Oncological emergencies

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This chapter covers important oncological emergencies, including hypercalcemia, superior venous caval obstruction, spinal cord compression and neutropenic sepsis.

Oncological emergencies

Neutropenic sepsis

Neutropenic sepsis is defined as a single temperature of 38.3^{0}C orally or temperature of 38^{0}C or more orally lasting an hour, in the presence of a neutrophil count of less than 500/microlitre (or 0.5x109/litre) or less than 1000/mcL and a predicted decline to less than 500/mcL over the next 48 hours (http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf).

Without the administration of timely antibiotics, mortality may be higher. Principles of management are:

1. Assess haemodynamic status
2. Look for the source of infection including intravenous access sites. (In many case, a source may not be found.)

3. Investigations including FBC, electrolytes and liver function tests, blood cultures (from periphery and central venous devices), Chest X-ray, urine analysis and cultures
4. Antibiotics need to be able to cover broad spectrum of organisms including gram positive, gram negative organisms and anaerobes. Because of the risk of pseudomonal infection, agents covering this organism are administered either as a single agent (anti pseudomonal penicillin or fourth generation cephalosporin) or in combination depending on institutional protocols. When there is haemodynamic compromise or a risk of MRSA infection, appropriate anti MRSA therapy is necessary.

Some low risk patients may be treated with oral antibiotics depending on institutional guidelines. Usually patients require admission to isolation beds.

NB: Granulocyte colony stimulating factors usually do not improve the outcomes in neutropenic sepsis unless in selected cases.

Hypercalcaemia

Hypercalcaemia refers to elevated calcium level in blood (normal range 2.2-2.6 mmol/L) that occurs in 10-20% patients with advanced cancers (most commonly in cancer of the breast, kidney, lung, prostate, head and neck and multiple myeloma). The frequency and severity of hypercalcaemia in cancer patients has decreased in the past decade due to early and wide spread use of bisphosphonates.

Mechanism

Pathogenesis involves either focal bone destruction (osteolytic) or, more frequently, para neoplastic syndrome.

1. Osteolytic hypercalcaemia is the result of direct bone invasion by the tumour or metastasis (e.g. breast cancer) releasing local cytokines resulting in activation of osteoclast activating factor which causes bone resorption and loss of calcium from bone into blood. RANK ligand (RANKL) is a receptor on pre osteoclasts which plays and important role in osteoclast maturation.
2. In para neoplastic hypercalcaemia, the tumour cells secrete parathyroid hormone related protein (PTHrP) which can induce bone resportion without the cancer directly invading the bone (e.g lung cancer). PTHrP is elevated in 80% of patients with hypercalcaemia in cancer.

Clinical presentation

Symptoms of hypercalcaemia include nausea, vomiting, constipation, polyuria and disorientation. A mnemonic for these effects is “Stones, bones, groans, thrones and psychiatric overtones”.

Stones (renal or biliary)

Bones (bone pain)

Groans (abdominal pain, nausea and vomiting)

Thrones (polyuria)

Psychiatric overtones (depression 30-40%, anxiety, cognitive dysfunction, insomnia, coma)

Clinical evidence of volume contraction secondary to progressive dehydration may be apparent. Severe hypercalcaemia (above 3.75-4.0 mmol/L) is a medical emergency and a poor prognostic sign. Investigations include specific biochemistry like PTH, ECG to detect arrhythmias and imaging with Bone Scan or PET-CT scan to identify metastatic bone disease.

Causes of hypercalcaemia in cancer patients

Apart from the mechanisms described above, many other causes like calcium supplementation may need to be considered in cancer patients.

Management

Treat the hypercalcaemia first and the cause later:

1. Hydration & diuresis – 1-2 L of isotonic saline (NS) over 2 hours with 30-40 mg of frusemide expands intravascular volume and enhances calcium excretion. In elderly and cardiac patients, rate of hydration needs to be slower.
2. Bisphosphonates – via a complex mechanism inhibit osteoclast and in turn both normal and pathological bone resorption. Commonly used bisphosphonates are:
    1. Zolendronic acid – infused as 4 mg in 100 mls of NS over 15 mins. Normalisation of serum calcium occurs in 4-10 days and lasts 4-6 weeks. Therefore, if re-treatment is required, dose is repeated after 7 days
    2. Ibandronate – 6 mg as 2 hour infusion or 50 mg PO daily
    3. Pamidronate - 90 mg IV over 1-2 hours
3. RANKL inhibitor – Denosumab 120 mg subcutaneously every month

NB: Bisphosphonates and Denosumab cause increasing risk of osteonecrosis of jaw following extraction of teeth or oral surgical procedures. Therefore, a dental review may be necessary to make sure the necessary dental procedures are completed prior to commencing therapy.

Calcitonin – a thyroid hormone given 4-8 IU/kg IM or SC every 6-8 hours can bring about a rapid decline in calcium levels, however tachyphylaxis limits its utility.

Superior vena cava syndrome

Superior vena cava syndrome (SVCS) is the clinical expression for obstruction of blood flow through the SVC. Malignancy (90%) is the most frequent cause of SVC obstruction. SVC obstruction in cancer patients can result from:

• Extrinsic compression of SVC

1. lung Cancer (65%)
2. lymphomas (15%)
3. other cancers (10%)

• Intrinsic compression

1. thrombosis associated with central venous devices (10%)

SVC obstruction is a strong predictor of poor prognosis in patients with non-small cell lung cancer.

Pathophysiology

As the flow of blood within the SVC becomes obstructed, venous collaterals form, establishing alternative pathways for the return of venous blood to the right atrium. Collateral veins may arise from the azygos, internal mammary, lateral thoracic, paraspinous, and oesophageal venous systems. However, even when well-developed collateral drainage patterns are present, central venous pressures remain elevated, producing the characteristic signs and symptoms of SVC syndrome.

Clinical presentation

Common symptoms and physical findings of SVCS are:

1. dyspnoea
2. headache
3. oedema and change in colour in the areas drained by SVC(examples-face and upper limb)
4. venous distension of neck, upper chest and arms
5. cough
6. Pemberton’s sign (development of facial flushing, distended neck and head superficial veins, inspiratory stridor and elevation of the jugular venous pressure (JVP) upon raising both of the patient's arms above his /her head simultaneously, as high as possible (Pemberton's maneuver)).

Diagnosis

1. Chest X ray (CXR) -- shows mediastinal widening and may show the presenting primary cause of SVCS.
2. CT scan Chest Abdomen and Pelvis with Contrast -- Easily and readily available in most centres (compared to MRI). It is useful for establishing the diagnosis and staging of the malignancy.
3. Tissue diagnosis – It is important to characterize the malignancy so that it can be treated with the appropriate modality.

Treatment

Treatment of SVC syndrome is divided into supportive and definitive therapy.

• Supportive measures

1. Head elevation -- To decrease the hydrostatic pressure and thereby the edema. There are no data documenting the effectiveness of this manoeuvre, but it is simple and without risk.
2. Glucocorticoid therapy (dexamethasone, 4 mg every 6 h) to relieve inflammation and oedema (to be avoided before biopsy if lymphoma is suspected as steroid induced tissue necrosis might obscure the diagnosis)

3. Loop diuretics (Frusemide) are also commonly used, but it is unclear whether venous pressure distal to the obstruction is affected by small changes in right atrial pressure.

• Definitive therapy

1. Radiation treatment to the malignant mass.
2. Chemotherapy – in chemo sensitive cancers like lymphoma, germ cell tumours or small cell lung cancer
3. SVC Stent – can be useful in cases of thrombosis and for patients not responding to cancer treatment
4. Removal of central venous device.

NB: It is advisable to avoid placement of intravenous lines in the arms so that fluid is not injected into the already compressed SVC.

Spinal cord compression and brain metastasis

Case study

Mr S, a 67 year old gentleman with a history of non-small cell lung cancer treated radically with chemotherapy and radiotherapy 1 year prior, presents with a 3-week history of escalating back pain, headaches and a 1-day history of bilateral lower limb weakness. On admission to hospital his lower limb power was grade 3-4 out of 5. Sensation was impaired from the level of T10. Urgent MRI spine demonstrates a metastasis at T9 causing spinal cord compression, as well vertebral metastases at C4 and L3. In the emergency department he has a witnessed tonic-clonic seizure lasting two minutes that self resolves. Subsequent contrasted CT brain demonstrates a left frontal lobe metastasis, measuring up to 3 cm with surrounding vasogenic oedema. Staging CT scan also demonstrates mediastinal nodal metastases and 2 liver metastases. What is the appropriate management strategy for this patient?

Spinal cord compression threatens mobility, independence and longevity in patients with metastatic cancer and may be the first presentation of curable malignancy in others. It most commonly occurs due to an enlarging vertebral metastasis encroaching on the epidural space or due to pathologic fracture of a vertebra infiltrated by malignancy. Immobilising the patient and obtaining urgent MRI whole spine (compression can occur at more than one level) should be priorities. Corticosteroids should be initiated on suspicion of cord compression. Currently guidelines suggest intravenous dexamethasone 10 mg immediately followed by 16 mg daily in divided doses. Higher dose corticosteroids may increase adverse effects without evidence of increasing effectiveness.[1] Bladder catheterisation is appropriate. Once spinal cord compression is confirmed, urgent neurosurgical opinion should be sought. There are potential improvements in outcomes for patients treated with surgery upfront, though appropriateness for this will depend upon spinal stability, patient and malignancy related factors.[2][3] For example, younger patients with low burden of metastatic

disease and reasonable life expectancy may be better served by upfront surgery whilst patients with radiosensitive cancers best served by radiotherapy alone. In patients who are not candidates for upfront surgery, the role of radiotherapy has been well established. Radiotherapy protocols can vary between institutions and may depend upon patient and tumour factors. Radiotherapy may also be appropriate after surgery. Chemotherapy as a sole treatment for spinal cord compression may rarely be appropriate in patients with highly chemotherapy responsive tumours, such as lymphoma.

For patients with brain metastases, obtaining seizure control is a medical priority. In the case of our patient with spinal cord compression, this could be particularly important. Corticosteroids may reduce peritumoural oedema with typical doses of 10 mg intravenous dexamethasone followed by 16 mg daily in divided doses. Antiepileptic treatment should be given to obtain seizure control, usually with intravenous phenytoin loading though choice may be influenced by concurrent medications. Benzodiazepines are useful in terminating seizures but have potential sedating effects. Surgical resection of brain metastases may improve outcomes including survival and should be considered, particularly in patients with a single metastasis, those with limited systemic disease and those with good prognosis otherwise.[4] Malignancy characteristics are also important in decision making in this regard. Patients who are not candidates for surgery should be considered for whole brain radiotherapy or radiosurgery, and radiotherapy is usually offered to patients after recovery from surgery.[5] With few exceptions, such as in lymphoma, chemotherapy is usually not helpful in the sole management of patients with cerebral metastases. Newer agents, such as small molecule epidermal growth factor receptor tyrosine kinase inhibitors in certain non-small cell lung cancer patients, may provide greater hope for control of intracerebral metastases compared to traditional chemotherapeutics.[6]

Tumour lysis syndrome

TLS occurs when there is rapid cell breakdown after chemotherapy most commonly for leukaemias and higher grade lymphomas with large tumour burdens that respond quickly to chemotherapy.[7] The metabolic changes are essentially caused by cell breakdown products. Potassium which is mainly intracellular spills into the blood which can cause cardiac arrhythmias and muscle weakness. Likewise phosphate is released which can result in renal failure due to the deposition of calcium phosphate crystals and the calcium levels decrease. Massive cell death and nuclear products liberated nucleic acids and adenine and guanine are broken down to uric acid which precipitates as urate crystals and causes urate renal failure. Lactic acidosis can occur.

To try to prevent tumour lysis syndrome, patients should be hydrated to achieve a high urine output and treated with allopurinol or rasburicase to decrease uric acid. Once tumour lysis is established patients may require dialysis.

References

1. ↑ Heimdal K, Hirschberg H, Slettebø H, Watne K, Nome O. *High incidence of serious side effects of high-dose dexamethasone treatment in patients with epidural spinal cord compression.* J Neurooncol 1992 Feb; 12(2):141-4 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/1560260.

2. ↑ Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, et al. *Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial.* Lancet 2005 Aug;366(9486):643-8 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/16112300.
3. ↑ Young RF, Post EM, King GA. *Treatment of spinal epidural metastases. Randomized prospective comparison of laminectomy and radiotherapy.* J Neurosurg 1980 Dec;53(6):741-8 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/7441333.
4. ↑ Barker FG 2nd. *Craniotomy for the resection of metastatic brain tumors in the U.S., 1988-2000: decreasing mortality and the effect of provider caseload.* Cancer 2004 Mar 1;100(5):999-1007 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/14983496.
5. ↑ Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. *Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial.* JAMA 1998 Nov 4;280 (17):1485-9 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/9809728.
6. ↑ Park SJ, Kim HT, Lee DH, Kim KP, Kim SW, Suh C, et al. *Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation.* Lung Cancer 2012 Sep;77(3):556-60 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/22677429.
7. ↑ Rampello E, Fricia T, Malaguarnera M. *The management of tumor lysis syndrome.* Nat Clin Pract Oncol 2006 Aug;3(8):438-47 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/16894389.