Principles of medical therapy

Contents

Introduction

Medications in cancer care are utilised to achieve the following goals:

1. to exert anti-cancer effects by killing or controlling cancer cells
2. to treat complications arising from anti-cancer therapies
3. to minimise the effects of cancer on body parts
4. to control symptoms from cancer and complications of cancer treatments.

Medications to achieve cancer cell death or cancer control

Chemotherapy, small molecules, monoclonal antibodies and hormonal agents are used for this purpose.

Chemotherapy

These agents achieve cancer control by several mechanisms. Some examples include:

1. damage to the DNA by various mechanisms during different phases of the cell cycle
2. inhibition of mitosis by interfering with microtubules.

Chemotherapy is used for the following purposes:

1. cure (e.g. leukaemia, lymphoma, germ cell tumours)
2. adjuvant, to eradicate micro metastasis following surgery or radiotherapy (e.g. breast, colon, ovarian cancers)
3. in combination with radiotherapy to sensitize radiotherapy (e.g. head and neck, rectum, lung ,cervical cancers)
4. palliation of symptoms and prolong survival (e.g. most metastatic cancers).

Small molecules

Many new medications inhibit various kinases along the signal transduction pathways that are associated with cell proliferation, survival, metastasis and angiogenesis.[1] Most of these agents inhibit the activity of these kinases by competing for ATP binding.

Medication	Target Kinases	Current Use
Imatinib	Bcr-abl	Chronic myeloid leukaemia, gastrointestinal stromal tumour
Erlotinib,gefitinib	EGFR	Non-small cell lung cancer
lapatinib	Her1 and 2 receptor	Breast cancer
Sunitinib	PDGFR, VEGFR, Kit	Renal, GIST
Afinitor	mTOR	Breast, renal

Monoclonal antibodies

Humanised monoclonal antibodies cause cancer cell death by the following mechanisms:[2]

1. direct action of antibody (receptor blockade or agonist activity, delivery of a drug or cytotoxic agent)
   E.g. Trastuzumab in HER2 positive breast cancer
2. Complement dependant cytotoxicity
3. Antibody-dependent cellular cytotoxicity (ADCC)
   E.g. Rituximab binds to CD 20 on lymphoma cells and stimulate ADCC
4. Regulation of T cell function
   E.g. Ipilimumab
   In cancers like melanoma, antigen presenting cells (APC) present tumour antigen to the T cell via MHC complex. When tumour antigen binds with T cell receptors (B7 on APC with B28 on T cells), this leads to T cell activation and release of inflammatory proteins. When intracellular CTLA4 molecule is expressed on the surface of the T cell, binding of CTLA4 to B7 turns off the T cell activation. Ipilimumab binds to the CTLA4 and inhibit the binding of CTLA4 and B7. This means the T cell remains activated. Ongoing release of inflammatory proteins is expected to exert tumour control.
5. Specific effect on tumour vasculature and stroma
   E.g. Bevacizumab binds to VEGFR on stromal tissues and inhibit angiogenesis within cancer deposits.

Hormonal agents

These agents inhibit the actions of various hormones on hormone responsive cancer cells. Side effects are usually related to hormone depletion.

Medication	How it works	Used in
Tamoxifen	Oestrogen receptor blockade	Breast cancer

Medication	How it works	Used in
Aromatase inhibitors	Inhibition of conversion of androgens to oestrogen	Breast cancer
Gonadotrophin releasing hormone(GnRH)	Decrease the ovarian production of oestrogen and testicular production of testosterone	Breast cancer and prostate cancer
Anti androgens	Androgen receptor blockade	Prostate cancer

Managing chemotherapy side effects

Most side effects are due to non-specific damage to normal cells. They do not always occur and not all the patients experience the same side effects.[3]

Examples:

1. Nausea, vomiting -- Some drugs are more emetogenic than others; prophylactic antiemetic medications use can decrease the incidence. Details are found in the “Medical oncology hand book for junior medical staff”[3] accessed via the following link: http://www.health.qld.gov.au/townsville/Documents/clinicians/med-onc-jnr-handbook.pdf
2. Alopecia -- Not all the medications cause alopecia. Most breast cancer medications cause complete alopecia; most colorectal regimens do not cause complete alopecia.
3. Myelosuppression and neutropenic sepsis -- Neutropenic sepsis is treated with broad spectrum antibiotics. Risk of neutropenia can be reduced by the use of granulocyte colony stimulating factors. Anaemia and thrombocytopenia can be treated with transfusions of packed red cells and platelets respectively.
4. Fatigue
5. Infertility -- Not all the drugs cause this side effect. It is important that pregnancy is avoided during and at least 12 months after completing chemotherapy. In ER negative cancers, ovarian suppression during chemotherapy can reduce the risk of infertility.
6. Effects on other organs -- E.g. cisplatin and neuropathy, anthracyclines and cardio toxicity, bleomycin and interstitial pneumonitis.

Medications to minimise the impact of cancer on organs

Examples:

Bisphosphonates (e.g. zelodronic acid, pamidronate) or RANKL inhibitor denosumab can decrease the incidence of skeletal related events in patients with bone metastasis from various cancers, including breast, prostate and multiple myeloma. Skeletal-related events include fracture, pain and hypercalcemia. These agents can also decrease the rate of osteoporosis/osteopenia caused by anti-hormonal agents like aromatase inhibitors.

Note: RANK is a surface receptor on pre-osteoclasts. RANK is activated by RANKL (RANK ligand) found on the surface of osteoblasts. Binding of RANK to RANKL leads to maturation of pre-osteoclasts to mature osteoclasts and subsequent destruction of the bones.[4]

Managing symptoms caused by cancer or complications of treatments

When we attempt to treat cancers, it is important to make sure the quality of life of the patients is improved or maintained by controlling the cancer-related symptoms and treatment-related complications. Patients with metastatic disease can gain important benefits when their care is shared between various health professionals, including palliative care professionals.

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