Oncology

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Emergencies in oncology

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Emergency situations in patients with malignancy can carry considerable morbidity and mortality. The more frequent oncological emergencies are listed in Table 1; they may present initially to clinicians other than oncologists. A high clinical suspicion and early detection of these conditions, combined with a low threshold to initiate investigation and treatment, will result in improved outcome for patients.

Superior vena cava obstruction

A diagnosis of superior vena cava obstruction (SVCO) is usually made from the clinical picture that arises from obstruction of the venous drainage of the upper body: oedema of the arms and face, distended neck and arm veins, headaches and a dusky skin colouration over the chest, arms and face. Collaterals may develop over a period of weeks and the direction of blood flow helps confirm the diagnosis. The most important clinical sign is loss of pulsation in the venous system of the neck. Obstruction of the SVC by mediastinal tumours occurs most frequently with lung cancers, especially small cell lung cancer. Other causes, including nonmalignant, are given in Table 2.

The severity of symptoms relates to the rate of degree of obstruction and the development of compensatory collateral venous drainage. The symptoms may worsen by lying flat or bending which further stresses the obstructed venous return. The common symptoms and signs in SVCO are given in Table 3.

Treatment strategies

Treatment of SVCO depends upon the aetiology and severity of the obstruction together with the patient's prognosis, and includes symptom relief as well as treating the underlying cause as described by Osler *et al.*[1] Although it is an emergency in the presence of airway compromise, treatment is directed at the underlying cause. Therefore, when possible, a histological diagnosis should be urgently obtained as some tumours that cause SVCO are better treated with chemotherapy than radiotherapy. For most tumours, mediastinal radiotherapy is the optimal treatment and relieves symptoms in up to 90% of patients within two weeks. Patients respond to being sat upright and being given oxygen therapy. In severe cases, high-dose intravenous dexamethasone should be started.

For patients with recurrent SVCO, or those where other therapeutic modalities are unsuitable, insertion of expandable wire stents under radiological guidance can give instantaneous symptomatic relief with an excellent response rate.[2,3] Although surgical bypass of the obstruction has been performed, it is usually reserved for patients with benign disorders.

For thrombosis within the SVC associated with central venous access catheters, the catheter should be removed and anticoagulation started. The incidence is reduced by administration of low-dose warfarin.[4]

The outcome of treatment depends upon the aetiology of the SVCO and response to therapy. Patients with lymphoma, small cell lung cancer and germ cell tumours can have an excellent response to treatment, even in the presence of SVCO.

Table 1. The most frequent oncological emergencies seen by, and referred to, oncologists.

- superior vena cava obstruction
- tumour lysis syndrome
- neutropenic sepsis
- malignant hypercalcaemia
- spinal cord compression

Table 2. Examples of conditions causing superior vena cava obstruction.[1]

Cause	Malignant	Nonmalignant
	Small cell lung cancer	Indwelling central venous catheter
	Nonsmall cell lung cancer	Retrosternal thyroid goitre
	Lymphoma	Thymoma
	Germ cell tumours	Histoplasmosis
	Breast cancer	Sarcoidosis
		Tuberculosis
		Benign teratoma
		Syphilis
		Dermoid cyst
		Infection
		Cystic hygroma

Tumour lysis syndrome

Tumour lysis syndrome (TLS) comprises several metabolic derangements including:

- hyperuricaemia
- hyperkalaemia
- hyperphosphataemia
- secondary hypocalcaemia.

These abnormalities complicate the treatment of bulky and highly proliferative tumours and can ultimately lead to renal failure and death. TLS results from the spontaneous or treatment-related apoptosis or cell lysis and usually occurs within five days of starting chemotherapy. The important risk factors that predispose patients to the development of TLS have been identified (Table 4).[5]

Treatment strategies

The most important issue is to identify those at risk and institute prophylactic measures before starting treatment. These measures include:

- allopurinol (a xanthine oxidase inhibitor)
- intravenous fluids
- urinary alkalinisation (pH 7.0–7.5) with sodium bicarbonate which increases the solubility of uric acid and reduces intratubular precipitation.

More recently, rasburicase (Fasturtec, Sanofi-Synthelabo) a recombinant urate oxidase that converts uric acid into more soluble allantoin, has been licensed for the treatment and prophylaxis of hyperuricaemia.[6,7]

During the initial high-risk period blood biochemistry should be measured every 4-6 hours,[8] together with close monitoring of fluid balance, body weight and blood pressure. In severe cases, renal dialysis may be required to treat hyperkalaemia or renal failure.

Neutropenic sepsis

Fever commonly occurs in patients with cancer. Febrile neutropenia, or neutropenic sepsis, is a common, expected complication of chemotherapy. If untreated, it has the potential of serious morbidity and mortality. Neutropenia (neutrophil count $<1.0 \times 10^9$/l) is usually secondary to chemotherapy, but can also occur with radiotherapy if large volumes of bone marrow are irradiated or may be part of pancytopenia due to malignant infiltration of the marrow. Neutropenic sepsis is defined as a fever of 38.0°C or higher for at least two hours when the neutrophil count is below 1.0×10^9/l or with a predicted decline to 0.5×10^9/l or lower.[9] The degree of neutropenia is the most important risk factor for developing sepsis. A neutrophil count below 0.5×10^9/l carries a greater risk of infection than one below 1.0×10^9/l. The anticipated duration of neutropenia (ie an expected duration of ≤7 days or >7 days) is a further important risk factor for febrile neutropenia.[10]

Treatment strategies

A thorough clinical history and physical examination are necessary to identify the potential source of infection. The classical signs of pain, inflammation and fever may be lacking since neutropenia alters the inflammatory response. Initial management should include resuscitation measures for shock if present. An infection screen should be taken including:

- blood cultures, peripheral and from central access catheters (if present)
- urine sample for culture
- chest X-ray
- throat swab for culture.

Treatment should not be delayed whilst awaiting culture results. Other investigations include full blood count to confirm the neutropenia and biochemical tests to assess renal and liver function.

Table 3. Common symptoms and physical findings of superior vena cava syndrome.

Symptoms	Patients affected (%)	Physical findings	Patients affected (%)
Dyspnoea	63	Venous distension of the neck	66
Facial swelling and head fullness	50	Venous distension of chest wall	54
Cough	24	Facial oedema	46
Arm swelling	18	Cyanosis	20
Chest pain	15	Plethora of face	19
Dysphagia	9	Oedema of arms	14

Table 4. Risk factors for tumour lysis syndrome.[5]

- Bulky chemosensitive disease, especially high-grade lymphomas
- High blast counts in leukaemia
- Elevated pretreatment serum uric acid
- Elevated serum lactate dehydrogenase
- Poor renal function

Key Points

Treatment of superior vena cava obstruction is determined by the underlying cause

Prevention is the most important aspect of managing tumour lysis syndrome

Neutropenic sepsis should be suspected in any patient receiving chemotherapy who becomes unwell; patients require urgent review

Hypercalcaemia is easily missed as the onset can be insidious

Spinal cord compression requires urgent diagnosis and treatment in order to maintain neurological function

KEY WORDS: hypercalcaemia, neutropenic sepsis, spinal cord compression, superior vena cava obstruction, tumour lysis syndrome

In the immunosuppressed patient, the pathogens associated with fever are in general bacteria, but in most patients the source of infection is not detected. The empirical antibiotic regimen must be broad and achieve high bactericidal levels. In most institutions, the usual policy is to give an intravenous injection of a combination of an aminoglycoside with either a cephalosporin or a broad-spectrum penicillin. Alternatively, monotherapy with a cephalosporin may be instituted. The majority of institutions have local antibiotic policies jointly agreed with microbiologists which are based on local antibiotic resistance patterns.

The guidelines of the Infectious Diseases Society of America suggest that patients at low risk of complicated neutropenic sepsis can be discharged with oral antibiotics if they are afebrile within three days of starting an empirical broad-spectrum antibiotic regimen. Continuation of intravenous antibiotics is recommended in the high-risk patients, even if they become afebrile within three days, although the regimen can be discontinued at 14 days if they are afebrile without evidence of infection, even if they remain neutropenic.[9]

If there is no response after 36–48 hours, the antibiotic regimen should be reviewed with microbiologist advice, and consideration given to antifungal therapy (eg amphotericin B). In two prospective randomised studies there were fewer fungal infections and less morbidity and mortality in febrile neutropenic patients who received early empiric amphotericin B.[11] Prophylactic antibiotics are being evaluated in a randomised clinical trial.

Colony-stimulating factors

Maintenance of chemotherapy dose is important for the effective treatment of most tumours. In an effort to shorten the duration of neutropenia, granulocyte colony-stimulating factor (G-CSF) can follow chemotherapy, being given before neutropenia develops. American Society of Clinical Oncology guidelines recommend the use of secondary prophylaxis with G-CSF only with those cancer chemotherapy regimens that carry a high risk (>40%) of myelosuppression.[12]

Careful monitoring of patients and their neutropenia, in conjunction with patient education and a high clinical suspicion, will help to improve the clinical outcome in patients at risk from neutropenic sepsis.

Hypercalcaemia

Hypercalcaemia (serum calcium >3.0 mmol/l) is the most common life-threatening metabolic abnormality in patients with cancer. The incidence varies depending on the underlying cancer, being highest in myeloma and breast cancer (approximately 40%), intermediate in nonsmall cell lung cancer (squamous cell) and uncommon in colon, prostate and small cell lung cancer.[13] It is often underdiagnosed and has a significant impact on quality of life if treated suboptimally.[14] Hypercalcaemia of malignancy is mediated by factors produced by the tumour that can affect calcium homeostasis of bone, the gastrointestinal tract and the kidney (Table 5).

The presenting symptoms and clinical signs can be vague and easily missed, having considerable overlap with those of underlying malignancy (Table 6). The severity of symptoms is related to the degree of hypercalcaemia and the rate of increase in calcaemia. Serum calcium measurements should be corrected for a low serum albumin:[16]

true serum calcium (mmol/l) = [(40-serum albumin) x 0.025] + serum calcium

Drugs that inhibit urinary calcium excretion or reduce renal blood flow should be discontinued (eg thiazide diuretics, nonsteroidal anti-inflammatory agents). Intravenous fluid resuscitation should be initiated and followed with bisphosphonate therapy.[17] Bisphosphonates, pyrophosphate analogues that inhibit bone resorption by osteoclasts, do not affect renal tubular absorption of calcium. Intravenous disodium pamidronate (Aredia, Novartis) is the most widely used bisphosphonate for hypercalcaemia. Newer bisphosphonates (eg zoledronic acid (Zometa, Novartis)) have a similar mechanism of action but are more

Table 5. Factors contributing to hypercalcaemia in malignancy.

Cause	Comments
Parathyroid hormone related peptide	Most common[15]
Prostaglandins (PGE)	
1, 25 (OH)2 vitamin D3	Increased in Hodgkin's disease, nonHodgkin's lymphoma, myeloma
Tumour necrosis factor	Involved in bone resorption and formation
Interleukin-6	
Transforming growth factor α Transforming growth factor β	

Table 6. Symptoms and clinical signs in malignant hypercalcaemia.

Symptoms	Clinical signs	Investigations
Fatigue	Dehydration	Serum calcium >3.0 mmol/l
Nausea and vomiting	Neurological weakness	ECG changes: • bradycardia • prolonged PR interval • short QT interval • widened T waves • arrhythmia
Constipation	Hyporeflexia	
Polyuria	Decreased consciousness	
Psychological disturbance		

potent and efficacious in normalising serum calcium.[18] Other strategies to control malignant hypercalcaemia include the use of corticosteroids and calcitonin. Calcitonin regulates bone turnover and calcium homeostasis with parathyroid hormone. Administered subcutaneously, it can rapidly normalise serum calcium but its use is limited by anaphylaxis.

The prognosis is poor for patients with malignant hypercalcaemia (in the order of a few months), but is significantly improved if the hypercalcaemia responds to antitumour therapy alone.[14] Correction of hypercalcaemia can make a considerable improvement in the patients' quality of life.

Spinal cord compression

Spinal cord compression from metastatic cancer affects up to 5% of patients and remains an important source of morbidity, despite treatment being effective in 90% of patients if there is early diagnosis.[19] The most common underlying tumours are listed in Table 7. The presenting symptoms can be vague and often become worse before the diagnosis is made (Tables 8 and 9). Any cancer patient complaining of back pain, bladder or bowel dysfunction with focal neurology or sensory level requires urgent investigation. Furthermore, the finding of bilateral upper motor neurone signs should be considered due to spinal cord compression until proved otherwise. Autonomic dysfunction occurs late and carries a poor prognosis. If spinal cord compression is missed or left untreated, patients can develop severe neurological deficits and double incontinence.

Table 7. Frequency of tumour types producing spinal cord compression.

Tumour type	Frequency (%)
Breast cancer	29
Lung cancer	17
Prostate	14
Lymphoma	5
Myeloma	4
Renal	4
Sarcoma	2
Other	23

Both plain X-ray imaging of the spine looking for vertebral collapse or associated vertebral disease and magnetic resonance imaging of the spinal axis are needed to define the presence and level(s) of spinal cord compression.[21] Gadolinium contrast enhancement will delineate leptomeningeal disease and intramedullary metastases.

Treatment strategies

High-dose intravenous corticosteroids should be initiated on clinical suspicion alone to prevent further evolution of neurological deficit. If appropriate, a neurosurgical opinion should be obtained about the potential for surgical decompression, especially if there is vertebral instability or the level of the compression has been previously irradiated. Otherwise, the definitive treatment is urgent local radiotherapy.[19] Occasionally, chemotherapy has a role in chemosensitive tumours, for example in germ cell tumours or lymphoma.

Pretreatment ambulatory function is the main determinant of post-treatment gait function.[22] Patient care requires a multidisciplinary team approach with active rehabilitation following treatment to optimise neurological recovery. The tumour type influences the time to presentation with spinal cord compression, the ambulatory function at presentation and patient response to therapy. Thus, the key to gait and continence preservation is prompt diagnosis and treatment. Ambulatory function can be preserved in over 80% of patients who are ambulatory at presentation.

Conclusions

A number of situations are encountered in patients with cancer that require urgent intervention. These patients may present to clinicians in a variety of

Table 8. The most common first symptoms compared with those present at the time of diagnosis of spinal cord compression.[20]

Symptom	1st symptom (%)	Present at diagnosis (%)
Back pain	94	97
Weakness	3	74
Autonomic dysfunction	0	52
Sensory loss	0.5	53

Table 9. Comparison of features of spinal cord, conus medullaris and cauda equina.

	Type of compression		
Clinical feature	**Spinal cord**	**Conus medullaris**	**Cauda equina**
Weakness	Symmetrical & profound	Symmetrical & variable	Asymmetrical, may be mild
Reflexes	Increased or absent knee & ankle reflex, extensor plantar reflex	Increased knee reflex, decreased ankle reflex, extensor plantar reflex	Decreased knee & ankle reflex, extensor plantar reflex
Sensory loss	Symmetrical, sensory level	Symmetrical, saddle distribution	Asymmetric, radicular pattern
Sphincters	Late loss	Early loss	Spared often
Progression	Rapid	Variable	Variable

specialties. A heightened awareness of these conditions, in conjunction with improved education of patients and those caring for them, will improve patient outcome.

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