Care in Cancer; T, temperature.

Figure 1 Initial management of febrile neutropenia.

Adapted from: de Naurois J, Novitzky-Basso I, Gill MJ, et al. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. *Ann Oncol* 2010; 21 Suppl 5:v252–v256. By permission of Oxford University Press.

High-risk Patients

Patients with FN who are at high risk as assessed by the MASCC criteria, or have high-risk features, should be admitted and treated with broad-spectrum i.v. antibiotics.

Knowledge of the local bacterial isolates and resistance patterns is crucially important in determining first-choice empirical therapy, since coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) or resistant Gram-negative bacteria may be required. The standard treatment for Gram-negative bacteria and MRSA is carbapenem, cephalosporin or

antipseudomonal penicillin (not ceftazidime, due to its low efficiency to cover Gram-positive bacteria) (Furno et al, 2002).

In clinically unstable patients with septic shock, respiratory distress or previous history of colonisation by *Pseudomonas aeruginosa*, the combination of an antipseudomonal beta-lactam with an aminoglycoside is the best choice.

In patients at high risk of infection with Gram-positive agents, catheter-related infection, resistance to penicillin, hypotension or shock, with no identifiable pathogen and severe mucositis, vancomycin can be used. In vancomycin-resistant infections, the use of linezolid is recommended.

Specific Indications for Alternative Therapy

Apart from the standard treatment with broad-spectrum antibacterial agents, there are a number of situations in clinical practice that require a specific therapeutic regimen. The duration of treatment may vary, and local antibacterial guidelines should be followed in these circumstances.

Central i.v. catheters

If catheter-related infection (CRI) is suspected, blood must be cultured from both the catheter and peripherally, in order to measure the differential time to positivity (DTTP), which is the difference in time between positivity of results for catheter culture versus peripheral blood culture. A DTTP of ≥ 2 hours is a highly sensitive and specific indicator of catheter-related bacteraemia.

All cases of CRI in the setting of FN require decision-making on the choice and duration of i.v. antibiotics, and the need for catheter removal.

When the patient is stable, the catheter should not be removed without microbiological evidence of infection. A glycopeptide such as vancomycin should be administered through the line, when possible, to cover Gram-positive organisms. Teicoplanin is a useful alternative, as it can be administered once daily as a line lock. Antibiotic lock therapy should always be combined with systemic antimicrobial treatment. In CRI due to coagulase-negative *Staphylococcus*, an attempt at preserving the catheter can be also made (Raad et al, 2009).

Removal of the line is indicated in the context of tunnel infections, persistent bacteraemia despite adequate treatment, atypical mycobacterial infection and candidaemia. With regard to CRI caused by *S. aureus*, the literature is divided. The recommendation should be to remove the line if at all possible, while recognising that with careful management it might be possible to maintain it for a short period.

Pneumonia

When a pneumonia is diagnosed based on clinical grounds and radiological imaging, antibiotic cover must be extended to treat atypical organisms, such as *Mycoplasma* and *Legionella*, by adding a macrolide to a beta-lactam antibiotic. Consideration of possible *Pneumocystis jirovecii* infection should be given in patients who present with high respiratory rate and/or desaturate readily off oxygen or on minimal exertion. Predisposing factors include prior corticosteroid therapy, prior lymphocytopenia, use of immune suppressants and exposure to purine analogues. High-dose co-trimoxazole is the treatment of choice for suspected *Pneumocystis* infection.

Cellulitis

The addition of vancomycin broadens the cover against skin pathogens.

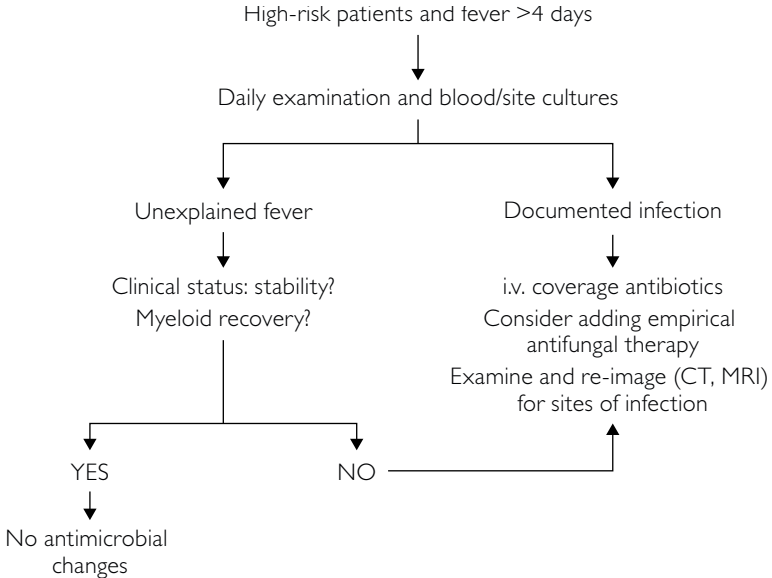
Diarrhoea

If clinical or microbiological evidence of intra-abdominal or pelvic sepsis exists, spectrum broadening for anaerobic organisms should be considered (e.g. add metronidazole). After microbiological evidence of infection is assessed, treatment should be tailored to the culture and antibiogram results. If diarrhoea is the main symptom, an assessment for *Clostridium difficile* is needed, and treatment with metronidazole should be started if suspected.

Candidiasis

Patients at risk of disseminated candidiasis are those with a prolonged neutropenia, mostly those with haematological malignancies undergoing myeloablative therapy. Candidaemia can be diagnosed on blood

culture; however, cultures may take several days to become positive. Therefore treatment is usually started empirically in patients whose fever fails to respond to broad-spectrum antibiotics after 3–7 days of appropriate treatment (Figure 2). A chest CT scan including liver and spleen screening should be performed before starting anti-*Candida* treatment, looking for typical changes.



CT, Computed tomography; i.v., intravenous; MRI, magnetic resonance imaging.

Figure 2 Algorithm of high-risk patients with prolonged febrile neutropaenia.

Adapted from: de Naurois J, Novitzky-Basso I, Gill MJ, et al. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. *Ann Oncol* 2010; 21 Suppl 5:v252–v256. By permission of Oxford University Press.

The first-line empirical treatment depends on each individual patient: liposomal amphotericin B or caspofungin are appropriate if the patient has already been exposed to an azole, or if the patient is known to be colonised with non-*albicans* *Candida*. Fluconazole can be chosen if the patient is at low risk of invasive aspergillosis, if local epidemiological data suggest low rates of azole-resistant isolates of *Candida*, and if the patient has not received an azole antifungal as prophylaxis.

Once begun, antifungal treatment should be continued until neutropenia has resolved, or for at least 14 days in patients with a demonstrated fungal infection.

Vesicular lesions/suspected viral infection

After appropriate samples are taken, therapy with acyclovir should be initiated. Ganciclovir should be substituted only when there is a high suspicion of invasive cytomegalovirus infection.

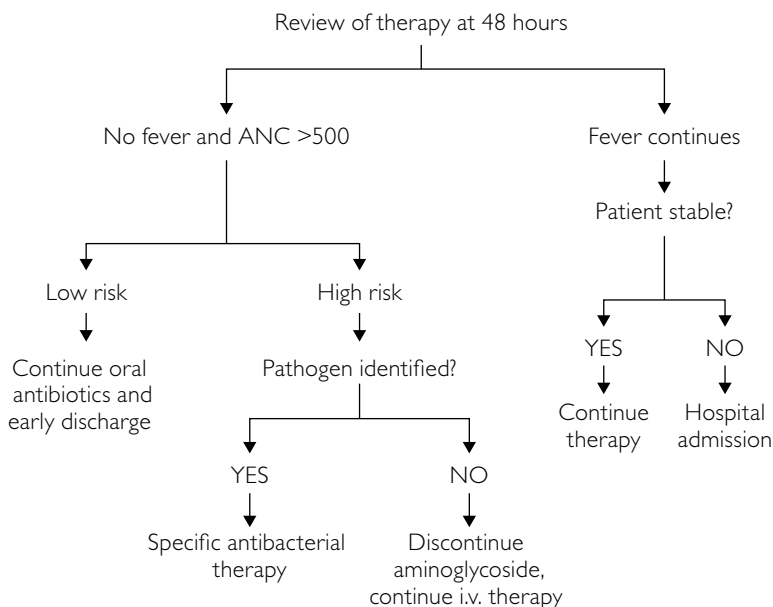
Suspected meningitis or encephalitis

Lumbar puncture is mandatory in these rare cases. Bacterial meningitis should be treated with ceftazidime plus ampicillin (to cover for *Listeria monocytogenes*) or meropenem. Viral encephalitis is treated with a high dose of acyclovir.

Follow-up and Duration of Therapy

Clinical follow-up will depend on the severity of symptoms, consisting of daily clinical exploration and analytical control, until the patient is afebrile and the leukocyte count is >500 neutrophils/mm³ (Figure 3).

- If the patient is afebrile and has >500 neutrophils at 48 hours:
 - If low-risk criteria and no cause established: rotate oral antibiotics.
 - If high-risk and no cause is found: if combination therapy is used, escalate to carbapenem monotherapy or antipseudomonal penicillin.
- If the patient remains febrile after 48 hours:
 - Clinically stable: continue with initial empirical treatment.
 - Clinical instability: rotation of a carbapenem antibacterial treatment and increased empirical antibacterial coverage, adding a glycopeptide to initial treatment. In some cases, a close collaboration with the Infectious Disease Department and the Intensive Care Unit will be necessary.



ANC, Absolute neutrophil count; i.v., intravenous.

Figure 3 Assessment of response and management.

Adapted with permission of the Infectious Diseases Society of America, from: Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2011; 52:e56–93; permission conveyed through Copyright Clearance Center Inc.

Declaration of Interest:

Dr Alonso has reported no conflicts of interest.

Dr Corral has reported no conflicts of interest.

Further Reading

Baden RL, Bensinger W, Angarone M, et al. NCCN Guidelines. Prevention and treatment of cancer related infections, Version 1.2013. National Comprehensive Cancer Network, 2013. Available at: <http://oralcancerfoundation.org/treatment/pdf/infections.pdf>. Date last accessed 20 January 2016.

- Carstensen M, Sørensen JB. Outpatient management of febrile neutropenia: time to revise the present treatment strategy. *J Support Oncol* 2008; 6:199–208.
- de Naurois J, Novitzky-Basso I, Gill MJ, et al. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. *Ann Oncol* 2010; 21 Suppl 5:v252–v256.
- Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2013; 31:794–810.
- Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2011; 52:e56–e93.
- Furno P, Bucaneve G, Del Favero A. Monotherapy or aminoglycoside-containing combinations for empirical antibiotic treatment of febrile neutropenic patients: a meta-analysis. *Lancet Infect Dis* 2002; 2:231–242.
- Hämäläinen S, Kuitinen T, Matinlauri I, et al. Neutropenic fever and severe sepsis in adult acute myeloid leukemia (AML) patients receiving intensive chemotherapy: Causes and consequences. *Leuk Lymphoma* 2008; 49:495–501.
- Innes H, Lim SL, Hall A, et al. Management of febrile neutropenia in solid tumours and lymphomas using the Multinational Association for Supportive Care in Cancer (MASCC) risk index: feasibility and safety in routine clinical practice. *Support Care Cancer* 2008; 16:485–491.
- Innes HE, Smith DB, O'Reilly SM, et al. Oral antibiotics with early hospital discharge compared with in-patient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: a prospective randomised controlled single centre study. *Br J Cancer* 2003; 89:43–49.
- Klastersky J, Ameye L, Maertens J, et al. Bacteraemia in febrile neutropenic cancer patients. *Int J Antimicrob Agents* 2007; 30 Suppl 1:S51–S59.
- Klastersky J. Management of fever in neutropenic patients with different risks of complications. *Clin Infect Dis* 2004; 39 Suppl 1:S32–S37.
- Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000; 18:3038–3051.
- Manterola A, Romero P, Martínez E, et al. Neutropenia and fever in the patient with cancer [Article in Spanish]. *An Sist Sanit Navar* 2004; 27 Suppl 3:33–43.
- Mermel LA, Maki DG. Detection of bacteremia in adults: consequences of culturing an inadequate volume of blood. *Ann Intern Med* 1993; 119:270–272.

- Paz-Ares L, Corral Jaime J, García-Carbonero R. Medical emergencies. In: Cavalli F, Hansen H, Kay S, et al. Textbook of Medical Oncology, 4th edition. London: Martin Dunitz, 2009; 323–350.
- Raad I, Kassar R, Ghannam D, et al. Management of the catheter in documented catheter-related coagulase-negative staphylococcal bacteremia: remove or retain? *Clin Infect Dis* 2009; 49:1187–1194.
- Sanchez-Muñoz A, García-Carbonero R, Cortés-Funes H, et al. Evolving treatment of fever and neutropenia in cancer patients [Article in Spanish]. *Rev Oncol* 2002; 4:297–307.
- Vidal L, Paul M, Ben dor I, et al. Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients: a systematic review and meta-analysis of randomized trials. *J Antimicrob Chemother* 2004; 54:29–37.

Immune–Haematological Emergencies in Cancer Patients

22

E. Martinelli

C. Cardone

V. Sforza

Faculty of Medicine, Second University of Naples, Naples, Italy

Drug-induced Hypersensitivity

Introduction

Drug-induced hypersensitivity syndrome (DIHS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS), is a rare and severe reaction to drugs, characterised by fever, skin reactions and lymphadenopathy, with involvement of internal organs (liver, kidney, lung and heart). The syndrome typically develops between 2 and 8 weeks after starting the causative drug, with a remitting clinical course despite drug withdrawal. The incidence of DIHS is about 1/1000, and the mortality rate is around 10%. DIHS is classified within the severe cutaneous adverse reactions (SCAR) syndromes, which also includes Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalised exanthematous pustulosis (AGEP) and exfoliative dermatitis.

Aetiology

The causative drugs most commonly implicated in the syndrome include anticonvulsants (i.e. phenobarbital, phenytoin), allopurinol, the sulphonamide group of antibiotics, antiretrovirals and, rarely, antineoplastic agents.

The causes of DIHS remain unclear and include immune-mediated reactions, drug metabolism, herpes virus (HHV6) infection and genetic predisposition. Immediate immune-mediated reactions involve T lymphocytes and, less frequently, immune complex or cytotoxic reactions.

Clinical Presentation

Fever is usually the first symptom, followed by skin lesions such as maculopapular eruption, exfoliative dermatitis, erythroderma, follicular and purpuric lesions, and, in 25% of cases, mucosal involvement. Lymphadenopathy is a common clinical sign, generally associated with internal organ involvement:

- Hepatosplenomegaly, hepatitis and, rarely, hepatic necrosis, resulting in liver failure
- Tubulo-interstitial nephritis, usually mild
- Pneumonitis, pleuritis and acute respiratory distress
- Myocarditis and pericarditis with associated symptoms
- Neurological disorders, such as meningo-encephalitis
- Gastrointestinal symptoms, including acute colitis and pancreatitis
- Haematological disorders.

Diagnosis

At least 3 of the following criteria are required for diagnosis: fever ($>38^{\circ}\text{C}$), skin reaction, lymph node enlargement at two sites, involvement of at least one internal organ, and blood count abnormalities (such as eosinophilia, leucocytosis, atypical lymphocytes, thrombocytopaenia, anaemia).

Laboratory Findings

- Hypogammaglobulinaemia, especially at the onset of disease
- Abnormal liver and renal function and muscle enzymes
- In case of virus HHV6 aetiology, serology may be useful
- Electrocardiogram (ECG), echocardiogram, chest X-ray and urinalysis, to assess possible internal organ involvement.

Management

- Immediate cessation of the suspected drug
- Early recognition of symptoms
- Systemic steroids are usually used, despite the lack of controlled clinical trials
- In case of worsening symptoms: intravenous (i.v.) steroid treatment, plasma exchange, rituximab and, if HHV6 reactivation, valganciclovir administration
- For skin reactions: topical corticosteroids, emollients and oral antihistamines.

Infusion-related Reactions with Drugs

Introduction

Drugs can induce hypersensitivity reactions (HSR), defined as any unforeseen reaction whose signs cannot be explained by the known toxicity of the drug. These reactions usually occur within 1 hour and are represented by rash, angio-oedema, dyspnoea, rhinitis, chest pain, hypotension or hypertension and anaphylactic reactions; they can also occur hours or days after infusion, and this last can be classified as DIHS. Acute HSR may be caused by platinum salts, taxanes and monoclonal antibodies such as cetuximab, panitumumab, bevacizumab, trastuzumab and rituximab. HSR should be recognised early and managed by physicians, due to its potential life-threatening risk.

Aetiology

Most HSR are classified as type I reactions (Table 1), where IgE causes degranulation of mast cells and basophils, leading to non-immune-mediated histamine and cytokine release, responsible for the early onset of symptoms like itching, chest pain and anaphylactic reactions. Other HSR reactions can be caused by the adaptive specific immune response directed by lymphocytes, and are either humoral or cell mediated. This is the case for types III and IV HSR, which can be observed with platinum salts (Table 1).

Table 1 Types of Hypersensitivity Reactions

Type of hypersensitivity	Mechanism	Symptoms
I	Mast cell and basophil degranulation	Early-onset symptoms: itching, chest pain, rash, anaphylactic reactions
II	Phagocyte and NK-cell activation	Haemolysis, thrombocytopenia
III	Immune complexes, phagocyte and NK-cell activation, complement fixation	Chronic urticaria, joint pain, proteinuria
IV	Macrophage and eosinophil activation, cytotoxicity	Delayed reactions

NK, Natural killer.

Clinical Features

Acute hypersensitivity symptoms are immediate, occurring during or within minutes of infusion, whereas mild reactions may occur hours or days after infusion. The first symptom is usually a mild rash.

Mild symptoms: urticaria, flushing, itching, pruritus, oedema of the face and hands, abdominal cramping and diarrhoea, back pain.

Severe symptoms: bronchospasm, chest pain, tachycardia, hypo- or hypertension with systemic anaphylaxis.

■ Platinum salt-related HSR:

- *Cisplatin*: occurring often within minutes of the start of infusion, with an overall incidence of 5%–20%
- *Carboplatin*: occurring early during infusion, with an incidence increasing after the 6th cycle (overall incidence 1%–44%); generally all reactions are moderate to severe
- *Oxaliplatin*: overall incidence of 10%–19%. The role of platinum-specific IgE antibodies is well documented; the risk of oxaliplatin-associated acute HSR increases with cumulative dose (>5 cycles), suggesting that sensitisation to the drug is needed; after severe HSR, desensitisation should be tried.

- Taxane-associated HSR: occurring in up to 30%, and decreasing to less than 4% with premedication using antihistamines and steroids; frequently occurring at first or second cycle, usually not IgE-mediated.

- **Monoclonal antibody-associated HSR:** may be non-allergic, cytokine-mediated reactions at the first administration.
 - *Rituximab:* serious reactions are reported in 2%–10% of patients, usually occurring during the first infusion
 - *Trastuzumab:* causes mild-to-moderate reactions during initial infusion in almost 40% of patients; most reactions occur within 2 hours and severe reactions are uncommon
 - *Cetuximab:* despite the routine use of premedication, severe reactions occur at the first infusion and are unlikely to be IgE-mediated; however, HSR can occur even after the second dose
 - *Panitumumab, ramucirumab and bevacizumab:* have a lower incidence of HSR.

The National Cancer Institute (NCI) has classified antibody-associated HSR into grades according to their severity (Table 2).

Table 2 NCI-CTCAE Definitions of Severity of HSR.

Adapted from: National Cancer Institute Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events and Common Toxicity Criteria [v4.0]. 15-12-2010. Available at: <http://levs.nci.nih.gov/ftp1/CTCAE/About.html>. Date last accessed 21 January 2016

NCI-CTCAE Grade 1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
Grade 2	Therapy or infusion interruption indicated, but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for <24 h
Grade 3	Prolonged; recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae
Grade 4	Life-threatening consequences with urgent intervention indicated
Grade 5	Death

CTCAE, Common Terminology Criteria for Adverse Events; i.v., intravenous; NSAIDs, non-steroidal anti-inflammatory drugs.

Treatment

Patients should be educated to immediately recognise HSR-related symptoms.

When a reaction occurs:

- Immediate interruption of the infusion
- Maintenance of i.v. line with saline solution

- Frequent vital sign assessment
- Antihistamine (H_1 and H_2 antagonists) administration at initial appearance of symptoms
- Cardiac and respiratory support (O_2 therapy)
- Corticosteroid administration
- Epinephrine administration (1 mg in 1 ml), in case of anaphylactic HSR.

When symptoms are completely resolved, the infusion may be restarted, lowering the rate of infusion to 50%. In case of life-threatening reactions, the causative drug is usually withdrawn.

Premedication with corticosteroids and antihistamine drugs is a successful strategy for re-administration of drugs, as is lowering the infusion rate for further administrations. Desensitisation protocols, based on the gradual reintroduction of small amounts of drugs and escalating up to full dose, have been proposed but are not implemented in clinical practice, as they are time-consuming.

The use of skin tests to predict an HSR to a drug is controversial, but could be useful to predict a cross-reaction when one platinum salt is replaced by another.

Adverse Transfusion Reactions with Blood Components

Introduction

A transfusion reaction is any adverse event occurring as a consequence of infusion of blood or its components. According to the time of onset, transfusion reactions are classified as acute (<24 hours) or delayed (occurring days after the termination of transfusion).

All transfusion reactions require immediate recognition and clinical management. However, the reactions included in Table 3 may be classified as the most common transfusion-related emergencies.

Table 3 Transfusion-related Emergencies

Condition	Aetiology	Clinical presentation	Management
Acute intravascular haemolytic reactions	ABO incompatibility Complement activation and cytokine response triggered by recipient's ABO IgM antibodies	Fever; chills, chest and lumbar pain, hypotension, tachycardia, DIC, oliguria, acute tubular necrosis, haemolysis (lactate dehydrogenase, indirect bilirubin, haptoglobin, haemoglobinuria, haemoglobinaemia)	Adequate blood pressure and respiration (vasopressors, bronchodilators) Diuretics (furosemide) or institution of fluid diuresis; target: > 100 mL/h
Allergic transfusion reactions	IgE-mediated; related to plasma protein infusion Common in IgA deficit (<7 IU)	Pruritus, hives, erythema with or without confluent rash; systemic reactions (anaphylaxis): bronchospasm, fever, hypotension, abdominal pain, nausea	<i>Mild reactions:</i> anti-H ₁ agent administration (diphenhydramine). If symptoms disappear, transfusion can be restored <i>Severe reactions:</i> high-dose i.v. steroids, anti-H ₁ agents, beta-2 agonists; adrenaline <i>In case of recurrence of anaphylaxis:</i> washed blood cell units; premedication with anti-H ₁ and anti-H ₂ agents, systemic steroids
FNHTR	Recipient's antibody reacting against donor's leukocytes, platelets; cytokine-mediated	Fever; cutaneous vasoconstriction	Antipyretics; cardiac support In case of recurrence: leukocyte-depleted blood units
TRALI	Donor's antibodies reacting with recipient's leukocytes; complement activation, leukocyte adhesion to pulmonary endothelial cells and diapedesis; pulmonary capillary leak syndrome	Severe dyspnoea, oxygen desaturation, hypotension, respiratory failure	Transfer to intensive care unit Close cardiac monitoring (Swan-Ganz catheter) Ventilator support (O ₂ administration or intubation) Steroid administration Leuko-depleted blood components, washed red cells. Use of filters may reduce the risk
TACO	Acute expansion of intravascular volume usually caused by high infusion rate; common in elderly, children and in cardiovascular instability	Headache, dyspnoea, tachycardia and signs of congestive heart failure	Cardiac and ventilator support Lower infusion rate (<1 mL/kg/h) Prophylactic diuretics may be administered
Bacterial contamination	Blood unit contamination usually by Gram-negative bacteria	Fever; hypotension, signs of septic shock	Cardiac and ventilator support Blood culture and appropriate antibiotics
TA-GVHD	Donor's immunocompetent T lymphocytes reacting against immune-incompetent recipient's lymphoid tissue	Onset: 8–10 days after transfusion (delayed) Fever; nausea, vomiting, diarrhoea Maculopapular rash, erythroderma, GVHD multiorgan involvement. Pancytopenia, abnormal liver function	Stem cell transplantation. Use of irradiated blood (2500 cGy) recommended in high risk of TA-GVHD

DIC, Disseminated intravascular coagulation; FNHTR, Febrile non-haemolytic transfusion reactions; i.v., intravenous; TACO, transfusion-associated circulatory overload; TA-GVHD, transfusion-associated graft-versus-host-disease; TRALI, transfusion-related acute lung injury.

Management

- Immediate interruption of blood component infusion
- Maintenance of i.v. line with saline (0.9%) infusion
- If a haemolytic reaction is suspected: institution of transfusion reaction work-up (obtain blood and urine to confirm haemoglobinaemia and haemoglobinuria, check paperwork, perform a direct antiglobulin test, repeat cross-match and serological testing [ABO and Rh])
- Complete a physical examination (vital signs, blood pressure, respiratory rate, pulse, SpO₂%) and diuresis monitoring
- Pathognomonic signs of acute intravascular haemolytic reactions, allergic transfusion reactions, transfusion-related acute lung injury (TRALI), and bacterial contamination should be considered in order to set up intensive care management.

Disseminated Intravascular Coagulation

Introduction

Disseminated intravascular coagulation (DIC) is an acquired syndrome characterised by widespread activation of the blood coagulation system and by excessive consumption of haemostatic factors and secondary fibrinolysis.

Activation of blood coagulation leads to the excessive generation and disseminated deposition of fibrin clots in the microcirculation, resulting in micro- or macro-thrombosis, with subsequent ischaemic necrosis and organ failure.

Activation of the fibrinolytic system results in the excessive consumption of haemostatic factors (platelets, factors V and VIII, protein C, antithrombin and fibrinogen) and secondary fibrinolysis, leading to excessive bleeding.

DIC usually results from exposure of tissue factor in the peripheral blood, triggering the extrinsic pathway of coagulation. The causes of DIC can be classified into several groups of disorders, the more common being:

- Severe infections: Gram-negative lipopolysaccharides and Gram-positive peptidoglycan, which cause generation or exposure of tissue factor activity in phagocytic, endothelial and tissue cells
- Malignant disorders (particularly mucin-secreting adenocarcinomas and acute promyelocytic leukaemia): tumour cells express or release tissue factor
- Obstetric complications (abruptio placentae, therapeutic abortion, retained dead foetus or products of conception, amniotic fluid embolism): placental tissue with tissue factor activity is exposed to the maternal circulation
- Shock of any cause: in ischaemic tissues, there is high exposure and release of tissue factor.

Clinical Features

The clinical presentation of DIC is usually related to the underlying inciting condition; however, the main clinical presentation is:

- In subacute or chronic DIC: thrombosis (e.g. deep venous thrombosis, pulmonary embolism), usually associated with hypercoagulability states; abnormal bleeding is uncommon.
- In acute DIC: bleeding often associated with simultaneous microvascular thromboses may lead to dysfunction and multiorgan failure, while mechanical disruption of red blood cells produces schistocytes and mild intravascular haemolysis (up to thrombotic thrombocytopenic purpura and haemolytic–uremic syndrome).

Bleeding involves at least three unrelated sites (ears, nose and throat, gastrointestinal and respiratory tract, site of venepuncture or i.v. infusion).

Other typical signs are:

- Skin abnormalities: petechiae, purpura, haemorrhagic bullae, purpura fulminans (skin necrosis of lower limbs), acrocyanosis, thrombosis, localised infarction and gangrene
- Confusion or disorientation

- Fever
- Signs of haemorrhage
- Signs of adult respiratory distress syndrome (ARDS).

Laboratory Tests

No laboratory tests or combination of tests can unequivocally confirm the diagnosis of DIC. Several scoring systems have been proposed. According to the International Society on Thrombosis and Haemostasis (ISTH) guidelines, a laboratory diagnosis of DIC can be made by scoring:

- Platelet count lower than $100\,000/\text{mm}^3$, or a rapid decline in platelet count ($>100 = 0$; $<100 = 1$; $<50 = 2$)
- Fibrinogen level ($>1\text{ g/l} = 0$; $<1\text{ g/l} = 1$)
- Prolonged prothrombin time ($<3\text{ sec} = 0$; $>3\text{ sec but } <6\text{ sec} = 1$; $>6\text{ sec} = 2$)
- Increased D-dimer level and fibrin degradation products (no increase = 0; moderate increase = 1; strong increase = 2).

DIC can be diagnosed if a patient affected by an underlying disorder known to be DIC-related has a total score ≥ 5 . If the score is < 5 , laboratory tests should be repeated. However, the laboratory tests used to diagnose DIC require an understanding of the underlying disease and the patient's clinical status.

- D-dimer test is a sensitive but non-specific test, potentially altered in many other clinical conditions including recent surgery, ascites, pleural effusion, soft-tissue bleeding and inflammation
- Underlying defects in protein synthesis (liver dysfunction, vitamin K deficiency) or other causes of thrombocytopenia (marrow replacement by tumour or effect of chemotherapy) may complicate laboratory findings.

The ISTH-DIC scoring system provides an assessment at a given moment in time; however, serial measurements are recommended to establish a definitive diagnosis of DIC.

Management

- Management of the underlying disorder
- Treatment of thrombocytopenia in a precariously low platelet count
- Cryoprecipitate (8–10 U) in bleeding manifestations if fibrinogen level is <1 g/l
- 1–2 U fresh frozen plasma to replace other haemostatic components, according with the severity of the depletion
- The role of heparin is controversial. Heparin is beneficial in the treatment of slowly evolving DIC with venous thrombosis or pulmonary embolism, but is not indicated in acute DIC with bleeding or bleeding risk (except in women with a retained dead foetus and evolving DIC)
- Antithrombin concentrate has been tested in clinical trials; however, its potential role in DIC therapy is still under investigation.

Declaration of Interest:

Dr Martinelli has reported no conflicts of interest.

Dr Cardone has reported no conflicts of interest.

Dr Sforza has reported no conflicts of interest.

Further Reading

Dasararaju R, Marques MB. Adverse effects of transfusion. *Cancer Control* 2015; 22:16–25.

Demoly P, Hillaire-Buys D. Classification and epidemiology of hypersensitivity drug reactions. *Immunol Allergy Clin North Am* 2004; 24:345–356.

Fernando SL. Drug-reaction eosinophilia and systemic symptoms and drug-induced hypersensitivity syndrome. *Australas J Dermatol* 2014; 55:15–23.

Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol* 2005; 5:309–316.

Joerger M. Prevention and handling of acute allergic and infusion reactions in oncology. *Ann Oncol* 2012; 23 Suppl 10:313–319.

Kusuma B, Schulz TK. Acute disseminated intravascular coagulation. *Hosp Phys* 2009; 45:35–40.

Levi M, Hunt BJ. A critical appraisal of point-of-care coagulation testing in critically ill patients. *J Thromb Haemost* 2015; 13:1960–1967.

- Li G, Daniels CE, Kojicic M, et al. The accuracy of natriuretic peptides (brain natriuretic peptide and N-terminal pro-brain natriuretic) in the differentiation between transfusion-related acute lung injury and transfusion-related circulatory overload in the critically ill. *Transfusion* 2009; 49:13–20.
- Makrilia N, Syrigou E, Kaklamanos I, et al. Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. *Met Based Drugs* 2010;2010. pii: 207084. doi: 10.1155/2010/207084. Epub 2010 Sep 20.
- Naisbitt DJ, Pirmohamed M, Park BK. Immunopharmacology of hypersensitivity reactions to drugs. *Curr Allergy Asthma Rep* 2003; 3:22–29.
- Taylor FB Jr, Toh CH, Hoots WK, et al; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001; 86:1327–1330.
- Torres R, Kenney B, Tormey CA. Diagnosis, treatment, and reporting of adverse effects of transfusion. *Lab Med* 2012; 43:217–231.

Bleeding Disorders

E. Martinelli

V. Sforza

C. Cardone

Faculty of Medicine, Second University of Naples, Naples, Italy

Introduction

Bleeding complications occur in approximately 10% of patients with cancer, and can be potentially life-threatening, so they should be adequately and promptly recognised and treated. The most frequent haemostatic defect causing bleeding in this setting is thrombocytopenia, representing 50% of all causes. Other disorders are represented by liver insufficiency with or without vitamin K deficiency, disseminated intravascular coagulation (DIC), inappropriate or excessive use of anticoagulants, as well as acquired haemophilia A (AHA) and acquired von Willebrand syndrome (AVWS).

Thrombocytopenia is a disorder characterised by a reduction in platelet number to $<150\,000$ cells/ μl blood. In cancer patients, thrombocytopenia can have different origins, such as chemotherapy, direct bone marrow involvement by cancer, as well as consumptive coagulopathy, immune-mediated mechanisms, infection or sequestration.

In patients with solid tumours treated with chemotherapy, bleeding due to thrombocytopenia is seen in 9%–15% of cases, especially with platelet counts $<10\,000/\mu\text{l}$; it is also associated with poor clinical outcomes and significantly increased resource utilisation.

Several risk factors have been recognised for chemotherapy-induced thrombocytopenia and bleeding, such as history of bleeding, poor bone marrow function with a low baseline platelet count, bone marrow metastases and poor performance status.

Generally, supportive transfusion therapies with platelet concentrates (PC), fresh frozen plasma (FFP) and plasma-derived or recombinant concentrates are recognised as standard treatments both during the acute episode and in prevention.

However, these treatments may be associated with complications and/or adverse events in cancer patients, such as allergic reactions (ALR) or anaphylactic reactions (ANR), transfusion-associated graft-versus-host disease (TA-GVHD), transfusion-transmitted bacteraemia (TTB), transfusion-related acute lung injury (TRALI), acute haemolytic transfusion reactions (AHTR) and febrile non-haemolytic transfusion reactions (FNHTR). Therefore, modifications such as leukocyte reduction and irradiation of the blood components to be transfused in cancer patients are recommended to reduce the risk of these complications.

Aetiology

Cancer and its related treatments may significantly alter the haemostatic system at various levels, such as the clotting system, platelet number and function, as well as the vessel wall. The main causes of bleeding are shown in Table 1.

Clotting System

Decreased production of clotting factors

- Liver involvement by cancer can cause defective or decreased synthesis of coagulation factors II, VII, IX, X, XI, XII, and XIII, prekallikrein, high-molecular-weight kininogen, plasminogen, antithrombin III, protein S and protein C
- Acquired von Willebrand's disease is seen in association with haematological malignancies
- Drug-induced: coumarin derivatives, cephalosporins, asparaginase.

Fibrinolysis

- Primary fibrinolysis, due to local or systemic activation of the fibrinolytic system, resulting in plasmin degradation of fibrin, fibrinogen,

Table 1 Causes of Bleeding In Cancer Patients.

Reprinted from: De Leeuw K, Schrijvers D. Bleeding disorders. In: Kosmidis PA, Schrijvers D, André F, Rottey S (Editors). *ESMO Handbook of Oncological Emergencies*. Oxon: Taylor and Francis, 2005; 131–139.

System	Syndrome	Occurrence
Clotting system	Decreased clotting factors; coagulation factor abnormalities	Liver disease Cholestasis Drug-induced Acquired von Willebrand's disease
	Disseminated intravascular clotting	Leukaemia cell procoagulant activity Bacteraemia Massive transfusion Shock
	Primary fibrinolysis; fibrinogenolysis	Leukaemia cell proteolytic activity Drug-induced
	Circulatory anticoagulants	Factor inhibitors Heparin-like anticoagulants
Thrombocytes	Thrombocytopenia	Immune thrombocytopenia Bone marrow infiltration Drug-induced
	Platelet dysfunction	Myeloproliferative syndromes Acute leukaemia Preleukaemia Hairy-cell leukaemia Drug-induced
Vessels	Vascular defects	Infiltration Hyperviscosity/leukostasis Extramedullary haematopoiesis

factor V and factor VIII, is observed in patients with sarcomas, breast, thyroid, colon and stomach cancer and haematological malignancies

- Secondary fibrinolysis due to DIC
- Solid tumours are capable of inducing fibrinolytic activity.

Thrombocytes

Thrombocytopenia

- Impaired production due to chemotherapy or radiotherapy
- Splenic sequestration in patients with splenomegaly

- Immune-mediated thrombocytopenia related to anti-HLA (human leucocyte antigen), paraproteins or antiplatelet-specific alloantibodies, may be seen in chronic lymphocytic leukaemia, non-Hodgkin's lymphoma, Hodgkin's disease, lung, breast and gastrointestinal (GI) cancer
- DIC is associated with acute myelocytic leukaemia, lymphoma and carcinoma of lung, breast, GI or urological origin. DIC most commonly complicates acute promyelocytic leukaemia, due to the presence of both thromboplastic material and fibrinolytic proteases in the promyelocytic subcellular components.

Abnormal platelet function

- Chronic myeloproliferative disorders with decreased platelet procoagulant activity and decreased aggregation and serotonin release, responses to adenosine diphosphate (ADP), epinephrine (adrenaline) or collagen
- Paraproteins may impair platelet aggregation (IgA myeloma, Waldenström's macroglobulinaemia, multiple myeloma, monoclonal gammopathy of undetermined significance)
- Thrombocytosis: platelet dysfunction can be associated with elevated platelet counts ($>700\,000/\mu\text{l}$)
- Hyperviscosity
- Acquired factor X deficiency in the setting of amyloidosis
- Circulating heparin-like anticoagulant
- Drug-induced: heparin, low-molecular-weight heparin, non-steroidal anti-inflammatory drugs (NSAIDs), beta-lactams, amphotericin B, plicamycin, vincristine, nitrofurantoin.

Evaluation

Symptoms

Depending on the extent and location of bleeding, patients may complain of palpitation, fatigue, dyspnoea, haematuria, epistaxis, headache or visual disturbances.

Clinical examination

Localised bleeding should be determined by clinical examination:

- Mucosal bleeding with gingival bleeding
- Skin lesions with spontaneous bruising, petechiae, purpura
- Bleeding from the sites of indwelling catheters or puncture sites
- Bleeding at pulmonary, central nervous system (CNS), GI or genitourinary sites.

Laboratory Examinations

Haematological evaluation

- Cytology: number and differentiation of white blood cells; number of platelets
- Blood film examination: schistocytes in DIC
- Platelet function tests, comprising platelet function closure time and bleeding time.

Coagulation parameters

- Activated partial thromboplastin time (aPTT) measures the intrinsic pathway and is prolonged by factor VIII and IX deficiency
- Prothrombin time (PT) measures the extrinsic pathway
- Both aPTT and PT are affected by factor X, factor V, prothrombin and fibrinogen
- Thrombin time measures the common pathway
- Fibrinogen and fibrinogen degradation products (D-dimers)
- Von Willebrand's factor
- Coombs' test
- Autoimmune thrombocytopaenia in association with autoimmune haemolytic anaemia gives a positive antiglobulin test.

Biochemical Analyses

- Urea, creatinine, liver function tests and protein electrophoresis.

Bone Marrow Examination

- In case of suspicion of immune-mediated thrombocytopenia
- Suspicion of plasma cell proliferation.

Echo of Abdomen

- To detect splenomegaly and liver metastases.

Prevention and Treatment

Prevention of Bleeding

Chemotherapy-induced thrombocytopenia

- If platelets <10 000/ μ l: platelet transfusion of 6–8 units every 1–2 days until platelet counts remain >10 000/ μ l
- For invasive procedures: platelets >30 000/ μ l
- For surgery: platelets >50 000/ μ l (Table 2).

Table 2 *Indications for Platelet Transfusions.*

Reprinted from: De Leeuw K, Schrijvers D. Bleeding disorders. In: Kosmidis PA, Schrijvers D, André F, Rottey S (Editors). *ESMO Handbook of Oncological Emergencies*. Oxon: Taylor and Francis, 2005; 131–139.

Trigger (platelets/ μ l)	Clinical status
<10 000	Stable, absence of active bleeding
10 000–20 000	Presence of coagulation disorders Infection with fever >38°C (and rapid decrease of platelets) Local injuries Severe mucositis, active bleeding Biopsy (except bone marrow biopsy)
<50 000	Surgery

Coagulation

- Antibiotic therapy: monitoring of PT and aPTT
- Heparin therapy: monitoring of aPTT
- Vitamin K antagonists: monitoring of international normalised ratio (INR).

Treatment of Bleeding

Chemotherapy-induced thrombocytopaenia

- Platelet transfusion until platelets $>30\,000/\mu\text{l}$
- Only products that are leukocyte-reduced (either by filtration or by irradiation) should be given to avoid early alloimmunisation
- Transfusion of 4–6 pooled random donor platelet concentrates is normally as effective as single-donor apheresis products, depending on the content of platelets and the duration of storage of each product
- Platelets should be given as random ABO-compatible (non-HLA-typed) transfusions
- HLA-matched transfusions or cross-matched platelets should be given only in patients refractory to at least 2 random platelet transfusions
- The effectiveness of platelet transfusion can be assessed by the corrected increment (increment in platelet counts from before to after transfusion, corrected for the number of units transfused and for the body surface area of the recipient) in platelet count at 1 hour, or the bleeding time 10–15 minutes after transfusion, and the observed clinical outcome after transfusion.

Thrombocytosis

Platelet dysfunction associated with elevated platelet counts ($>700\,000/\mu\text{l}$) can be corrected by platelet apheresis.

Platelet dysfunction

Platelet dysfunction due to paraproteinaemia can be treated with plasma apheresis.

Coagulation disturbances

Liver disease

Bleeding due to liver disease, causing defective or decreased synthesis of coagulation factors II, VII, IX, X, XI, XII, and XIII, prekallikrein, high-molecular-weight kininogen, plasminogen, antithrombin III, protein S and protein C, can be corrected by replacement of vitamin K or the appropriate coagulation factors.

Acquired von Willebrand's disease

- Infusion of cryoprecipitate: factor VIII and von Willebrand's factor at a dose of 25 IU/kg, with as target a factor VIII level of >30% of normal level, until bleeding stops (usually 2–4 days)
- Desmopressin administered at a dose of 0.3 µg per kilogram body weight by continuous intravenous infusion for 30 minutes.

Fibrinolysis

- Tranexamic acid 500 mg every 8–12 hours orally or intravenously
- Epsilon-aminocaproic acid 5–10 g, slow intravenous loading dose, followed by 1–2 g/h for 24 hours followed by oral administration (Figure 1).

Disseminated intravascular coagulation

- Observation in patients who are not bleeding and platelet count >10 000/µl and no coagulopathy
- Platelet transfusion if platelet count is <10 000/µl
- Coagulopathy: FFP, fibrinogen concentrate or cryoprecipitate.

Local bleeding

- Local bleeding should be controlled by local measurements
- In case of visible bleeding, pressure may stop bleeding if the clotting system is intact

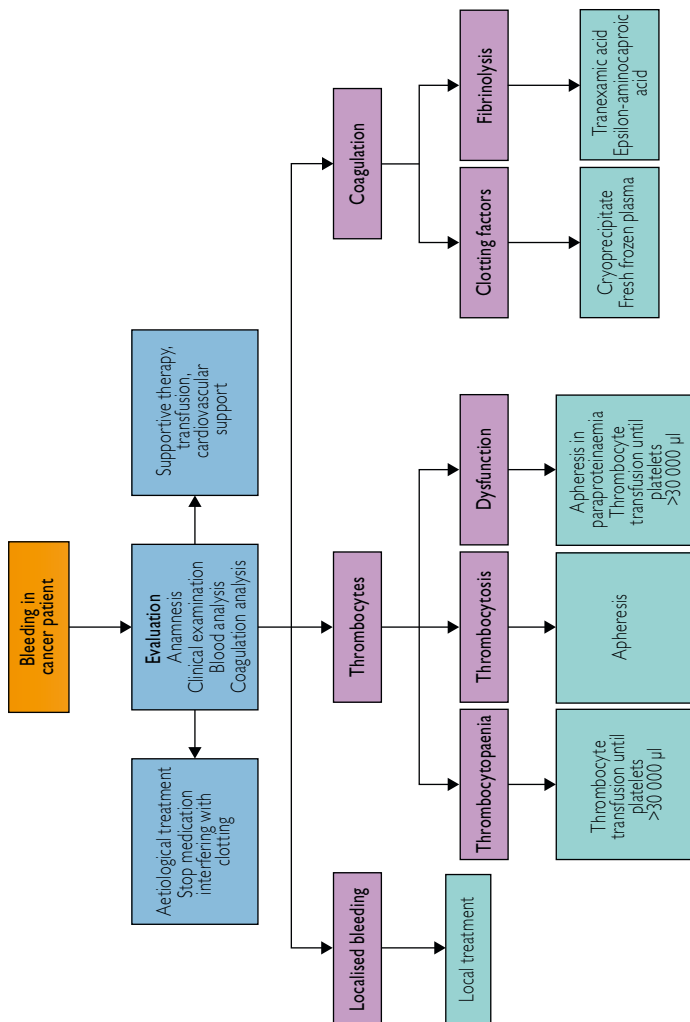


Figure 3 Algorithm of bleeding in the cancer patient.

Reprinted from: De Leeuw K, Schrijvers D. Bleeding disorders. In: Kosmidis PA, Schrijvers D, André F, Rottey S (Editors). ESMO Handbook of Oncological Emergencies. Oxon: Taylor and Francis, 2005; 131–139.

- Heat (laser) coagulation may be used in the local treatment of GI bleeding
- Arterial embolisation by angiography may be used to stop arterial bleeding in different organ systems
- Surgical intervention may be necessary to control local bleeding
- Radiotherapy may be used to give haemostatic radiation in case of urogenital or pulmonary bleeding.

Conclusion

Bleeding is a life-threatening condition in cancer patients. Prevention and treatment should be integrated in chemotherapy protocols.

Declaration of Interest:

Dr Martinelli has reported no conflicts of interest.

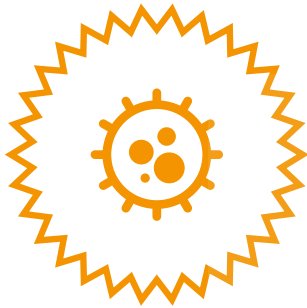
Dr Sforza has reported no conflicts of interest.

Dr Cardone has reported no conflicts of interest.

Further Reading

- Elting LE, Rubenstein EB, Martin CG, et al. Incidence, cost, and outcomes of bleeding and chemotherapy dose modification among solid tumor patients with chemotherapy-induced thrombocytopenia. *J Clin Oncol* 2001; 19:1137–1146.
- Federici AB, Intini D, Lattuada A, et al. Supportive transfusion therapy in cancer patients with acquired defects of hemostasis. *Thromb Res* 2014; 133 Suppl 2:S56–S62.
- Mannucci PM. Treatment of von Willebrand's disease. *N Engl J Med* 2004; 351:683–694.
- McMahon BJ, Kwaan HC. Thrombotic and bleeding complications associated with chemotherapy. *Semin Thromb Hemost* 2012; 38:808–817.
- Schiffer CA, Anderson KC, Bennett CL, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; 19:1519–1538.
- Wandt H, Ehninger G, Gallmeier WM. New strategies for prophylactic platelet transfusion in patients with hematologic diseases. *Oncologist* 2001; 6:446–450.

IV - Cancer pain



Management of Cancer Pain

24

M. A. Öztürk¹

O. Yazıcı²

A. A. Sağ³

¹Department of Medical Oncology, Marmara University Faculty of Medicine, Istanbul, Turkey

²Department of Medical Oncology, Ankara Numune Research & Education Hospital, Ankara, Turkey

³Division of Interventional Radiology, Department of Radiology, Koc University School of Medicine, Istanbul, Turkey

Introduction

Pain is a subjective and unpleasant sensation, increasingly recognised as the “fifth vital sign” in cancer patients. Cancer-related pain is one of the most feared and debilitating symptoms that affects patients. The prevalence of pain in patients with advanced disease may be increased up to 74%. Nociceptive, neuropathic and mixed mechanisms are involved in the aetiology. In 9.8%–55.3% of cancer patients, pain is not adequately treated.

Basic Science of Pain

Noci-physiology consists of 4 stages:

1. **Transduction** – Peripheral (myelin-free) nerve endings are stimulated (via chemical, mechanical or thermal stimuli).
2. **Transmission** – The nociceptor transmits a signal to the central nervous system, using two fibre systems: A fibres (myelinated, providing sharp acute pain, mainly from mechanical or thermal transduction), and C fibres (unmyelinated, providing chronic pain mainly from chemical transduction).

3. **Perception** – Multiple neuronal centres from brainstem to cerebral cortex convert the noci-signal into the feeling of “pain”. Pain stimulates the entire brain, affecting behaviour.
4. **Modulation** – The brain activates pain suppression mechanisms.

Aetiology

The aetiology of cancer pain and its differential diagnosis is given in Table 1.

Table 1 Differential Diagnosis in Cancer Patients with Pain

Non-oncological pain (must consider in all patients)
Acute coronary syndrome Pulmonary embolism
Somatic receptor-mediated pain
Bone pain (periosteal invasion/pathological fracture) Pleural invasion Mucous membrane invasion/ulceration Nerve compression/invasion Post-procedure
Visceral receptor-mediated pain
Haemorrhage into a tumour Peritoneal carcinomatosis Ureteric obstruction Constipation/ileus
Syndromic pain
<i>Treatment-related pain:</i> Chemotherapy (infusion-induced vascular pain/toxicities) Hormone therapy-induced pain Growth factor-induced pain (marrow space) Post-surgical pain (including phantom pain) Post-radiotherapy pain (mucositis/neuropathy/myelopathy)
<i>Referred pain</i>
<i>Paraneoplastic pain:</i> muscle cramps, pemphigus, hypertrophic osteoarthropathy
<i>Neuropathic pain:</i> Postherpetic neuralgia (herpes zoster) Leptomeningeal metastases
<i>Functional pain</i>

Evaluation

Anamnesis

The first step in evaluation of cancer patients with pain begins with a detailed history of the pain, the underlying malignancy and comorbidities. The adverse effects of pain on physical and psychosocial well-being of the patient should be noted. The medications and therapeutic interventions which have failed to control the pain should also be checked. On physical examination, painful site(s) of the body should be carefully evaluated. The extent of the tumour, the description of pain by the patient, pathological findings on imaging and laboratory tests should be assessed to determine the underlying pathophysiology. Characteristics such as location, intensity, temporal patterns, regions of radiation and factors triggering and relieving the pain should be elicited. Sharp, burning or blunt features should be distinguished from each other. By assessing all of these characteristics, nociceptive or neuropathic pain syndromes will be identified.

Intensity may be the first sign measured by self-reporting scales. The most widely used scales are the verbal rating scale and visual analogue scale. Reassessment of pain intensity should be done with the same rating scale and specific time frame.

Temporal features (type of onset, duration and daily variations of pain): acute pain presents with sudden onset; however, chronic cancer pain has an unidentified onset and shows a fluctuating course over time. In patients with chronic pain, periodic pain flares are termed as “break-through pain”. In order to control these, the concept of “rescue” dosing is created during treatment of these patients.

Types of Cancer Pain

The complex mechanisms and characteristics of pain can be classified into four major groups: “nociceptive”, “neuropathic”, “psychogenic” or “mixed” pain.

Continuous tissue injury causes *nociceptive pain*. The injury can be located in somatic structures such as bone, joints or muscles. It is frequently characterised as throbbing- or pressure-like pain. Injury of visceral regions

leads to visceral nociceptive pain, characterised as stabbing or sharp, when pain is caused by injury related to capsulated organs like the liver or pleura. On the other hand, visceral pain reveals itself as “crampy” when caused by obstruction of the bowels.

Abnormal function or damage to nerve tissue cause *neuropathic pain*, defined as burning, tingling or electrical pain.

The underlying psychological disturbances lead to the sensation of *psychogenic pain*. This type of pain is seldom observed in cancer patients.

Cancer pain syndromes

In cancer patients, the qualitative convergence of symptoms and signs suggests cancer pain syndromes. These syndromes can be divided into two major subgroups. Acute pain syndromes are generally associated with diagnostic interventions (e.g. biopsies), therapeutic interventions (e.g. stent replacement), cancer treatment (e.g. infusion pain, hand-foot syndrome, oral mucositis, myalgias) and the cancer itself (e.g. tumour rupture, pathological bone fractures). On the contrary, chronic syndromes are associated with the tumour itself and/or with an anticancer therapy. They can be somatic nociceptive, visceral nociceptive, or neuropathic. The diagnosis of cancer pain syndrome is crucial to define aetiologies and to guide diagnosis and therapeutic interventions (Table 1).

Intensity and Measurements

The intensity of the pain should be evaluated with one of the following tools:

- Visual analogue scale
- Brief pain inventory
- McGill pain questionnaire
- Memorial pain assessment card.

Clinical Examination

A careful clinical examination should be performed to detect the cause

of the pain.

Technical Examinations

These should be reserved for when the origin of pain is doubtful, or when it influences treatment:

- Plain radiographs
- Computed tomography (CT) scan to evaluate bone, soft tissue structures and organs (e.g. brain)
- Magnetic resonance imaging (MRI) to evaluate the spine
- Echography/Doppler echography
- Radioisotopes in case of bone metastases.

Treatment

Non-opioid Analgesics

These include aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen.

According to the “analgesic ladder” for the treatment of chronic cancer pain endorsed by the World Health Organisation (WHO), non-opioids are usually given to patients with low to moderate pain as first-step analgesics. They can be associated with opioid drugs to enhance the analgesia and to limit or reduce the necessary opioid dose, and hence the potential side effects. The treatment of choice in patients with moderate to severe cancer pain is opioids.

Acetaminophen

- As single agent or in opioid combination (e.g. + codeine)
- Risk of accidental overdose and hepatotoxicity
- Patients should be advised not to drink alcohol while using this drug
- The US Food and Drug Administration (FDA) recommends the prescription of combinations containing ≤ 325 mg acetaminophen

- Maximum daily dose: 4 g/day.

NSAIDs

Analgesic and anti-inflammatory effects come from cyclooxygenase (COX) inhibition. NSAIDs with selective COX-2 inhibition have significant anti-inflammatory effects and less gastrointestinal (GI) side effects. Studies have shown that excessive COX-2 inhibition causes increased cardiovascular mortality, which led to the withdrawal of some selective COX-2 inhibitors.

- As single agent or with an opioid to increase the analgesic effect
- Very effective in bone pain and pain due to inflammatory conditions
- Analgesic effect does not increase after certain doses, but side effects do
- Cardiovascular side effects (prothrombotic events and hypertension)
- Nephrotoxicity in the long term
- Hepatotoxicity & GI system (GIS) toxicity
- Think of using proton-pump inhibitor (PPI) prophylaxis in patients with GI risks.

Opioid Analgesics

These agents express their analgesic effects via binding to the specific mu, kappa and delta receptors. They are mostly used in the treatment of moderate to severe chronic cancer pain.

While using opioids, clinicians should pay attention to:

- Nature of the pain (intensity and frequency)
- Previous opioid exposure
- Which opioid to choose (advantages and disadvantages)?
 - Which opioids are available?
 - Route of administration (e.g. GIS obstruction)?

- Onset of action?
- Duration of action?
- Side effects (e.g. renal failure patients)?
- Titration of the dose
- Addition of non-opioids and/or adjuvant analgesics
- Overdose
- Opioid abuse and misuse (legal responsibilities).

Tramadol, tapentadol

These are relatively weak opioids, binding to mu and serotonin receptors, and causing norepinephrine reuptake inhibition. They act centrally, and are widely used in the treatment of cancer pain.

Tramadol: maximal dose 4×100 mg/day (in patients with normal hepatic and renal function), need to decrease the dose with increasing age and organ dysfunction.

Tapentadol: 50–100 mg orally, every 4 hours, maximal dose 500–600 mg/day.

Codeine

A weak opioid, converted to morphine via CYP2D6. Effects and side effects may vary depending on personal metabolism. A combination with acetaminophen exists. Not a front-line option in patients with severe cancer pain.

Meperidine

Not recommended in the treatment of chronic cancer pain. Renal failure patients are at risk of toxicity because of the accumulation of metabolites.

Morphine

Used as a standard when comparing the potency of different opioids. Morphine has a short half-life. It has suitable formulations for different

administration routes (oral [p.o.], intravenous [i.v.], subcutaneous [s.c.], rectal). Not a first-line choice in chronic pain, but a good initial option for patients (especially opioid-naive) with severe pain, and a rescue in patients with breakthrough pain. Should be used with caution in patients with kidney dysfunction.

Fentanyl

Parenteral and transdermal routes are suitable for chronic pain, and the transmucosal route is preferred in breakthrough pain. Due to lack of active metabolites, fentanyl is relatively safe in renal failure patients.

Oxycodone, hydrocodone, hydromorphone and oxymorphone are other potent opioids used in moderate to severe chronic cancer pain.

If opioids are not sufficient in controlling the cancer pain

- Re-evaluate the patient (e.g. disease progression, non-cancer conditions)
- Detailed physical examination
- Check the dose and the route of administration
- Check the compliance of the patient
- Assess any psychological condition(s) that may interfere with the treatment
- Assess the need for non-opioids and/or adjuvants
- Think about opioid rotation.

Principles of Treatment

“An appropriate drug for a specific situation”. An algorithm for the management of cancer pain is presented in Figure 1.

Morphine i.v. or s.c.: 10–20 mg every 4 hours with escape of 10 mg; calculate daily dose needed for pain control and change to other route of administration (equianalgesic dose).

Morphine p.o.: 10–20 mg every 4 hours with escape of 10 mg; calculate daily dose needed for pain control and change to sustained-release (SR)

morphine (dose is same as daily dose of immediate-acting morphine). It is necessary to know the different equivalent doses of the different drugs (Table 2).

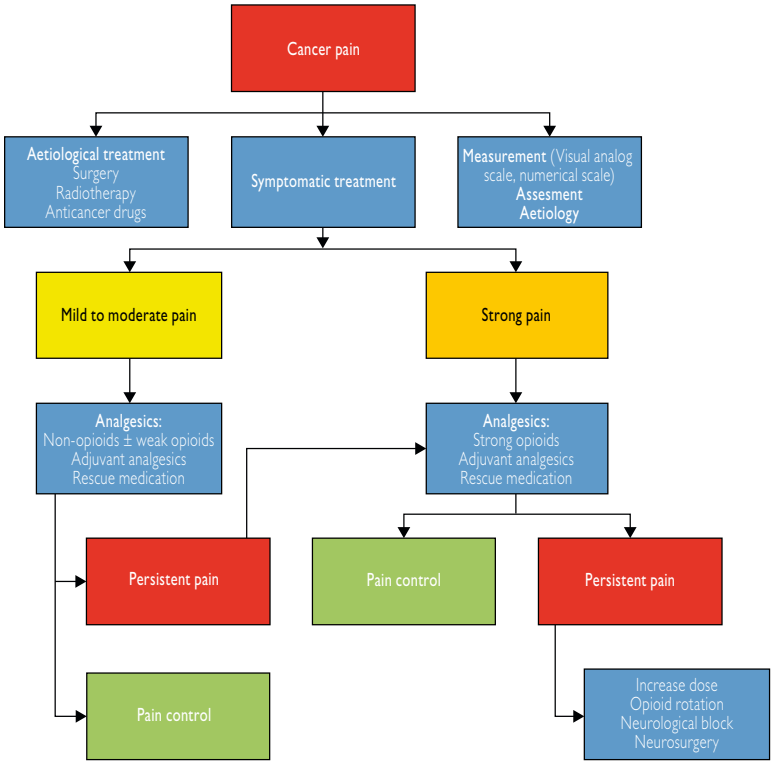


Figure 1 Algorithm for cancer pain management.
 Reprinted from: Di Palma M. Management of cancer pain. In: Kosmidis PA, Schrijvers D, André F, Rottey S (Editors). ESMO Handbook of Oncological Emergencies. Oxon: Taylor and Francis, 2005; 140–147.

Table 2 Equianalgesic Doses and Activity of Opioids

Opioid	Route of administration	Equianalgesic dose	Activity (hours)
Morphine	Oral	30 mg	4
	Subcutaneous	10 mg	4
	Intravenous	10 mg	4
SR Morphine	Oral	30 mg	12–24
SR Hydromorphone	Oral	4 mg	12–24
Fentanyl patch	Transcutaneous	8 µg	72
Oxycodone	Oral	15–20 mg	3–5
Hydrocodone	Oral	30–45 mg	3–5

SR, Sustained-release.

In the context of an emergency, avoid morphine with a long half-life (requires 6–24 hours to be active). Only physicians familiar with opioids should titrate morphine. In other situations, start treatment by a conventional dose of morphine (compare with above). Surveillance of vital signs is necessary and naloxone (antidote) must be available. Example of protocol for titration: morphine 2 mg i.v./5 minutes until disappearance of pain.

Opioids are usually not efficient in neuropathic pain, but should be tried. Tricyclic antidepressants or anticonvulsants may be used.

Appropriate Route of Administration

Most analgesics are given orally. However, opioids may also be given s.c. or i.v. In specific situations, they may be given intrathecally. There are also patches available to administer opioids transcutaneously. These should not be used to treat acute pain. Once the pain is controlled, they may be started with an overlap with a short-acting opioid.

By the Clock

Analgesics should be taken at fixed hours to prevent pain. In addition, escape medications should be prescribed. Transcutaneous patches may facilitate the continuous administration of opioids.

Use of adjuvant treatment if necessary

- Bone metastases: corticosteroids, bisphosphonates
- Tricyclic antidepressant drugs: amitriptyline, clomipramine, oripramine
- Anticonvulsant drugs: gabapentin, carbamazepine
- Tumour-related headache (oedema): corticosteroids
- Visceral dilatation: antispasmodics
- Muscle spasm: benzodiazepines
- Other treatment modalities:
 - Radiotherapy
 - Neurological blocks.

Anticipate and Treat Side Effects

- Use antiemetics and laxatives with opioids
- Start with a lower dose in elderly patients (e.g. 50% of normal dose)
- Be aware of anticholinergic effects of tricyclic antidepressants
- Opioid rotation: if a specific opioid causes too many side effects, change to another opioid:
 - Calculate equianalgesic dose
 - Decrease equianalgesic dose by 25%–50%, except for fentanyl
 - Rescue dose is 5%–10% of total daily dose.
- Special situations:
 - *Patients with pre-existing treatment who present with acute pain:* in this subset of patients, the most crucial point is to understand the reason why the pain is not controlled by treatment
 - *For a new cause of pain:* treat the new cause with the appropriate drug + aetiology

- For a progressive disease: (1) adapt according to the WHO pain ladder; (2) increase the dose of the drug by 50%–100%; and (3) add a new drug.

Opioid overdose is characterised by sedation and respiratory depression. When detected, the presence of myosis is a useful sign to diagnose a morphine overdose. Naloxone is the antagonist of opioids. It is administered i.v. at a dose of 0.1 mg every 2–3 minutes, until a dose of 0.4–2 mg is reached. In case of fever, transdermal fentanyl should be used with caution, since the risk of over-dosage is elevated, due to increased resorption.

Interventional Treatments for Cancer Pain Management

Patients with cancer-related pain may benefit from minimally-invasive image-guided procedures. This applies especially to those who do not reach satisfactory relief using opioid therapy and/or analgesic adjuvants. The goal of pain-directed interventional radiology is to direct treatment toward painful tumours or treating pain modulation-associated and inflammation-associated capsular nerves, periosteal nerves, peripheral nerves, nerve roots or spinal cord spaces.

■ Cautionary scenarios:

- In general, patients with acute neurological compromise should be considered directly for surgical intervention.
- Patients with painful appendicular skeletal lytic lesions disrupting major weight-bearing trabecular pathways may benefit from adjunctive cementoplasty or direct surgical stabilisation.
- Visceral cancer pain can be difficult to control with opioids, and is especially suited for nerve block (sympathetic afferent nociceptor neurone blockade; for example, coeliac plexus block).
- Interventional procedures often provide more rapid pain relief than radiation therapy, and can be performed in a single session as opposed to multiple sessions. However, they do carry varying degrees of procedural risk depending on the specific procedure.

- Ablation or embolisation of superficial lesions requires careful treatment planning. Multi-modality skin protection (insulation and active thermal counter-measures), using relatively large embolic particle size, will help to prevent development of chronic skin ulcers after treatment.
- Neurone blockade:
 - *Non-neurolytic nerve block*: sympathetic blockade using a bolus injection or scheduled infusional administration of local anaesthetic. Often used for visceral nerve-mediated cancer pain, which is typically unresponsive to opioids, but can also be useful for somatic nerve-mediated pain such as intercostal block for pathological rib fractures.
 - *Neurolytic nerve block*: neurolytic dose (e.g. alcohol) is targeted to destroy nerve tissue. Coeliac plexus block and superior hypogastric plexus block are two examples. Neurolysis can also be achieved by applying thermal injury (cryoablation or radiofrequency ablation). Pain may still return in 3–6 months due to nerve regeneration (if the axolemma remains intact).
- Implants:
 - *Infusional nerve block*: a perineural, epidural or intrathecal catheter is placed, and local anaesthetic infusion is performed in a scheduled fashion. If survival is anticipated to exceed 2 months, subcutaneous tunnelling of the catheter may reduce infection rates.
 - *Neurostimulator implantation*: an epidural electrode is implanted to stimulate the specific level of the spine relating to the patient's pain.
- Stabilisation:
 - Pathological vertebral compression fractures can be stabilised by injecting cement (vertebroplasty) or restoring vertebral body height, and then injecting cement (kyphoplasty), which may be preferred if there is significant kyphosis or posterior vertebral cortex lesion involvement.

- Cementoplasty can be performed in the sacrum (sacroplasty) for compression fracture stabilisation and resultant pain relief. The exothermic reaction of cement solidification may attenuate nerve endings, causing pain modulation as well.
- Ablation:
 - Energy can be directed to a nerve, tumour or extended nerve/tumour interface with the goal of tissue destruction. Thermal (radiofrequency ablation, microwave ablation, high-intensity-focused ultrasound [HIFU], cryoablation) and non-thermal (irreversible electroporation, alcohol ablation) methods can also be used, guided by ultrasound (superficial structures), CT (bone and bone interfaces, deep thoracic or abdominal structures) or MRI (useful for subtle soft tissue lesions and extremities).
- Embolisation:
 - Capsular pain from liver metastatic disease can be ameliorated by embolisation (injection of embolic agents into the tumour vasculature, angiographically). Chemotherapeutic agents can be combined (“chemo-embolisation”).

Declaration of Interest:

Dr Öztürk has reported no conflicts of interest.

Dr Yazıcı has reported no conflicts of interest.

Dr Sag has reported no conflicts of interest.

Further Reading

Apolone G, Corli O, Caraceni A, et al; Cancer Pain Outcome Research Study Group (CPOR SG) Investigators. Pattern and quality of care of cancer pain management. Results from the Cancer Pain Outcome Research Study Group. *Br J Cancer* 2009; 100:1566–1574.

Cherny NJ, Chang V, Frager G, et al. Opioid pharmacotherapy in the management of cancer pain: a survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. *Cancer* 1995; 76:1283–1293.

- Davies A, Buchanan A, Zeppetella G, et al. Breakthrough cancer pain: an observational study of 1000 European oncology patients. *J Pain Symptom Manage* 2013; 46:619–628.
- Donnelly S, Davis MP, Walsh D, Naughton M; World Health Organization. Morphine in cancer pain management: a practical guide. *Support Care Cancer* 2002; 10:13–35.
- Foley KM. Acute and chronic cancer pain syndromes. *Oxford Textbook of Palliative Medicine*, 3rd edition. New York: Oxford University Press, 2004; 298.
- Foley K. Management of cancer pain. In: De Vita VT Jr, Hellman S, Rosenberg SA (Editors). *Cancer: Principles and Practice of Oncology*, 6th edition. Philadelphia: Lippincott-Raven, 2002; 2977–3012.
- Goudas LC, Bloch R, Gialeli-Goudas M, et al. The epidemiology of cancer pain. *Cancer Invest* 2005; 23:182–190.
- Gourlay GK. Treatment of cancer pain with transdermal fentanyl. *Lancet Oncol* 2001; 2:165–172.
- Ripamonti CI, Santini D, Maranzano E, et al. Management of cancer pain: ESMO Clinical Practice Guidelines. *Ann Oncol* 2012; 23(Suppl 7):vii139–vii154.
- van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, et al. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007; 18:1437–1449.
- Walid MS, Donahue SN, Darmohray DM, et al. The fifth vital sign – what does it mean? *Pain Pract* 2008; 8:417–422.
- World Health Organization. *Cancer Pain Relief*, 2nd edition. Geneva: World Health Organization, 1996.

IV - Psychological complications



Psychological Complications

25

N. Blanco-Piñero¹

E. Nogales-Fernández²

L. de la Cruz-Merino²

¹Department of Psychiatry, Faculty of Medicine, University of Seville, Seville, Spain

²Medical Oncology Department, Hospital Universitario Virgen Macarena, Seville, Spain

Definition

Cancer represents a rupture in the individual's personal development. The intensity of this rupture will depend on the motivations, priorities and beliefs on which the patient's life is based. Hence, the potential destabilising power of cancer is due both to the individual subjective characteristics of each patient, and to the objective characteristics of the disease and of the treatments required. We must rather consider cancer as a set of intense individual stressors that are integrated in a complete life experience, and whose traumatic potential is great. Thus, cancer may suppress the patient's ability to personally meet the demands of each situation linked to the disease and its treatment. Therefore, the psychological and personal characteristics resulting from the different stages of the disease may complicate the adherence to treatment and, consequently, the evolution of the disease.

In this regard, the concept of “*mental or personal vulnerability*” becomes very important to adequately manage patients. We will define this concept as the tendency that a patient has to express suffering resulting from a situation or experience (such as cancer and/or its treatments), through psychosomatic, psychological or emotional symptoms and/or negative reactions. Therefore, patients will be highly influenced by the unpredictable and uncontrollable aspects relating to the onset of cancer, which make patients redefine themselves and their personal situation.

Moreover, the concept of “*adapting to cancer*” refers to the process of personal adjustment that the patient must carry out in parallel with the evolution of the disease, with the aim of promoting his/her independence and quality of life. For this reason, we consider it important to highlight that adaptation to cancer does not imply the absence of emotional suffering, but it does mean that this distress will not prevent the patient from adequately adhering to the medical prescriptions and treatments, and that in no case will it affect the desire to survive and recover. Hence, those patients who show that they are adapting adequately to the disease will be the ones who fight to achieve adequate emotional control (allowing them to follow the treatment regimens prescribed) and try to improve their quality of life. These patients will also display an adequate interest and attitude to continue with their life, making an effort to minimise the interruptions that their physical condition may provoke at any moment.

Description of the Process

The various stages through which the disease and its treatment pass involve different psychological and/or emotional risks. The **first stage** faced by a cancer patient will be when he/she *suspects* that he/she is suffering from a potentially fatal disease. Thus, the experience of the patient who visits the doctor because of a specific irregularity, and who receives diagnostic confirmation, will be very different from that of the patient who receives an unexpected diagnosis. In the first case, a more explosive emotional response could be expected when compared with the second, which more likely would leave the patient in shock, due to facing his/her own death so aggressively and abruptly. Both situations can create a whole range of emotional reactions that will even affect the patient’s adherence to the medical treatments required.

Thus, the *diagnosis* as the **second stage** leads the patient into a world of medical procedures, which is very much influenced by the prejudices and social myths that surround it. The psychological responses that can be expected in a recently diagnosed cancer patient will vary in accordance with the type of tumour, the stage, the symptoms and the treatments actually received and potentially received in the future.

Then, the most relevant treatment protocols begin to be applied, resulting in a series of side effects and undesired consequences for the patient, who enters a **third stage**. To face on one hand therapeutic processes, and on the other the appearance of incapacitating symptoms, is usually associated with increased anxiety, feelings of panic and loss of control, apart from the fear of death that the patient will experience throughout this process. Many studies have been carried out on the psychological effects of *surgical, chemotherapy and radiotherapy treatments*, and have explained not only the physical, but also the psychological and emotional consequences that these treatments have on patients.

Acute emotions of anxiety and anguish that are observed at the time of diagnosis will reduce over time, and will give way to a more sedate emotional state, although not free of fear and suffering. However, as the disease persists over time, each change in treatment or illness assessment will exacerbate this emotional state, but with a shorter duration. In this way, whatever the case, the period of actively fighting the disease tends to extend over time and creates a huge number of new situations for patients, which require an effort to be assumed and integrated into their daily lives.

Once the active treatment process has ended and when the patient remains, at least temporarily, *disease-free*, the first reaction observed is satisfaction and joy. This period could be considered as the **fourth stage**. However, in this period of time in which patients have to reintegrate themselves in their daily life, they will also face the limitations that the illness and/or its treatments have caused. This will imply feelings of frustration, helplessness and sadness. This (in addition to the fear of disease recurrence) results in an attitude of hypervigilance and insecurity, which is greatly increased by the coherent spacing over time of medical appointments, with a marked exacerbation of the emotional symptoms as these appointments come nearer.

The above-mentioned state is defined as “*Damocles syndrome*” and alludes to the continuous fear of recurrence of the cancer that underlies the recovery of cancer survivors. This fear involves the awareness of vulnerability and the lack of control over their own lives, which cancer survivors find it difficult to overcome. Moreover, it is also at this time that patients are capable of assessing their own strength, due to having

come through such a traumatic experience and being capable of recovering from the consequences.

The diagnosis of a metastatic process or a relapse awakens the same psychological processes in the patient as at the first diagnosis (**fifth stage**), but the fears and insecurities observed at this point are usually more intense, given that they involve the “failure of previous treatments”, “going through the same thing again” and “if it doesn’t work again”. All of the attitudes and emotions that are included within these patterns of thinking will again threaten the patients’ capacity to adequately deal with their situation. At these times it is very important for professionals to focus on caring for the most subjective aspects, since the patient already knows and is managing many of the objective difficulties that the new treatments will involve.

Finally the **sixth and last stage**, the time at which the patient receives the news that nothing can be done to cure the disease, causes a new process of rupture. The patient has gone from “being a healthy individual” to “an ill patient”, from “an individual who has beaten cancer” to “a patient who is ill again” and, lastly, from “a patient who is fighting against the disease” to “an individual who is going to die from it”. In these dichotomies we can observe how the subject goes from being a “patient”, a person who requires the care and guidance of a professional to live with his/her illness, to an “individual”, a person who must redefine his/her expectations, fears, priorities and values so he/she can adjust to the different moments of his/her life. As such, in the **terminal** phase, the individual enters a stage of great existential and philosophical reflection that will determine the quality with which he/she will face the end of his/her life. The terminal process involves patients in giving answers, closing chapters and giving their life meaning, and therefore if they freeze emotionally and excessively avoid the situation, we must consider that they are adjusting poorly.

Technical Procedures Involved

The assessment of the symptoms presented by the patient, the moment at which they appear and their duration will be key elements for discerning whether or not the patient is adapting adequately to the situation or

whether, by contrast, he/she is suffering from a psychopathological clinical profile as a result of the disease.

Hence, a mental illness in cancer patients has a series of particular characteristics that differentiate them from the cancer-free population. As a result of the disease and its treatments, the patient may present a vegetative and/or cognitive mood that may be confused with the manifestation of a non-existent psychopathological profile. The confusion that can be created in the evaluation of the psychological and emotional state of the patient leads to two contrasting situations.

On one hand, if there is the slightest sign of emotional suffering, the patient could be treated unnecessarily, turning an adaptation process that could be normal into a pathological process. On the other hand, it may be considered that these expressions of emotional suffering are normal reactions to the situation that the patient is experiencing, and therefore are not to be addressed. Thus, those who really show an abnormal response to their illness might not receive the appropriate treatment.

Once the potential vulnerabilities of the patient have been identified, they can be addressed and potentially managed, both through the sense of security given by the objective care of the illness, and through empathy for the patient and his/her family group.

In this sense, the caregiver must not only have a clear understanding of the adjustment and adaptation processes that must be expected of a patient who is dealing with his/her disease adequately, but also of the potential complications that could arise in these processes, and their repercussions on the patient's capacity to adhere to the treatments required. In order to carry out the processes of patient evaluation and support, communication skills must be one of the main resources in the oncologist's arsenal of therapeutic tools.

Predictive and Prognosis Markers

In Table 1 we aim to identify some risk factors which can predispose patients to present disproportionate or maladjusted responses throughout the disease and its treatments.

Table 1 Vulnerability Factors in Adaptation to Cancer

Dimension	Vulnerability factors	Consequences
Social	Poor social and/or family support With dependents in their care	Feeling of loneliness, abandonment, incomprehension, rejection, anguish, sadness and anxiety
	Low income	Anxiety resulting from a lack of objective resources for meeting obligations and addressing responsibilities
	Previous experiences of caring for patients	Fears and insecurities linked to these experiences, and to the experience of dependence
Personal	Gender	Women usually appear more affected due to difficulties in controlling emotions. Men tend to avoid being emotional in their experiences
	Age	Young adults are usually the most vulnerable
	Personal resources: intellectual, emotional	Low IQ or poor qualifications will make the situation patients are facing difficult to understand
	Personality traits and coping strategies	The tendency to worry, to be fatalistic, have poor emotional control and avoid confronting situations are predictive factors of poor adjustment to the illness
	Personal psychological history	<ul style="list-style-type: none"> ■ Greater psychological fragility when history of major psychopathological events: psychotic symptoms, major depression, etc ■ Also in those who have a greater predisposition to emotional suffering (anxiety, depression) ■ Potential drug interactions, and onset facilitation of psychopathological symptoms in vulnerable patients, due to chemotherapy treatments
	Previous experiences with illness and death	Creates fear
Medical	Poorly controlled acute symptoms: asphyxia, pain, etc	Feeling of helplessness, lack of control, physical suffering that affect psychological coping
	Advanced stages of the disease	Increased dependence and mortality awareness; fear and disorientation when facing the end of life
	Experiences of therapeutic failure	Anger and feelings of injustice and despair
	Location of the tumour	Facilitation of fantasies about the seriousness of the illness and the probability of survival
	Dysfunctional consequences of treatment	Increase in the experience of dependence, social rejection and helplessness
	Poor relationship with the referring oncologist and problems with the organisation of the service, bureaucracy	Anger; sense of helplessness and lack of control, insecurity and distrust, expectations of poor evolution

In this regard, whether cancer patients experience their illness as an opportunity for personal growth and reaffirmation, or as a devastating experience that could even trigger psychopathological symptoms, will depend, among other factors, on the assessment made by the patients of their personal situation, and on the resources that they have at their disposal in order to face it. This assessment will set in motion the coping processes that will allow them to deal with a potentially fatal disease, whose treatment is usually highly aggressive.

Clinical Results

Many studies have concluded by linking the symptoms of depression and anxiety with cancer in general and with each moment that can be defined throughout the treatment process. However, and despite the profuse literature that can be found in relation to the incidence of psychiatric symptoms in cancer patients, a stable and single incidence value cannot be established: the reported prevalence varies between 18% and 50% of patients. This great variability of data remains when we attempt to determine the incidence of more specific profiles such as depression, anxiety, post-traumatic stress or adaptive disorders. This wide disparity of results has various explanations, but the most important is the wide diversity of methodologies used.

Whatever the incidence, however, what has to be confirmed (more or less unanimously) is that cancer patients are more vulnerable to psychological suffering. The incidence of these symptoms is higher in patients who have physical or functional limitations as a result of cancer or its treatment.

Most of the studies consulted focus on very specific moments in the cancer treatment process. Thus, following diagnosis, an increase in the incidence of anxiety symptoms is observed in patients who adapt poorly at this moment. Once active treatment against the disease is introduced, symptoms of depression are likely to present a higher prevalence. Post-traumatic symptoms, if they appear, tend to evolve in parallel with the cancer treatment and recovery processes.

Potential Future Developments

Due both to the increase in survival rates, and to the change in attitude that is occurring from within medicine itself, the patient's quality of life is a necessary measurement to assess the real and multidimensional effectiveness of treatment protocols.

Thus, the objective of medical intervention in the treatment of cancer patients must be to pursue patient recovery whenever possible, and to boost the patient's well-being in all cases. To reach this goal, treating cancer from a holistic perspective is mandatory, with the aim of simultaneously alleviating the physical and psychological suffering.

In conclusion, we can consider that the assessment of quality of life becomes one of the best measurements of treatment results, along with survival, in cancer populations. As stated previously, we should understand that, with regard to the future of oncological intervention, we must integrate into medical training both the knowledge of emotional suffering resulting from the course of the disease and its treatments, and the communication skills necessary for the detection and support of this distress.

Likewise, we consider that the creation of multidisciplinary work teams for treating cancer patients, in which the integral suffering of the patient is addressed in a coordinated and systematic way, is mandatory.

Declaration of Interest:

Dr Blanco-Piñero has reported no conflicts of interest.

Dr Nogales-Fernández has reported no conflicts of interest.

Dr de la Cruz-Merino has reported no conflicts of interest.

Further Reading

Brennan J. Adjustment to cancer – coping or personal transition? *Psychooncology* 2001; 10:1–18.

Bultz BD, Carlson LE. A commentary on “Effects of screening for psychological distress on patient outcomes in cancer: a systematic review”. *J Psychosom Res* 2013; 75:18–19.

- Franks HM, Roesch SC. Appraisals and coping in people living with cancer: a meta-analysis. *Psychooncology* 2006; 15:1027–1037.
- Gurevich M, Devins GM, Rodin GM. Stress response syndromes and cancer: conceptual and assessment issues. *Psychosomatics* 2002; 43:259–281.
- Jacobsen P, Andrykowski M. Tertiary prevention in cancer care: understanding and addressing the psychological dimensions of cancer during the active treatment period. *Am Psychol* 2015; 70:134–145.
- Lutgendorf SK, Andersen BL. Biobehavioral approaches to cancer progression and survival. *Am Psychol* 2015; 70:186–197.
- Nayaka N, Bidstrup PE, Eplöv LF, et al. Mental vulnerability and survival after cancer. *Epidemiology* 2009; 20:916–920.
- Ryan H, Schofield P, Cockburn J, et al. How to recognize and manage psychological distress in cancer patients. *Eur J Cancer Care* 2005; 14:7–15.
- Tamagawa R, Garland S, Vaska M, Carlson LE. Who benefits from psychosocial interventions in oncology? A systematic review of psychological moderators of treatment outcome. *J Behav Med* 2012; 35:658–673.
- Zabora J, BrintzenhofeSzoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. *Psychooncology* 2001; 10:19–28.

Index

References to figures are indicated by ‘f’.

References to tables are indicated by ‘t’.

A

Abdominal infections, in neutropaenia, 183–193, 208

C. difficile *see* *Clostridium difficile*-associated diarrhoea (CDAD)

clinical features, 183, 187–188, 188t

diagnosis, 188–189, 189t, 190t

differential diagnosis, 189t

management, 191t, 192t

necrotising gastritis, 184

neutropaenic enterocolitis *see*

Neutropaenic enterocolitis (NEC)

pathophysiology, 186–187, 187t

risk factors, 185, 186t

severity, 183

Abdominal pain, 189t, 190t

Ablation, pain management, 257, 258

Absolute neutrophil count (ANC),

208, 209, 213f, 218f

Acetaminophen, 202, 249–250

Achlorhydria, 184

Acrolein, 88

Activated partial thromboplastin time (aPTT), 24, 237, 239

Acute coronary syndrome, 12–13, 246t

Acute kidney injury *see* Acute renal failure (ARF)

Acute renal failure (ARF), 85, 88–90

diagnosis and treatment, 90t

intrinsic, 89, 90t

mechanisms and causes, 88–89, 90t

post-renal, 89, 90t

pre-renal, 88–89, 90t

in tumour lysis syndrome, 103, 104t, 105

Acute tubular necrosis (ATN), 89

Acyclovir, 217

“Adapting to cancer”, 264, 266

Afatinib, 175, 176t

Aflibercept, 11t, 63t, 176t

Airway compromise, in superior vena cava obstruction, 30

Alkylating agents, cystitis due to, 88

Allantoin, 110, 168f

Allergic reactions

erythropoietic agents causing, 205

transfusions causing, 227t, 234

Allopurinol, in tumour lysis syndrome, 108–109, 108t

prevention by, 107–110

treatment, 111–112

Aminoglycosides, 44, 53, 192t, 214, 218f

Amphotericin B, 53, 142, 216, 236

Amyloidosis, 236

Anaemia, in cancer, 197–207

adaptive measures, 201

aetiology, 197–198

clinical features/examination, 199–201

definition and haemoglobin levels, 197, 197t

evaluation, 198–201

- macrocytic, 200
- megaloblastic, 200
- microcytic, 200
- normocytic, 200
- treatment, 201–206
 - erythropoietin *see* Erythropoietic agents
 - iron supplementation, 206
 - transfusions *see* Blood transfusion
- Anaemia of chronic disease, 198
- Anaerobic infections, 53
- Analgesics *see also* Non-steroidal anti-inflammatory drugs (NSAIDs); Pain management
 - administration route and timing, 254–255
 - extravasation management, 64
 - non-opioid, 249–250
 - opioid *see* Opioids
 - oral mucositis, 170
 - “rescue” dosing, 247, 252
 - side effects, treatment, 255–256
- “Analgesic ladder”, 249
- Anaphylaxis, 224, 226
- Anion gap, 120
- Anthracyclines
 - dose-related cardiotoxicity, 6–7, 9
 - extravasation, management, 65
 - liposomal, 7
 - type I cardiac dysfunction due to, 6t, 6–10
- Antiangiogenic drugs
 - hypertension-associated, 10–12,
 - myocardial ischaemia due to, 12
 - venous thromboembolism due to, 19
- Antibiotic lock therapy (ALT), 44, 214
- Antibiotic therapy
 - bacterial pneumonia, 141–142, 141t
 - choice, in septic shock, 52–53
 - community-acquired pneumonia, 141, 141t
 - diarrhoea management, 180
 - febrile neutropaenia, 141, 213–214, 217
 - intravascular catheter-related infection prevention, 40
 - intravascular catheter-related infection treatment, 44
 - neutropaenic enterocolitis, 192t
 - oral mucositis prevention, 168
 - septic shock, 52–53
- Anticancer drugs *see* Chemotherapy/antineoplastic drugs
- Anticoagulants/anticoagulation, 24–27
 - brain metastases and, 27–28
 - catheter obstruction management, 47
 - contraindications, 27
 - novel, 25
 - superior vena cava obstruction, 37
- Anticonvulsants
 - DIHS, 221
 - pain management, 254, 255
 - persistent/intractable hiccups, 152
 - seizures in brain metastases, 79, 80
- Antidiarrhoeal agents, 179, 180
- Antidiuretic hormone (ADH), 122
 - inappropriate secretion *see* Syndrome of inappropriate antidiuretic hormone secretion
 - release, 115, 116, 117
- Antiepileptic therapy *see* Anticonvulsants
- Anti-factor Xa, 24, 26, 27
- Antifungal therapy
 - febrile neutropaenia, 216–217
 - intravascular catheter-related infection treatment, 44
 - oral mucositis prevention, 168
- Antihistamines, 202, 223, 224, 226

- Anti-hypertensive therapy, 11
 - Anti-inflammatory agents *see also*
 - Non-steroidal anti-inflammatory drugs (NSAIDs)
 - oral mucositis prevention, 169
 - Antimicrobial therapy *see also*
 - Antibiotic therapy; Antifungal therapy
 - oral mucositis prevention, 168
 - septic shock treatment, 51–53
 - Antineoplastic drugs *see*
 - Chemotherapy/antineoplastic drugs
 - Antithrombin concentrate, 231
 - Anti-VEGF antibody *see* Bevacizumab
 - Anxiety, 126t, 133, 152, 160, 265, 269
 - Anxiolytics, dyspnoea relief, 133
 - Apheresis, 239, 241f
 - Apixaban, 25
 - Aprepitant, 162
 - Arrhythmias, 13–14
 - Arsenic trioxide, 14
 - Arterial blood gas analysis, 130
 - Arterial embolisation, 242
 - Arterial hypertension *see* Hypertension
 - Arterial thromboembolism, 202
 - Arteriography, in haemoptysis, 147
 - Aspergillosis, invasive, 142
 - Aspergillus*, pneumonia, 138, 140, 142
 - Aspiration pneumonia, 138
 - Aspirin, 37, 249
 - Axitinib, 11t
 - Azotaemia, pre-renal, 89
- B**
- Baclofen, 151–152
 - Bacteraemia, 41, 42, 43t, 44, 45, 208, 209, 214, 215, 219, 234, 235t
 - Bacterial infections *see also specific infections*
 - blood transfusions and, 202
 - diarrhoea and, 177, 178
 - febrile neutropaenia, 209, 213–214, 217
 - intravascular catheter-related, 44
 - pneumonia, 138, 139t, 141–142
 - septic shock in cancer patients, 50, 51t, 52–53
 - Benzydamine oral rinse, 169
 - Bevacizumab, 6t, 8, 19, 128t, 145t, 159t, 176t, 223
 - brain oedema management, 79
 - hypersensitivity reaction to, 225
 - hypertension associated, 10, 11t
 - intracranial bleeding not associated, 80
 - myocardial ischaemia due to, 12t
 - Biological agents, type II cardiac dysfunction due to, 5, 6t, 7–8
 - Biomarkers
 - cardiospecific, 9
 - venous thromboembolism, 20
 - Bisphosphonates, 99–100
 - Bleeding, 23–27, 36t, 46, 80, 89, 115, 144–148, 179, 184, 188, 189t, 190t, 191, 192
 - anaemia due to, 198, 200
 - bronchial tree *see* Haemoptysis
 - in disseminated intravascular coagulation, 228–231
 - in liver disease, 240
 - local, treatment, 240, 241f
 - in septic shock, 55
 - in thrombocytopenia, 233
 - Bleeding disorders, 233–242
 - aetiology, 234–236, 235t
 - algorithm, management, 241f
 - clinical features/examination, 236–237
 - evaluation, 236–238, 241f
 - prevention (of bleeding), 238–239

treatment (of bleeding), 239–242, 241f

Bleomycin, 129, 128t, 159t, 63t
lung injury, 131, 133

Blood concentrates, for haemoptysis, 146

Blood cultures, 190t
febrile neutropaenia, 210
intravascular catheter-related infection diagnosis, 41–42, 214
septic shock, 52

Blood loss, haemoptysis, 144, 147

Blood pH, 119, 130, 131

Blood pressure, 8, 21, 50t, 55, 116, 117, 129, 161, 211t, 227t, 228
elevated, 10–12, 11t, 205

Blood smear, 199

Blood transfusion, 50t
advantages, 202–203
in anaemia, 201–203
in bleeding disorders, 234
indications, 201
limitations, 201–202
reactions, 202, 226–228, 227t, 234
in septic shock, 56

Blood urea nitrogen (BUN), 88, 90, 116

Bone
calcium resorption, inhibition, 99–101
destruction, 95
metastases, 97, 249, 255
pain, 247–250, 258

Bone marrow
anaemia, 198, 200
bleeding disorders, 233
examination, 238
transplantation, 117, 138

Brachytherapy, 87

Bradycardia, 13, 14

BRAF inhibitors, 78

Brain metastases, 27, 77–82
anticoagulation in, 27–28
complications, 78–81
intracranial haemorrhage, 79–80
intracranial pressure elevation, 78–80
neurocognitive impairment, 80–81
seizures, 79
evaluation and treatment, 77–78
future strategies, 81–82
leptomeningeal carcinomatosis and, 81
signs and symptoms, 77–78
spinal cord compression vs, 71

Brain natriuretic peptide (BNP), 9, 130

Brain oedema *see* Cerebral oedema

Breathing, 30, 49, 54, 125, 127, 129

Breathlessness *see* Dyspnoea

Breath sounds, 129

Bronchial arteries, bleeding from, 144

Bronchial diseases, haemoptysis due to, 145t

Bronchodilators, in dyspnoea, 132

Bronchoscopy, haemoptysis, 33, 140, 146–148, 150

C

Calcitonin, 100

Calcium
absorption (intestinal), 95–96, 101
bone resorption, inhibition, 99–101
elevated *see* Hypercalcaemia
excretion (urinary), 97, 99, 100
normal serum levels, 95
reabsorption (renal), 99
removal/chelation, 100

Calcium channel blockers (CCBs), 11, 13

- Calcium gluconate, 111
- Calciuria, 99
- Caloric intake, in septic shock, 55
- Candidiasis, 215–217
- Cannulation, 61
- Capecitabine, 174
 - diarrhoea due to, 173–174
 - myocardial ischaemia due to, 12, 12t
- Carboplatin, hypersensitivity reactions, 224
- Cardiac disorders
 - in cancer, 3–16
 - extravasation of chemotherapy and, 60
 - hiccups due to, 149t
- Cardiac failure *see* Heart failure
- Cardiac output, decreased, 4, 54, 119, 129
- Cardiac tamponade, 3–5
- Cardiomyocyte dysfunction, 8
- Cardioprotectants, 7
- Cardiotoxicity, chemotherapy-induced
 - anthracycline-induced, 6–7
 - evaluation and treatment, 8–10, 9f
 - monoclonal antibodies causing, 7–8
 - targeted agents causing, 7–8
- Cardiotoxicity, radiotherapy-induced, 15–16
- Cardiovascular complications, 3–68
 - of anaemia, 199
 - extravasation of chemotherapy and, 60
 - of hypercalcaemia, 97
- Cardiovascular insufficiency, in septic shock, 53–54
- Caspofungin, 142, 216
- Catheter(s)
 - central venous *see* Central venous catheters (CVCs)
 - urinary, 87
- Catheter-related blood stream infections (CRBSI), 40, 42, 43t, 214–215 *see also* Intravascular catheter-related infections (ICRI)
- Cellular immunity, impaired,
 - pulmonary infections, 137, 137t
- Cellulitis, 215
- Cementoplasty, 256, 258
- Central venous access device (CVAD), 61
- Central venous catheters (CVCs)
 - complications, 39–48
 - extravasation, 61
 - febrile neutropaenia, 210, 212
 - infections *see* Intravascular catheter-related infections (ICRI)
 - malfunction, 47
 - obstruction, 47
 - thrombosis, 45–47
 - placement, 61
- Central venous oxygen saturation (ScvO₂), 50, 51
- Central venous pressure (CVP), 50, 51, 54
- Cerebral oedema, 78
 - hyponatraemia-induced, 118, 119
 - superior vena cava syndrome, 31, 33, 34t, 35
- Cetuximab, 175, 223, 225
- Chelation therapy, calcium removal, 100
- Chemoreceptor trigger zone, 160
- Chemosensitive tumours, 35, 73, 75
- Chemotherapy/antineoplastic drugs
 - adverse effects *see* Chemotherapy complications/adverse effects
 - brain metastases treatment, 78
 - discontinuation, in dyspnoea, 133
 - extravasation *see* Extravasation of chemotherapy
 - non-vesicants/irritants/vesicants, 58,

- 59, 62, 63t, 64, 66
- rechallenge, dyspnoea and, 133
- spinal cord compression
 - management, 73, 74f, 75
 - superior vena cava obstruction
 - management, 36–37
- Chemotherapy complications/adverse effects
 - arrhythmias, 13–14
 - arterial hypertension, 10–12, 11t
 - cardiac failure *see* Heart failure
 - diarrhoea *see* Diarrhoea
 - DIHS, 221
 - dyspnoea, 128, 128t
 - hyponatraemia, 117
 - left ventricular dysfunction, 5–6, 6t
 - local reactions, 58–68
 - lung toxicity, 128, 128t, 132
 - myocardial ischaemia, 12–13, 12t
 - nausea/vomiting due to *see* Nausea and vomiting
 - neutropaenic enterocolitis, 185, 186t
 - oral mucositis, 164, 166–169
 - pericardial effusions, 4
 - psychological effects, 265
 - QT prolongation, 14–15
 - thrombocytopenia *see* Thrombocytopenia
 - Thrombocytopenia
 - thromboembolism, 19
 - type I cardiac dysfunction, 5, 6–7, 6t
- Chemotherapy-induced cystitis (CIC), 88
- Chest pain, 4, 13, 21, 138, 223, 224
- Chest X-ray
 - dyspnoea, 130
 - febrile neutropaenia, 210
 - haemoptysis, 145
 - pulmonary infections, 139, 139t, 140
 - superior vena cava obstruction, 33
 - venous thromboembolism, 21
- Cheyne–Stokes breathing, 129
- Chlorhexidine mouthwash, 168
- Chlorpromazine, 151, 152, 163
- Chronic myeloproliferative disorders, 236
- Chronic obstructive pulmonary disease (COPD), 125, 129, 131, 132, 138
- Chronic radiation enteritis, 177
- Cisplatin
 - extravasation, 58, 63t, 64, 65
 - hiccups, 149t
 - hypersensitivity reactions, 224
 - hyponatraemia, 117
 - myocardial ischaemia due to, 12
 - mucositis, 164
 - nausea, 159t
 - nephrotoxicity, 89, 90t
- Clostridium difficile*, toxin, 177–178, 188
- Clostridium difficile*-associated diarrhoea (CDAD), 177–178, 183, 185, 189t, 190t, 215
 - CT findings, 191t
 - pathophysiology, 187, 187t
 - risk factors, 185, 186t
- CLOT study, 24
- Clotting factors
 - bleeding disorders due to, 234, 235t
 - in disseminated intravascular coagulation, 228
- Coagulation, 228, 233, 234
 - assessment, 237
 - bleeding disorders due to, 234, 235t
 - by heat (laser), 242
 - inhibitors, in septic shock, 55–56
- Coagulation disturbances, 234–235, 234t
 - bleeding prevention, 239
 - treatment, 240
- Coagulation factors *see* Clotting factors

- Coagulopathy, 80, 145t, 146, 187t, 190t, 192t, 233, 240
- Codeine, 249, 251
- Coeliac plexus block, 178, 256-257
- Cognitive impairment, brain metastases and, 80-81
- Cold compresses, 64
- Colonoscopy, 188-189
- Complete blood count (CBC), 52, 130, 150, 180, 199, 200, 209
- Compression stockings, 23
- Computed tomography (CT)
 - abdominal infections, 184, 189t, 191t
 - brain metastases, 80
 - cancer pain, 249
 - dyspnoea, 130
 - haemoptysis, 145
 - nausea, 161
 - NEC, 179
 - neutropenia, 210
 - pulmonary infections, 139
 - renal failure, 86
 - spinal cord compression, 73
 - superior vena cava obstruction, 33
 - thromboembolism, 21
- Congestive heart failure (CHF), 5
 - anthracycline-induced, 6-8
 - blood transfusions and, 202
 - hyponatraemia, 115
 - tumour-lysis syndrome, 105
- Continuous erythropoiesis receptor activator (CERA), 203
- Control, loss of, 265
- Coronary artery disease, 12-13
- Corticosteroids
 - adverse effects, 73-74
 - cancer pain, 255
 - diarrhoea, 175
 - dyspnoea treatment, 131-132
 - equivalent doses/different agents, 132t
 - extravasation management, 64
 - haemoptysis, 150
 - "high-dose", in spinal cord compression, 73
 - hypercalcaemia management, 101
 - hypersensitivity reaction treatment, 226
 - hypoglycaemia, 121
 - "low-dose", in spinal cord compression, 73
 - for nausea/vomiting, 162, 163
 - pulmonary infections, 142
 - spinal cord compression management, 73-74
 - septic shock treatment, 51, 53, 55
- Cough
 - dyspnoea, 128-129
 - pulmonary infections, 138
 - superior vena cava, 33t, 34t
 - thromboembolism, 21
- COX-2 inhibitors, 250
- Creatinine, clearance, 11, 54, 65, 212, 238
- Creatinine, serum, 88, 104t, 109, 150, 209
- Crizotinib, 13, 14, 159t, 176t
- Cryoprecipitate, 192t, 231, 240, 241f
- Cryotherapy, oral mucositis prevention, 168-169
- CTLA-4 inhibitors, 78, 176f
- Cultures *see* Blood cultures
- Cyclophosphamide, 4, 7, 8, 63t, 88, 116t, 117, 121, 122
- CYP3A4 inhibitors, 15
- Cystitis, 85, 87
 - chemotherapy-induced, 88
 - haemorrhagic, 117, 121
 - non-infectious, 87-88
 - radiation-induced, 87

Cytokines
 proinflammatory, 18, 166, 187t
 in septic shock, 56
Cytomegalovirus (CMV)
 abdominal infections, 183, 189t
 pneumonia, 137t, 140, 142
Cytotoxic agents *see* Chemotherapy/
 antineoplastic drugs

D

Dabigatran etexilate, 25
Dalteparin
 thromboembolism prevention, 22,
 23t
 thromboembolism treatment, 24, 24t
“Damocles syndrome”, 265
Darbepoetin-alpha, 203, 204t, 205
Daunorubicin,
 cardiotoxicity, 7
 vesicant potential, 63t, 64, 65
D-dimer testing, 20, 46, 230, 237
Decompressive neurosurgery, 79
Decompressive surgery, 75
Deep venous thrombosis (DVT), 17,
 19, 20, 20t, 21t, 22, 25, 26, 46
Defibrillation, 15
Denosumab, 100
Depression, 74, 80, 97, 152, 158, 160,
 256, 269
Desensitisation protocols, 226
Desmopressin, 240
Dexamethasone, 132t
 brain oedema management, 78–80
 hiccups, 149t
 nausea/vomiting treatment, 162,
 163
 spinal cord compression, 73
Dexrazoxane, 7, 65
Dextrose, 107, 121

Diabetes insipidus, nephrogenic, 97
Dialysis, 100, 111, 205
Diaphragmatic muscle, spasms, 148
Diarrhoea, 172–182
 assessment, 178–179
 C. difficile *see* *Clostridium difficile*-
 associated diarrhoea (CDAD)
 causes (non-chemotherapy),
 177–178
 chemotherapy-induced, 173–175,
 176t, 181
 treatment, 180
 classification, 172
 complicated, 179, 180–181
 in febrile neutropaenia, 215
 management/treatment, 179–181
 risk factors, 172–173
 severity grading, 173, 173t, 179
 uncomplicated, treatment, 179–180
Diet/nutrition *see also* Enteral nutrition
 diarrhoea management, 179, 180
 in septic shock, 55
Differential time to positivity (DTTP),
 214
Differentiation syndrome, 133
Dihydropyrimidine dehydrogenase
 (DPD) deficiency, 174
1,25-Dihydroxyvitamin D, 95–96
Dimethylsulphoxide (DMSO), 64, 65
Dinaciclib, 104
Disseminated intravascular
 coagulation (DIC), 56, 228–231,
 235
 causes, 228–229, 235–236
 clinical features, 229
 laboratory tests, diagnosis, 230, 237
 management, 231, 240
 scoring systems, 230
Diuresis, forced, 121–122
Diuretics, 34, 97, 99, 111, 115t, 121

- DMSO (dimethylsulphoxide), 65
- DNA-binding agents, 62
- DNA topoisomerase II, 65
- Dobutamine, 54
- Docetaxel, 12t, 63t, 128t, 149t, 159t, 175, 186t, 187t
- Documentation, extravasation, 66, 67f
- Doxepin, 170
- Doxorubicin, 7
 - cardiotoxicity, 6–7, 6t, 9
 - extravasation, 63t, 64, 65
 - lung toxicity, 128t
 - nausea, 159t
- Drug(s) *see also specific drugs/drug groups*
 - decreased clotting factors due to, 234
 - hypersensitivity reactions *see* Hypersensitivity reactions (HSR)
 - hypersensitivity syndrome (DIHS), 221
 - persistent/intractable hiccups due to, 149t, 150
 - platelet dysfunction due to, 236
- Drug–drug interactions, 14, 109
- Drug-induced hypersensitivity syndrome (DIHS), 221–223
- Drug reaction with eosinophilia and systemic symptoms (DRESS), 221–223
- Dyspnoea, 125–135, 199
 - acute, 127–128
 - aetiology, 126, 126t
 - anaemia, 202, 205
 - antineoplastic therapy causing, 128, 128t, 133
 - bleeding disorders, 236
 - cardiac complications, 4
 - chronic, 128
 - clinical examination, 129
 - definition, 125
 - evaluation, 127
 - evaluation of tolerance, 130–131
 - haematological emergencies, 223
 - history and timing, 127–128, 129
 - inspiratory vs expiratory, 129
 - investigations, 130
 - language/terminology, 126, 127
 - management, 131–134
 - in pulmonary infections, 138
 - quantification, 127
 - refractory, 133
 - septic shock, 54
 - superior vena cava obstruction and, 30–31, 33t
 - symptoms associated, 128
 - thromboembolism, 21
- Dysuria, 87
- ## E
- Echocardiography, 4, 8, 9, 42, 130
- Edoxaban, 25
- Elbow flexure, cannulation, 59–60, 61
- Electrocardiography (ECG), 4, 12–15, 130, 223
- Electrolyte disturbances
 - QT prolongation and, 14, 15
 - tumour lysis syndrome, 111
- Electrolyte measurement, in dyspnoea, 130
- Embolisation, 147, 242, 257, 258
- Emesis *see* Nausea and vomiting
- Emotional response (to cancer), 266–267 *see also* Psychological effects of cancer
 - to diagnosis, 264–265
 - to post-treatment stage, 265
- Emotional suffering, 263–265, 267, 270

Encephalitis,
 in febrile neutropaenia, 217
 hypersensitivity reactions, 222
Endocrine complications, 114–122
Endoscopy, 150, 162, 188–189, 200
Endothelial cell activation, 18
Endothelin-1, 10
Enoxaparin
 thromboembolism prevention, 22,
 23, 23t
 thromboembolism treatment, 24,
 24t, 25
Enteral nutrition
 diarrhoea due to, 178
 in septic shock, 55
Enterococcus infection, intravascular
 catheter-related, 43f, 45, 51t
Enterocolitis, neutropaenic *see*
 Neutropaenic enterocolitis (NEC)
Epidermal growth factor receptor
 (EGFR) inhibitors, 78, 175, 176t
Epidural venous plexus obstruction, 71
Epinephrine, 120, 226, 236
Epirubicin, cardiotoxicity, 6t, 7, 9
Epoetin alfa, 203, 204t
Epoetin beta, 204t
Epsilon-aminocaproic acid, 87, 240
ErbB2 signalling, 8
Erythropoiesis-stimulating agents
 (ESAs), 203, 204, 205
 advantages, 206
 limitations, 205
Erythropoietic agents, 203–206
 advantages, 206
 dosages, 204–205, 204t
 indications, 204–205
 limitations, 205
Erythropoietin (EPO), 203, 206
 biosimilar, 203–204
Erythropoietin-alpha, 203, 204t

Erythropoietin-beta, 203, 204t
Euvolaemic hyponatraemia, 115t,
 116–117, 118
External beam radiation therapy
 (EBRT), 73 *see also* Radiotherapy
Extravasation kit, 64
Extravasation of chemotherapy, 58–68
 differential diagnosis and grading,
 58–59
 documentation and follow-up, 66,
 67f
 epidemiology, 59
 management, 63–66
 antidotes, 65–66
 surgical, 66
 risk factors, 59–62, 60t
 patient-related, 59–60, 60t
 procedure-related, 60t, 61
 staff-related, 60, 60t
 substance-related, 60t, 62, 63t

F

Factor V, 19, 235, 237
Factor VIII, 20, 235, 237, 240
Factor VIII coagulant protein, 18
Factor Xa, 18, 24
 inhibition, 24–27
Factor X deficiency, 236 / inhibition, 25
Fatigue, 4, 13, 97, 120, 127, 148, 172,
 197, 199, 202, 206, 236
Fear of death, 265
Fear of recurrence, 265
Febrile neutropaenia, 208–220
 aetiology and epidemiology,
 208–209
 assessment and investigations,
 209–210
 bacterial infections, 209, 212,
 213–214, 217

- candidiasis, 215–217
- catheter-related infection, 214–215
- cellulitis, 215
- diarrhoea, 215
- duration, 212
- high-risk patients, 211–212, 213–214, 213f, 216f
- low-risk patients, 210, 212–213, 213f
- MASCC Scoring index, 210–212, 211t
- meningitis/encephalitis, 217
- pneumonia, 215
- prolonged, algorithm, 216f
- risk factors/risk groups, 210–212, 211t
- treatment, 141, 212–217, 213f
 - antibiotics, 141, 212, 213–214, 217
 - duration, 217
 - follow-up, 217, 218f
 - viral infections, 217
- Febuxostat, 107t, 108f, 109, 112
- Fentanyl, 170, 252, 254t, 255, 256
- Ferritin, 198, 206
- Fever
 - abdominal infections, 183, 184, 185, 187, 188, 188t, 189t, 190t, 192t, 193
 - cancer pain, 256
 - diarrhoea, 179
 - drug-induced hypersensitivity syndrome, 221, 222, 227t, 230, 238t
 - dyspnoea, 128, 129
 - febrile neutropaenia, 208, 209, 211, 211t, 213, 216, 216f, 218f
 - ICRI, 41, 42
 - pulmonary infections, 138, 141
 - septic shock, 49, 52
 - SVCS, 36
- Fibrin degradation products, 230, 237
- Fibrinogen, 228, 230, 231, 234, 237, 240
- Fibrinolysis, 228, 234, 235, 235t, 240, 240f
- Fibrinolytic system, 228, 234
 - inhibition, in VTE, 18
- Fluconazole, 44, 216
- Fluid overload, 105, 111, 121
- Fluid retention, 74, 115, 116, 117, 118, 119, 121
- Fluid therapy *see also* Hydration
 - crystalloids, 53, 107, 111
 - diarrhoea, 180
 - neutropaenic enterocolitis, 192t
 - septic shock, 53–54
 - tumour lysis syndrome, 107–108, 111
- Fluoropyrimidines, diarrhoea due to, 173–174
- 5-Fluorouracil (5-FU), 168, 173
 - abdominal infections due to, 186t
 - diarrhoea due to, 173–174
 - metabolism, 174
 - myocardial ischaemia due to, 12, 12t, 13
 - mucositis, 164, 168
 - nausea, 159t
- Folate, 198, 200
- Fondaparinux, 25
 - thromboembolism prevention, 22, 23t
 - thromboembolism treatment, 25
- Forced diuresis, complication, 121–122
- Foreign bodies, infected, septic shock, 52
- Fosaprepitant, 162, 163
- Fraction of inspired oxygen (FiO₂), 128, 131
- FRAGEM study, 22
- Fresh frozen plasma (FFP), 231, 234, 240
- Fungal infections
 - intravascular catheter-related, 44, 45
 - pneumonia, 138, 139t, 141

septic shock, 53
Furosemide, 99, 111, 117, 119, 122

G

Gabapentin, 152, 255
Ganciclovir, 53, 142, 217
Gastritis, necrotising (NG), 184, 192t
Gastrointestinal complications, 155–193
 bleeding, 242
Gastrointestinal disorders
 hiccups due to, 149t
 nausea/vomiting due to, 159–160
Gastrointestinal infections *see*
 Abdominal infections, in
 neutropaenia
Gemcitabine, 22, 63t, 133, 149t, 159t
Germ cell tumours, 35, 36, 38, 73, 106t
Gilbert's syndrome, 174
Glomerular filtration rate (GFR), 11,
 24, 88–90, 97, 201
Glucagon, 120, 121
Glucocorticoids *see* Corticosteroids
Gluconeogenesis, 120
Glucose
 blood, fasting levels, 121
 blood, levels, 55, 115t
 homeostasis, 120
Glucose-6-phosphate dehydrogenase
 (G6PD) deficiency, 110, 112
Glycogen, 120
Graft-*versus*-host disease, acute, 191t,
 227t
Gram-negative bacteria, 43f, 44, 45,
 139t, 192t, 227t
 febrile neutropaenia, 50, 52,
 213–214
Gram-positive bacteria, 50, 52, 209,
 212, 214
Granisetron, 162

Granulocyte colony-stimulating factor
 (G-CSF), 56, 192t
Granulocyte–macrophage colony-
 stimulating factor (GM-CSF), 56
Growth factors, 56, 141, 169 *see also*
 Vascular endothelial growth factor
 (VEGF)

H

Haematocrit (Hct), 50f, 200, 201
Haematological malignancies *see also*
 Leukaemia; Lymphoma
 abdominal infections, 193
 anaemia, 203
 bleeding, 234, 235
 CVC, 44
 febrile neutropaenia, 208, 215
 mucositis, 169
 pulmonary infections, 140
 tumour lysis syndrome, 103, 105
Haematopoietic growth factors, 56
Haematopoietic stem cell
 transplantation (HSCT), 138, 140,
 164, 212
Haemoglobin levels, 186t, 190t, 197,
 197t, 201, 206 *see also* Anaemia
Haemolysis, 89, 90t, 110, 198, 200,
 201, 224t, 227t, 229
Haemolytic anaemia, 201, 237
Haemolytic reactions, to transfusions,
 227t, 228, 234
Haemoptysis, 144–148
 causes, 144, 145t
 dyspnoea, in, 128
 evaluation, 145–146
 massive, 144, 146, 147
 treatment and supportive care,
 146–147
 thromboembolism, in, 21

- Haemorrhage *see* Bleeding
- Haemostasis, 18
- Haemothorax, 39, 129, 134
- Heart failure, chemotherapy-related, 5–10
 - aetiology, 5–8, 6t
 - congestive *see* Congestive heart failure (CHF)
 - evaluation and treatment, 8–10, 9f
 - types, 5
- Heparin
 - disseminated intravascular coagulation management, 231
 - in anaemia, 205
 - in bleeding disorders, 236, 239
 - in CVD, 46
 - in septic shock, 55–56
 - in thromboembolism, 22, 23t, 24, 27
- Heparin-induced thrombocytopenia, 24, 27
- Hepatocellular carcinoma, brain metastases, 80
- HER2-targeting agents, 8, 78
- Herpes virus 6 (HHV6), 137t, 221, 222, 223
- Hiccups, persistent/intractable, 148–152
 - aetiology, 148, 149t
 - evaluation, 150
 - treatment, 151–152
- Histone deacetylase inhibitors, 14
- Holistic management of cancer, 270
- Hormonal therapy, 19, 75
- Humoural immunity, impaired, 137, 137t
- Hyaluronidase, 64, 66
- Hydration *see also* Fluid therapy
 - in hypercalcaemia, 99
 - tumour lysis syndrome prevention, 107–108
 - tumour lysis syndrome treatment, 111
 - vigorous, 117
 - diuresis and, 121
 - intravenous, 88
- Hydrocephalus, obstructive, 79
- Hydrocodone, 252, 254t
- Hydrocortisone, 55, 132t
- Hygiene, intravascular catheter-related infection prevention, 40
- Hyperbaric oxygen, 87
- Hypercalcaemia (of malignancy), 95–102
 - aetiology, 95–96
 - definition, 95
 - differential diagnosis, 96, 96t
 - evaluation, 97–98, 98f
 - in nausea, 158
 - refractory, 100
 - treatment, 98–101
- Hyperglycaemia, 49, 55, 130, 149t, 158, 187t
- Hyperkalaemia, in tumour lysis syndrome, 103, 104t, 111
- Hyperparathyroidism, 96, 96t, 97, 98f
- Hyperphosphataemia, 97
 - in tumour lysis syndrome, 103, 104t, 111
- Hypersensitivity reactions (HSR), 223–226
 - acute, 223, 224
 - aetiology, 223
 - clinical features, 224–225
 - monoclonal antibody-associated, 225
 - platinum salt-related, 224
 - severity (NCI-CTCAE definitions), 225, 225t
 - taxane-associated, 224
 - treatment, 225–226
 - types, 223, 224t
- Hypersensitivity syndrome, drug-induced (DIHS), 221–223

- allopurinol, 108–109, 221
 - Hypertension
 - antineoplastic agents-associated, 10–12, 11t
 - erythropoietic agents causing, 205
 - hypercalcaemia-related, 97
 - hypersensitivity reactions-related, 223, 224
 - intracranial, 77
 - nausea causing, 160
 - thromboembolism-related, 27
 - tumour lysis syndrome-related, 105
 - Hyperuricaemia, in tumour lysis syndrome, 103, 104t, 107
 - prevention, 108–109
 - treatment, 111–112
 - Hypervigilance, 265
 - Hypervolaemic hyponatraemia, 115, 115t, 116–117, 121
 - Hypoalbuminaemia, 178
 - Hypocalcaemia, in tumour lysis syndrome, 103, 104t, 111
 - Hypoglycaemia
 - dyspnoea and, 130
 - tumour-induced, 120–121
 - Hypokalaemia, 15, 74, 118, 149t, 161, 172, 178
 - Hyponatraemia, 114–119, 121
 - acute, 122
 - causes, 114–115, 115t
 - chemotherapy causing, 117
 - chronic, 118, 119
 - definition, 114
 - diagnosis, 118
 - factitious, 115t
 - pathogenesis in syndrome of inappropriate antidiuretic hormone secretion, 116–117
 - rate of correction, 119
 - signs and symptoms, 118
 - subtypes, 115t
 - treatment, 118–119
 - Hypotension, 5, 34t, 49, 104t, 131, 140, 151, 187t, 188t, 214, 227t
 - Hypoventilation, 131
 - Hypovolaemia, 53, 106t, 111, 115t, 116
 - Hypovolaemic hyponatraemia, 115, 115t, 117, 118
 - Hypoxaemia, 50t, 54, 129, 131, 139t, 211
 - Hypoxanthine, 107–108, 109
- I**
- Idarubicin, cardiotoxicity, 7
 - Ideal bodyweight (IBW), 55
 - Ileocaecal area, neutropaenic enterocolitis, 184
 - Imatinib, 6t, 8, 128t, 176t
 - Immune checkpoint inhibitors, 132, 133, 175
 - Immune-haematological emergencies, 195–242 *see also* Anaemia, in cancer; Bleeding disorders; Febrile neutropaenia
 - Immune-mediated thrombocytopenia, 236
 - Immunoglobulin E (IgE), 223, 224, 225, 227t
 - Immunomodulatory agents, 19, 175
 - Immunosuppression, pulmonary infections, 136, 137, 137t, 138, 140
 - Infection(s)
 - abdominal *see* Abdominal infections, in neutropaenia
 - disseminated intravascular coagulation due to, 229
 - intravascular catheter-related *see* Intravascular catheter-related infections (ICRI)

in neutropaenia *see* Febrile neutropaenia; Neutropaenia pulmonary *see* Pulmonary infections
septic shock, 49, 50
Inferior vena cava (IVC) filter, 25–28
Influenza, 137t, 139t, 142
Infusional nerve block, 257
Infusion-related reactions, 223–226
Inotropic agents, 51
Insecurity, 265, 268t
Insulin
 levels, hypoglycaemia and, 121
 therapy in septic shock, 55
 tumour-induced hypoglycaemia, 120
Insulinomas, 121
International normalised ratio (INR), 26, 239
Intestinal obstruction, 161, 162
Intracranial haemorrhage
 brain metastases and, 27–28, 77–80
 cardiac complications and, 10
 management, 80
Intracranial hypertension, 78–79
 acute, bleeding and, 80
Intravascular catheter-related infections (ICRI), 39–45, 61, 214–215
 clinical presentation, 40–41
 evaluation, 41–42
 prevention, 40
 treatment, 42–45, 43f, 214–215
Intravenous infusion, extravasation *see* Extravasation of chemotherapy
Intravenous saline, 99
Irinotecan, 63t, 128t, 149t, 159t, 173, 174
Iron
 deficiency, 198, 200, 206
 overload, 202
 supplementation in anaemia, 206

Irritants (antineoplastic agents), 62, 63t
Itraconazole, 142

K

Kussmaul breathing, 129

L

Lactate dehydrogenase (LDH), 106t, 201
Lactate levels, 119–120
Lactic acidosis, 49, 119–120
Laryngeal oedema, 30, 34t, 35
Laser coagulation, 242
Laser therapy,
 haemoptysis treatment, 147
 oral mucositis prevention, 169
Laxatives, 177, 255
Left ventricular dysfunction (LVD), 5, 6–7, 6t, 8, 10, 11
Left ventricular ejection fraction (LVEF), 5, 8, 9f, 10
Legionella, 137t, 139t, 140, 215
Leptomeningeal carcinomatosis (LC), 81
Leukaemia
 acute promyelocytic, 14, 133, 229, 236
 Burkitt, 106t
 chronic lymphocytic, 104, 236
 corticosteroids, 101
 glucocorticoids, 73
 lactic acidosis, 119
 neutropaenia duration, 212
 tumour lysis syndrome, 103
Leukoreduction, 202
Liver disease
 bleeding due to, treatment, 235t, 240
 hyponatraemia and syndrome of

inappropriate antidiuretic hormone secretion, 115

Liver metastases, 159, 238, 258

Loperamide, 162, 179–180

Low level laser therapy (LLLT), 169

Low molecular weight heparin (LMWH), 22, 23t, 24, 26, 27

abnormal platelet function, 236

catheter-related thrombosis treatment, 46

in septic shock, 55–56

thromboembolism prevention, 22, 23t, 205

thromboembolism treatment, 24, 24t, 26

Lung cancer, 4, 15, 71, 77, 78, 95, 106t, 116t, 138

superior vena cava obstruction due to, 31, 32t, 34, 35, 35f, 36

Lung infections *see* Pulmonary infections

Lung toxicity

clinical features, 129

drugs causing, 128, 128t, 131, 133

corticosteroid treatment, 132

discontinuation and rechallenge, 133

Lymphadenopathy, 222

Lymphoma

cardiotoxicity, 4, 15

DIC, 236

hiccups, 149t

hypercalcaemia, 95–96, 101

lactic acidosis, 119

NEC, 185

neutropaenia, 211t

renal involvement, 122

spinal cord compression, 71

superior vena cava obstruction due to, 32t, 35, 35f, 36–38

thromboembolism, 17, 19

tumour lysis syndrome, 103

M

Magnesium infusion, 15

Magnetic resonance imaging (MRI)

brain metastases, 78, 80, 81, 86

cancer pain, 249, 258

obstructive bowel disease, 161

spinal cord compression, 72, 74f, 75

superior vena cava obstruction, 33

Mannitol, 79, 111, 121

MASCC Scoring index, 210–212, 211t, 213f

Mean arterial pressure (MAP), 50, 51, 54

Mean corpuscular volume (MCV), 200

Mediastinal metastases, 32t, 33

Mediastinal tumours (primary), 32t

Melanoma,

brain metastases, 27, 77, 78, 80

cardiotoxicity, 4

haemoptysis, 145t

SCC, 75

Melphalan, 63t, 116t, 164, 168

Meningitis

in febrile neutropaenia, 217

in hiccups, 149t

in nausea, 160, 161

in SIADH, 116t

“Mental or personal vulnerability”, 263, 265, 267, 268t, 269

Meperidine, 251

MESNA, 88

Metabolic acidosis, 119–120, 172

Metabolic alkalosis, 122, 161

Metabolic complications, 93–122

nausea/vomiting due to, 158

Metabolic disorders, hiccups due to, 149t
Metastases, psychological effects, 266
Methicillin-resistant *S. aureus* (MRSA), 44, 141t, 213
Methotrexate, nephrotoxicity, 121, 122
Methylprednisolone, 101, 132t, 162
Metoclopramide, 151, 152, 162
Milk-alkali syndrome, 18f, 97
Mixed venous oxygen saturation (SvO₂), 50, 51
Monoclonal antibodies *see also specific mAbs*
 cardiotoxicity, 7–8, 9f, 10
 diarrhoea due to, 175, 176t
 hypercalcaemia treatment, 100
 hypersensitivity reaction due to, 223, 225
Morphine, 251–256
 administration and dosage, 252–254, 254t
 dyspnoea treatment, 132
 oral mucositis pain management, 170
 SVC treatment, 34
Mouthwashes, 168
Mucositis *see* Oral mucositis (OM)
Mucous membranes, pallor, 199
Multiple myeloma, 71, 96, 103, 106t, 115t, 137t
Muscle weakness, spinal cord compression and, 72
Mycobacterial infection, 44, 137t, 215
Mycoplasma, 215
Myocardial depression, sepsis-related, 54
Myocardial ischaemia, 12–13, 12t, 150

N

Naloxone, 254, 256
Nausea and vomiting, 157–163
 acute, 157
 aetiology, 158–160, 159t, 161
 anticipatory, 157, 158
 breakthrough, 158
 chemotherapy-induced, 157–158, 159t
 ADH release and hyponatraemia, 117
 emetogenicity of drugs, 159t
 hyponatraemia, 117
 treatment, 162–163
 delayed, 157–158
 investigations, 161
 pathophysiology, 160
 risk factors, 160
 treatment, 162–163
Necrotising gastritis (NG), 184, 192t
Nephrostomy tubes, percutaneous, 86
Nephrotoxic compounds, 89, 122
Nerve block, 256, 257
 infusional, 257
Neurocognitive impairment, 80–81
Neurokinin-1 receptor antagonists, 162–163
Neurological complications, 69–82, 122, 256
 brain metastases *see* Brain metastases
 spinal cord compression *see* Spinal cord compression (SCC)
Neurological disorders, nausea/vomiting due to, 160, 162
Neurolytic nerve block, 257
Neuroprotection, 81
Neuropsychiatric disturbances, 97
Neurostimulator implantation, 257

- Neutropaenia, 181, 208
 - abdominal infections *see*
 - Abdominal infections
 - definition, 208, 209
 - diarrhoea, 179, 181
 - duration, 212
 - febrile *see* Febrile neutropaenia
 - haematopoietic growth factor use in, 56
 - oral mucositis in, 164
 - pathogens causing infections, 209
 - pulmonary infections, 137t, 140, 141, 141t
 - septic shock, antibiotic therapy, 53
 - Neutropaenic enterocolitis (NEC), 178–179, 183
 - CT findings, 191t
 - definition and features, 184
 - diagnostic criteria, 189t
 - management, 191, 192t
 - mortality, 184
 - pathophysiology, 186, 187t
 - risk factors, 185, 186t
 - Neutrophil counts, 208, 209, 217
 - Nitrates, 13
 - Nitric oxide, 10
 - Nociception, 245–246
 - Non-Hodgkin's lymphoma *see* Lymphoma
 - Non-infectious cystitis, 85, 87–88
 - Non-small-cell lung cancer, 32t, 35f, 36, 37
 - Non-steroidal anti-inflammatory drugs (NSAIDs), 249–250
 - bleeding disorders, 236
 - oral mucositis prevention, 169
 - pre-renal azotaemia due to, 89
 - Non-vesicants, 62, 63t
 - Norepinephrine, 54, 192t, 251
 - Novel oral anticoagulants (NOACs), 25
 - Nutrition *see* Diet/nutrition; Enteral nutrition
 - Nutritional deficiency, anaemia, 198, 200
- O**
- Obstructive bowel disease, 159, 161
 - Octreotide, 180
 - Oedema
 - brain *see* Cerebral oedema
 - cancer pain, 255
 - extravasation, 62, 67
 - hypersensitivity reactions, 224
 - interstitial, 30
 - laryngeal, 30, 35
 - vasogenic, 71, 73
 - Olanzapine, 152, 163
 - Oliguria, 49, 105, 111
 - Omeprazole, 192t
 - Oncological emergencies, definition, 85
 - Ondansetron, 162
 - Opioids, 250–252
 - choice and dose titration, 250–251
 - diarrhoea, treatment, 179
 - dyspnoea treatment, 132
 - in emergency, 254
 - equianalgesic doses and activity, 254t, 255
 - nausea, due to, 158
 - oral mucositis pain management, 170
 - overdose, 256
 - pain control inadequate, 252
 - rotation, 255
 - Oral care/hygiene, 167
 - Oral coating agents, 168
 - Oral cryotherapy, 168–169
 - Oral mucositis (OM), 164–171
 - biological stages/pathophysiology, 166–167

- clinical features, 164
 - definition and frequency, 164
 - evaluation and scoring systems, 165, 165t
 - management, 167–170
 - supportive care, 170
 - potential future developments, 170–171
 - preventive treatment, 167–169
 - Osteoclasts, activation, 95, 99, 100
 - Osteolytic metastases, 95, 96t
 - Osteomyelitis, 43f, 45
 - Oxaliplatin,
 - extravasation, 63t
 - hypersensitivity reactions, 224
 - nausea, 159t
 - Oxidative stress, 5
 - Oxycodone, 252, 254t
 - Oxygen, hyperbaric, 87
 - Oxygen saturation, 50, 51, 127, 131
 - Oxygen therapy, 21, 54
 - dyspnoea, 131
 - septic shock, 54
 - Oxyhaemoglobin saturation, 50, 51
 - Oxypurinol, 109
- P**
- Paclitaxel, 7, 12t, 13, 14, 63t, 128t, 149t, 159t
 - Pain (in cancer), 245–259
 - in abdominal infections, 184, 185, 188t, 189t, 190t, 192t
 - aetiology, 246t
 - “breakthrough”, 247, 252
 - differential diagnosis, 246t
 - in dyspnoea, 127, 128
 - evaluation, 247–249
 - in extravasation, 62, 64
 - in hypersensitivity reactions, 223, 224t, 224, 227t
 - intensity and scales, 247, 248
 - investigations (imaging), 249
 - neuropathic, 248, 254
 - nociceptive, 247–248
 - nociceptive, 245–246
 - oral mucositis, 164, 165t, 166–170
 - perception, 245–246
 - prevalence in cancer, 245
 - psychogenic, 248
 - skeletal lesions, 256
 - somatic receptor-mediated, 246t, 247
 - spinal cord compression, 72, 73
 - syndromic, 246t
 - temporal features, 247
 - types, 247–248
 - visceral, 246t, 248, 256, 257
 - Pain management, 245–259 *see also* Analgesia
 - adjuvant treatment, 255
 - administration route, 254
 - interventional treatment, 256–258
 - neurone blockade, 257
 - non-opioid analgesics, 249–250
 - opioids *see* Opioids
 - principles and algorithm, 252–253, 253f
 - side effects, treatment, 255–256
 - timing of doses, 254–255
 - Pain syndromes (acute/chronic), 248
 - Palifermin, 169
 - Pallor, 199
 - Palonosetron, 162
 - Pamidronate, 99, 100
 - Pancreatic adenocarcinoma, 22
 - Panitumumab, 159t, 175, 176t, 223, 225
 - Paradoxical respiration, 131
 - Paraproteins, 236
 - Parathyroid hormone (PTH), 96
 - hypercalcaemia and, 96, 97, 98f

- Parathyroid hormone-related protein (PTHrP), 95, 96t, 98, 99
- Paravasation *see* Extravasation of chemotherapy
- Parenteral nutrition, 39, 44, 55, 168, 192t
- Pathogen-associated molecular patterns (PAMPs), 49
- Pathological fractures, 126, 246t, 248, 257
- Pazopanib, 11t, 176t
- Pericardial complications, 3–5, 126t, 149t, 150
- Pericardial effusion, malignant, 3–5
- Pericardiocentesis, 4, 5
- Peripherally inserted CVCs (PICCs), 39, 61
- Personal adjustment, to cancer, 264, 265, 267, 268t
- Personal factors, vulnerability in cancer, 263, 265, 268t, 269
- pH
 blood, 119, 130, 131
 urine, 103, 107, 108
- Phosphataemia, 97
- Phosphate, intravenous, 100
- Phrenic nerve irritation, hiccups, 148, 149t
- Plasma osmolality, 118
- Plasminogen activator inhibitor-1, 18
- Platelet(s) *see also*
 Thrombocytopenia
 abnormal function, 235t, 236, 239
 activation, 18
 apheresis, 239
 bleeding disorders due to, 233, 235t
 count, 230, 233, 238, 238t, 240
- Platelet function tests, 237
- Platelet transfusion, 234, 238, 238t, 239
 in chemotherapy-induced
 thrombocytopenia, 239
 in disseminated intravascular coagulation, 231, 240
 effectiveness, assessment, 239
 indications, 238, 238t
 in septic shock, 56
- Platinum salt-related hypersensitivity reaction, 224
- Pleural effusions, management, 134
- Pleurodesis, 134
- Pneumocystis carinii (jirovecii)*
 pneumonia, 137t, 138, 139t, 215
 treatment, 53, 142
- Pneumonia *see also* Pulmonary infections
 aspiration, 138
 bacterial, 138, 139t
 treatment, 141–142, 141t
 community-acquired, treatment, 141, 141t
 febrile neutropenia and, 215
 fungal, 138
 treatment, 142
 interstitial, septic shock, 53
Pneumocystis carinii (jirovecii), 53, 137t, 138, 139t, 142, 215
 post-obstructive, 138
 septic shock and, 52
 viral, treatment, 142
- Pneumonitis, 126t, 133, 222
- Polymerase chain reaction (PCR), 140, 188, 190t
- Port-A-Caths (PAC), 61, 62t
- Port-pocket infection, 40, 45
- Posterior leukoencephalopathy syndrome, reversible, 10
- Prednisone, 132t, 142
- Procoagulants, tumour cells
 producing, 18
- PROSPECT-CONKO-004 study, 22

- Prostate cancer, spinal cord
compression in, 71, 73, 75
- Protease-activated receptor-1 (PAR-1),
18
- Protease-activated receptor-2 (PAR-2),
18
- Protein synthesis defects, 230
- Proteinuria, 11, 224t
- Prothrombin time (PT), 146, 230, 237,
239
- Pro-thrombotic state in cancer, 18
- P-selectin, 18
- Pseudomembranous colitis, 185–189
see also Clostridium difficile-
associated diarrhoea (CDAD)
chemotherapy-induced, 187
- Pseudomonas aeruginosa* infection,
44, 51t, 53, 141t, 214
- Psychogenic pain, 248
- Psychological complications, 263–271
potential future developments, 270
predictive/prognostic markers, 267,
268t, 269
symptom assessment, 266–267
symptoms and clinical results, 269
- Psychological effects of cancer,
263–264
adaptation to cancer, 264, 267, 268t
disease stages/process, 264–266
of diagnosis, 264–265, 269
of relapse or metastases, 266
of remission, 265
of terminal disease diagnosis, 266
of treatments, 265, 269
psychopathological profile, 267, 269
- Pulmonary arteries, bleeding from, 144
- Pulmonary diseases, haemoptysis due
to, 145t
- Pulmonary embolism (PE), 17, 21t,
46, 229, 231, 246t
- Pulmonary infections, 136–143, 208
see also Pneumonia
aetiology, 136–137, 137t
clinical features, 137–138
diagnosis, 139–140, 139t
febrile neutropaenia and, 208, 215
risk factors and prevention, 142–143
treatment, 140–142, 141t
- Pulmonary rehabilitation, 134
- Pulsus paradoxus, 4
- ## Q
- QT prolongation, 14–15
- QTc (corrected QT interval), 15
- Quality of life (QoL), 39, 157, 164, 270
adaptation to cancer and, 264
anaemia and, 197
brain metastases and, 77, 80
cardiac complications and, 3
CVC, 39
diarrhoea effect, 172, 180, 181
hiccups and, 148, 151, 152
mucositis and, 170
thromboembolism and, 26
- Quinolones, 14, 141t, 209, 212
- ## R
- Radiation enteritis, 177
- Radiation-induced cystitis (RIC), 87
- Radiology
interventional, pain-directed, 256
superior vena cava obstruction
evaluation, 33
- Radioresistant tumours, 74f, 75
- Radiotherapy
anaemia induced by, 198
bleeding treatment, 242
brain metastases treatment, 78, 80, 81

cancer pain, 246t, 253t, 255
cardiotoxicity, 15–16
diarrhoea due to, 177, 179–181
nausea/vomiting due to, 158
oral mucositis due to, 164, 166, 167
psychological effects, 265
radiation-induced cystitis due to, 87
spinal cord compression
management, 73, 74f, 75
side-effects, 36
superior vena cava obstruction, 36,
37
thrombocytopenia, 235
Ramucirumab, 11t, 225
RANKL (nuclear factor kappa-B
ligand), 95, 100
Rasburicase, 105, 107, 108f, 109, 110,
111, 112
Recall phenomenon, 59
Red blood cells, 56, 198–201
Relapse, psychological effects, 266
Renal abnormalities, hypertension
and, 10–11
Renal complications, 83–91
of hypercalcaemia, 97
tumour lysis syndrome, 103
Renal failure *see* Acute renal failure
(ARF)
Renal perfusion, reduced, 88, 199
Renal replacement therapy, 100, 105,
111
Renal vasoconstriction, 89, 97
Respiratory acidosis, 131
Respiratory complications, 123–153
Respiratory failure, 125–135
evaluation, 130–131
Respiratory rate, 21, 54, 129, 199,
215, 228
Respiratory tract infections *see*
Pulmonary infections

Reticulocyte count, 200
Reticulocyte index (RI), 200
Rituximab, hypersensitivity reaction,
223, 225
Rivaroxaban, 25

S

Saline infusion, 89, 122
Sedation, palliative, 133
Seizures, 10, 79, 105, 118, 121, 205
Selective serotonin reuptake inhibitors,
116t, 158
Sensory loss, 72
Sepsis, 42, 44, 49–56, 181
abdominal infections, 184,
187–188, 187t, 189t, 192t
acute renal failure in, 89, 90t
diarrhoea, 179, 181
intra-abdominal, 52
Septic shock, 49–57
bacterial pathogens causing, 51t
diagnostic criteria, 49
refractory, management, 51
resistant, management, 51
treatment/management, 49–56
algorithm, 50f
antimicrobial therapy, 51–53
of cardiovascular insufficiency,
53–54
coagulation inhibitors, 55–56
corticosteroid therapy, 55
cytokines, 56
early management, 49–50
haematopoietic growth factors, 56
hyperglycaemia, 55
nutrition (enteral), 55
oxygen support, 54
transfusion management, 56
Serotonin antagonists, 162

- Severe cutaneous adverse reaction (SCAR) syndromes, 221
- Shock
 - disseminated intravascular coagulation due to, 229
 - low-output, 4
 - septic *see* Septic shock
- Sigmoidoscopy, 188–189
- Signal transduction pathways, in oral mucositis, 166
- Skin lesions, 221, 222, 223, 230, 237
- Small-cell lung cancer, 32t, 35, 35f, 36, 37, 117
- Social factors, vulnerability in adaptation to cancer, 268t
- Sodium 2-mercaptoethane sulphonate (MESNA), 88
- Sodium bicarbonate, 107, 122
- Sodium EDTA, 100
- Sorafenib, 19, 159t, 176t
 - hypertension-associated, 10, 11, 11t, 12
 - myocardial ischaemia due to, 12t
- Spinal cord compression (SCC), 71–76
 - clinical features, 72
 - differential diagnosis, 72–73
 - evaluation, 72
 - incidence and causes, 71
 - management, 73–75, 74f
- Splenomegaly, 198, 235, 238
- Src/Ab kinase inhibitors, 14
- Staphylococcus*, coagulase-negative, 43f, 45, 209, 214
- Staphylococcus aureus*
 - intravascular catheter-related infection, 42, 43f, 44, 45, 51t, 209, 215
 - methicillin-resistant (MRSA), 44, 213
 - pulmonary infections, 141t
- Stenting, superior vena cava obstruction, 34–35, 35f, 38
 - complications, 35, 36t
- Stereotactic body radiation therapy (SBRT), 73, 75
- Stereotactic radiosurgery (SRS), 73, 78
- Streptococci, viridans, 209
- Strongyloides stercoralis*, 137t, 138
- Subxiphoid pericardiostomy, 5
- Sucralfate, 168
- Sudden cardiac death, 14, 15
- Sunitinib, 6t, 8, 10, 11t, 19
- Superior vena cava, 30
 - compression, 30, 31
 - stenting, 34–35, 35f, 36t, 38
- Superior vena cava obstruction (SVCO), 30–38
 - aetiology, 31, 32t
 - investigations, 32–33
 - physiology, 30–31, 31f
 - radiology, 33
 - symptoms and signs, 32–33, 33t
 - treatment, 33, 34–37, 35f, 36t, 38
- Superior vena cava syndrome (SCS), 30–38
 - grading system, 34t
 - treatment, 34–37, 35f, 36t, 38
- Surgery
 - abdominal infections, 186t, 192t
 - anaemia, 205
 - brain metastases, 78–79
 - extravasation management, 66
 - in haemoptysis, 147, 148, 150
 - renal failure, 86, 87
 - spinal cord compression management, 73, 75
 - in superior vena cava syndrome, 37
 - tumour lysis, 103
 - venous thromboembolism due to, 19, 20t, 21t, 22, 23, 27

vertebral fractures, 257
Syndrome of inappropriate antidiuretic hormone secretion (SIADH), 114–119
causes, 116–117, 116t
diagnosis, 118
hyponatraemia pathogenesis, 116–117
treatment, 118
Systemic inflammatory response syndrome (SIRS), 49

T

Tapentadol, 251
Targeted agents
 cardiotoxicity, 7–8
 diarrhoea due to, 175, 176t
 lung toxicity, 128, 128t
 mucositis, 164, 171
Taxane-associated hypersensitivity reaction, 224
Teicoplanin, 214
Terminal disease, psychological effects, 266
Thalidomide, 13, 19, 128t
Thoracic disorders, hiccups due to, 149t
Thoracic pain, 12–13
Thrombin time, 237
Thrombocytes *see* Platelet(s)
Thrombocytopaenia, 233
 autoimmune, 236, 237
 causes, 230, 233, 235–236, 235t
 chemotherapy-induced, 233
 prevention, 238
 treatment of bleeding, 239
 in disseminated intravascular coagulation, 228, 230, 236
 immune-mediated, 236
 in septic shock, 55
 treatment, 231, 239
Thrombocytosis, 236, 239
Thrombolytic therapy, 25
 in catheter obstruction, 47
 in catheter-related thrombosis, 46
 in superior vena cava obstruction, 37
Thromboprophylaxis, 22–23, 23t
 duration, 23
Thrombosis
 catheter-related (central venous catheter), 45–47
 coronary, 12
 in disseminated intravascular coagulation, 228, 229
 obstructive, in superior vena cava obstruction, 36
 pathogenesis, 18–20
Thymic carcinoma, 37
Thymoma, 37
Tinzaparin, 24, 24t
Tissue factor (TF), 18, 20, 228, 229
Tissue hypoperfusion, lactic acidosis, 119
Tissue necrosis, 64, 165t
Torsade de pointes (TdP), 14, 15
Toxoplasmosis, pulmonary infection, 137t, 138
Tramadol, 251
Tranexamic acid, 240, 241f
Transferrin saturation (TSAT) level, 206
Transfusion-related emergencies, 226–228, 227t, 234
Transfusions *see* Blood transfusion; Platelet transfusion
Transoesophageal echocardiography, 42
Trastuzumab
 cardiac dysfunction due to, 7–8
 management, 8, 9f, 10

diarrhoea, 176t
hypersensitivity reaction, 223, 225
nausea, 159t
Tricyclic antidepressants, 170, 254, 255
Trimethoprim-sulfamethoxazole
(TMP-SMX), 142
Troponin I, 9
Trousseau's syndrome, 17, 104t
Tuberculosis, 32t, 96t, 138, 139t
Tumour lysis syndrome (TLS),
103–113
clinical and laboratory types, 104t,
105
diagnostic classification (Cairo-
Bishop), 104t, 105
mortality, 105
pathogenesis, 103–104
predisposing factors, 105, 106t
prevention, 107–110, 107t
risk stratification, 105, 106t, 107t
signs and symptoms, 105
treatment, 111–112
tumours-associated, 103, 104, 106t
Tunnel infection, 40, 45, 211, 215
Typhlitis, 53, 184 *see also*
Neutropaenic enterocolitis (NEC)
Tyrosine kinase inhibitors (TKIs), 8, 78
diarrhoea due to, 175
QT prolongation due to, 14
tumour lysis syndrome after, 103–104

U

Ulceration, oral mucositis, 164, 165t,
166
Unfractionated heparin (UFH), 22,
23t, 24
Urate crystals, 103
Urate oxidase, 110
Ureter, stones in, 86, 87

Ureteral stents, 86
Urethral strictures, 85–86
Uric acid, metabolism, 108, 109, 110
Uric acid-lowering agents, 108–109,
108f, 111–112
Urinary catheters, 87
Urinary incontinence, 71, 86–88
Urinary tract obstruction (UO), 85–87,
89
low, 85–86
upper, 86–87
Urinary urgency, 87
Urine
alkalinisation, 107, 108
osmolality, 118
pH, 103, 107, 108
Urine output
septic shock, 49, 50, 54
tumour lysis syndrome prevention,
107
urinary tract obstruction, 85, 86
Urological complications, 83–88

V

Vagus nerve irritation, hiccups, 148,
149t, 150
Valproic acid, 152
Vancomycin, 44, 214
Vascular endothelial growth factor
(VEGF), 10, 12, 18
inhibition, diarrhoea due to, 175
spinal cord compression and, 71
Vascular endothelial growth factor
(VEGF) antibody *see* Bevacizumab
Vasoconstriction, 64, 89, 97, 168
Vasogenic oedema, 71, 73
Vasopressin *see also* Antidiuretic
hormone (ADH)
in septic shock, 54

Vasopressors, 50t, 51, 54, 192t
Venous pressure, elevated, 30, 60
Venous thromboembolism (VTE),
17–29
 blood transfusions, risk with, 202
 brain metastases and, 27–28
 clinical features, 20t, 21, 21t
 diagnosis, 20–21, 20t, 21t
 erythropoietic agents, risk with, 205
 long-term treatment, 26–27
 pathophysiology, 18–20
 prevention, 22–23, 23t
 recurrence, 17, 26–27
 risk and incidence, 17, 22
 risk factors, 19, 22, 23
 treatment, 23–28
 Wells Criteria, 20–21, 20t, 21t
Ventilation, mechanical, 54
Ventricular arrhythmias, 13, 14
Vertebral fractures, stabilisation, 257
Vertebral metastases, 71, 72
Vesicants, 62, 63t, 64, 66
Vesicular lesions, 217
Viral infections
 blood transfusions and, 202
 in febrile neutropaenia, 217
 in nausea, 160
 pneumonia, treatment, 142
Vitamin B12, 198, 200
Vitamin D metabolites, 98
Vitamin K, 240
Vitamin K analogues (VKAs), 26
 Deficiency, 230, 233
Vitamin K antagonists, 239
Vomiting *see* Nausea and vomiting
Vomiting centre, 160
Von Willebrand's disease, acquired,
233, 234, 235t, 240
Vulnerability, mental/personal, 263,
265, 267, 268t, 269

W

Warfarin, 26
Warm compresses, 64, 66
Water restriction, 118
Water retention, 115, 116, 117, 118,
121
Wells Criteria, 20–21, 20t, 21t
“White uniform” syndrome, 158
Whole brain radiotherapy (WBRT),
78, 80, 81

X

Xanthine, 107–108, 109
Xanthine nephropathy, 109
Xanthine oxidase, 108, 109
 inhibitors, 108–109

Z

Zinc supplements, 169
Zoledronate, 99–100

ESMO HANDBOOK OF ONCOLOGICAL EMERGENCIES

2ND EDITION

Edited by Mariano Provencio Pulla

The aim of the present edition of the ESMO Handbook of Oncological Emergencies is to approach the new advances and developments in the field of oncological emergency treatments, for the benefit of oncology specialists, but also for those who are just starting out in this profession. Since the first edition of this book in 2005, there have been substantial developments in the way oncological emergencies are treated, such as new treatments or new drug effects, making this update necessary. We have also considered it important to include new chapters so that the book remains a reference in oncology. We hope to fulfil the expectations of our audience.

ESMO Handbook Series
European Society for Medical Oncology
Via Luigi Taddei 4, 6962 Viganello-Lugano, Switzerland



ESMO Press · ISBN 978-88-906359-9-1
www.esmo.org

