Khajotia and Poovaneswaran, Prensa Med Argent 2013, 99:10
http://dx.doi.org/10.4172/lpma.1000102

La Prensa Medica Argentina

Review Article

An Overview of Oncologic Emergencies - What Family Physicians and their Patients Need to Know

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Abstract

Over the years, the number of cancer patients globally has increased exponentially, and the problem is now a growing one.

Family Physicians take care of their patients on a day-to-day basis and are commonly the first to suspect and refer patients with malignancies. Consequently, early suspicion of a potential malignant process by the family physician is essential for prompt referral of the patient to a speciality centre, thereby resulting in early diagnosis and treatment, with a consequent reduction in both morbidity and mortality.

Hence, it is imperative for family physicians to be well acquainted with the knowledge of potential oncological emergencies which they could commonly encounter in the course of their busy medical practice.

Keywords

Hypercalcaemia; Bisphosphonates; Lymphoma; Neutropenia; Dexamethasone

Introduction

The incidence for most cancers is decreasing in the United States and many other developed nations. However, in contrast, the incidence and mortality rates are increasing in the developing world because of an increasing incidence of smoking, adoption of a sedentary lifestyle and increased intake of a calorie-rich diet. Consequently, the incidence of lung and colon cancers in some developing nations is greater than those in the United States and other western countries.

Worldwide, it was estimated that there were about 12.7 million new cancer cases and 7.6 million cancer deaths in 2008 alone [1].

However, cancer incidence amongst males and females varies widely across countries. Amongst men, lung cancer is the commonest cause of cancer in most parts of Eastern Europe and Asia; liver cancer in West Africa; prostate cancer in North America, Australia, Western and Northern Europe, and South America; esophageal cancer in East Africa; bladder cancer in Egypt and Kaposi's sarcoma in central parts of Africa. Amongst women, the most frequently diagnosed cancer is breast cancer in most parts of the world, including North America, parts of South America and Western Asia, Australia and North Africa; liver cancer in Vietnam and Mongolia; cervical cancer in Central America, South America, Sub-Saharan Africa, and India; and lung cancer in North Korea and China [2].

As malignancies become more common, it is imperative for cancer patients and their treating family physicians to be aware of the vital symptoms and signs and various emergency conditions that trigger the need for immediate medical attention.

It has to be emphasized that cancer patients are at risk from a wide variety of medical emergencies. These may arise from the direct local effects of the tumour, from its metastases or from generalized effects associated with the disease known as *paraneoplastic syndromes*. Some medical emergencies can arise as a result of anti-neoplastic therapy, a treatment targeted at preventing the growth of malignant cancerous cells.

Because such conditions may require specific emergency management, the recognition of these clinical emergencies by clinicians is critically important, as quite often they are predictable, and can be prevented or adequately managed if diagnosed early, thereby reducing morbidity.

Oncological emergencies can be broadly classified into 4 categories, namely:

- Metabolic
- Haematological
- Structural, and,
- Treatment-related emergencies

Metabolic Causes

Hypercalcaemia

This is the commonest life-threatening metabolic disorder associated with malignancy [3]. The overall incidence is 5-10% amongst all cancer patients [3]. Patients usually present with non-specific symptoms such as nausea, thirst, vomiting, lethargy, constipation, weakness or confusion. Since these symptoms are largely non-specific and generalized, their significance can be recognized only if the treating physician has a high-index of clinical suspicion. The common mechanisms responsible for these symptoms are cytokine release due to osteolytic metastases and tumour secretion of parathyroid hormone-related peptide. In myeloma patients, the primary cause of hypercalcemia is widespread tumor-induced bone destruction. This is mainly due to increased osteoclastic bone resorption caused by potent cytokines expressed or secreted locally by the myeloma cells (receptor activator of nuclear factor-κB ligand) [RANKL] [4].

Treatment consists of rehydration, initially with 4-6 litres of

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Received: August 02, 2013 **Accepted:** September 23, 2013 **Published:** September 26, 2013

isotonic saline infusion over 24 hours, followed by bisphosphonates, alongwith a single dose of intravenous pamidronate or zolendronic acid. Corticosteroids in a dose of 60 mg/day orally may be effective in treating hypercalcaemia. In such cases, it can be used alone or in combination with bisphosphonates [3]. It is especially useful in patients with haematologic malignancies such as myeloma or lymphoma. Plicamycin is also effective, but it is mainly used only in refractory hypercalcaemia [3]. Once intravascular hydration is completed, loop diuretics such as furosemide is useful to help flush the excess calcium from the system, thereby maintaining adequate renal function. However, it must be remembered that inspite of aggressive treatment, it usually takes 2-4 days for the serum calcium levels to normalize.

Preclinical data from murine models of humoral hypercalcemia of malignancy suggest that inhibition of RANKL, using OPG-Fc, causes greater suppression of bone resorption and hypercalcemia than do bisphosphonates [5]. As of now, the most advanced anti-RANKL is a fully human monoclonal antibody to RANKL, namely denosumab (Amgen Inc., Thousand Oaks, CA, USA). Clinical trials with denosumab are ongoing in patients with multiple myeloma and recent data suggest that it is efficacious [6]. Similarly, trials are also underway in bone metastases from breast malignancies, prostate cancer, and other solid tumors.

Hyponatraemia

This is usually part of the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). Approximately 1-2% of cancer patients develop SIADH. It is usually seen in small-cell lung carcinomas, carcinoid tumours and lymphomas. In some cases, chemotherapeutic agents such as vincristine, ifosphamide and cyclophosphamide have been implicated as well, in the causation of hyponatremia.

Management of SIADH is directed towards the treatment of the underlying malignancy and fluid restriction to between 500 ml-1litre, over 24 hours. In intractable cases, demeclocycline 0.6 to 1.2 g/day may be beneficial.

Acute tumour lysis syndrome

It is a metabolic complication of either rapid tumour-cell turnover (seen commonly in lymphomas and leaukaemias) or chemotherapy-induced tumour necrosis. It is characterized by hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia. It is important to identify patients at risk in such cases, and commence preventative management strategies which include hydration, urine alkalinisation and allopurinol.

Lactic acidosis

This is a relatively rare metabolic complication of malignancy [7]. When present, type B (without hypoxia) lactic acidosis, is usually seen inmalignancies. It is usually associated with lymphoreticular malignancies (commonly, acute leukaemias and high grade lymphomas) and less commonly with solid tumours, unless it is well advanced (as seen in hepatic metastasis).

The purpose of treatment is to restore the pH but not raise it above 7.2 and maintain bicarbonate around 8-10 mmol/l. This is done bygiving 50-100 meq bicarbonate over 30 to 60 minutes as isotonic/hypertonic solution. One must becautious as bicarbonate itself may exacerbate lacticacidosis. In extreme cases, dialysis may be required, but the dialysate itself contains lactate which may interfere with the laboratory estimation of blood lactate. However, it is not known to aggravate the acidosis.

Haematological Causes

Febrile neutropenia

Oncological therapy may cause neutropenia (decrease in white blood cells) and consequently render such patients at high risk for developing sepsis. Patients at risk should be advised to have a thermometer at home to monitor their temperature, and if they develop a fever it is imperative that they seek urgent medical attention.

Fever commonly occurs during chemotherapy-induced neutropenia. Ten percent to fifty percent of patients with solid tumors and >80% of those with hematologic malignancies will develop fever during one or more chemotherapy cycles associated with neutropenia [8]. Assessment of risk for potential severe infection should be undertaken at the time of fever. High-risk patients are considered to be those with prolonged (>7 days duration) and profound neutropenia (absolute neutrophil count [ANC] <100 cells/mm^3 following cytotoxic chemotherapy) and/or significant medical co-morbid conditions such as hypotension, neurologic complications or pneumonia. Such patients require admission to hospital for further management.

In comparison, low-risk patients are considered those with short (<7 days duration) neutropenic periods and noco-existent comorbid conditions. Such patients are candidates for oral therapy [9].

This risk classification is performed using the Multinational Association for Supportive Care in Cancer (MASCC) scoring system. This scoring system states that a high-risk patient is one who has a MASCC score of <21, while a low-risk patient is one with a MASCC score of > 21.

High-risk patients must be hospitalised for intravenous antibiotic therapy. Management of these patients also involves barrier nursing, wherein the patient is managed in a single room with strict aseptic precautions. In addition, cultures from all potential portals of infection are regularly collected and sent for pathological examination.

In such cases, monotherapy with an antipseudomonal beta-lactam agent, such as cefepime, a carbapenem such as meropenem or imipenem-cilastatin, or piperacillin-tazobactam, is recommended. Other antimicrobials such as aminoglycosides, fluoroquinolones orvancomycin may be addedif antimicrobial resistance is suspected or proven, or if complications such as hypotension and pneumonia develop [9].

However, it must be remembered that vancomycin or other agents active against aerobic gram-positive cocci are not recommended as a standard part of the initial antibiotic regimen for fever and neutropenia. These agents should be considered for specific conditions such as catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability [9].

Modifications to initial therapy in high-risk patients include [9]:

i) Methicillin-resistant Staphylococcus aureus (MRSA): Consider early use of vancomycin, linezolid, or daptomycin.

ii) Vancomycin-resistant enterococcus (VRE): Consider early addition of linezolid or daptomycin.

iii) Extended-spectrum beta-lactamase (ESBLs): Consider early use of a carbapenem

iv) Klebsiella pneumoniae carbapenemase (KPCs): Consider early use of polymyxin-colistin ortigecycline.

Most penicillin-allergic patients tolerate cephalosporins, but those with a history of an immediate-type hypersensitivity reaction (urticaria and bronchospasm) should be treated with a combination that avoids beta-lactams and carbapenems, such as ciprofloxacin plus clindamycin or aztreonam plus vancomycin.

Low-risk patients should be treated with initial outpatient oral or intravenous antibiotics:

a) Ciprofloxacin plus amoxicillin-clavulanate in combinationis recommended for oral outpatient treatment. Other oral medications include levofloxacin or ciprofloxacin monotherapy or ciprofloxacin plus clindamycin.

Note: Patients receiving fluoroquinolone prophylaxis should not receive oral empirical therapy with a fluoroquinolone. Hospital re-admission or continued stay in the hospital is required for persistent fever or signs and symptoms of worsening infection.

Duration of treatment

In patients with pathologically documented infections appropriate antibiotics should continue for at least the duration of neutropenia (until ANC is > 500 cells/mm3) or longer, if clinically necessary, or for a minimum duration of at least 5 days, which includes a minimum duration of two days after resolution of the fever.

In patients with unexplained fever, theantibiotic regimeshould be continued until there are clear signs of marrow recovery. This is indicated by an increasing ANC that exceeds 500 cells/mm^3 [3]. In cases where the entire treatment course has been completed and all signs and symptoms of a documented infection have resolved, patients who remain neutropenic should be administered oral fluoroquinolone prophylaxis until marrow recovery [9].

Leukostasis

High numbers of circulating leukaemic cells obstruct circulation in the brain and lungs by forming aggregates and thrombi in small veins. If haematocrit is above 30%, the risk is further increased. In such cases, clinical presentation may include altered sensorium, frontal headaches, papilloedema or retinal venous distension, dyspnoea, hypoxaemia and cardiac failure. Leukostasis is a serious oncologic emergency in which the mortality can be as high as 40% if left untreated. Management includes prompt hydration, alkalinisation, allopurinol, exchange transfusion, induction chemotherapy, focal radiation to affected organs and leukopheresis.

The immediate aim is to reduce the number of circulating malignant WBCs. This can be achieved by using induction chemotherapy with hydroxyurea (which inhibits the DNA synthesis of malignant cells) in combination with emergent leukopharesis which facilitates the removal of WBCs from the circulation by a process of filtration. In patients with acute myeloid leukemia (AML) presenting with white blood cell (WBC) counts higher than 100,000/mm^3 or signs and symptoms indicative of leukostasis, hydroxyurea is given 1 to 3 g orally every 6 hours, in combination with emergent leukapheresis. However, in acute lymphocytic leukemia (ALL), the threshold to initiate leukapheresis is usually higher than 200,000/mm^3, and patients may be treated with vincristine, steroids, or both. The replacement of fresh-frozen plasma that occurs in conjunction with leukapheresis may improve the coagulopathy that may be present in these patients, thereby reducing the risk of hemorrhage. However, leukapheresis has never been shown convincingly to reduce the risk of developing leukostasis or to reduce early mortality [10].

Leukopharesis can reduce WBC counts by 25%-50%, by removing as many as 10^{11} to 10^{12} total WBCs during a single treatment. It is essential to administer definitive cytoreductive therapy (chemotherapy) within a short time following leukopharesis, as malignant cells can rapidly replicate, rendering leukopharesis ineffective. At present, there are no evidence-based guidelines about when to start or stop leukopharesis.

Structural Causes

Epidural spinal cord compression

Spinal cord compression is the second commonest neurological emergency after cerebral metastasis and this is most often due to extradural spread from vertebral metastases [11]. Failure to recognize this common neurological emergency results in severe disability with consequent paraplegia and urinary incontinence. The dorsal cord is the commonest site of compression by the metastatic lesion in these patients, with the primary tumour most frequently being in the breast, lung, prostate or kidney. Hence, spinal pain in a cancer patient should be assumed to be due to a spinal metastastatic lesion, unless proven otherwise, and investigated vigorously.

The investigation of choice in these patients is an MRI scan of the entire spine as there may be multiple levels of compression. Management includes high-dose dexamethasone (16 mg/24 hours) along with radiotherapy. Neurosurgical intervention is recommended if there is no definite diagnosis in a patient with a rapidly deteriorating neurologic status. Emergency chemotherapy may be useful in lymphomas, neuroblastomas and Ewing's sarcomas. Laminectomy decompression is usually sufficient to relieve tumours that reach epidural space via intervertebral foramina. However, the prognosis following surgery has not been shown to be superiorto that following radiotherapy.

In case of suspected metastatic epidural spinal cord compression surgical decompression has proven to be beneficial if a patient meets the *Patchell criteria* [12]. These are:

Inclusion criteria

- Tissue-proven cancer, not of CNS or spinal column origin
- Radiographic spinal cord displacement
- ≥ 1 neurological sign, symptom or pain
- Single area (one level or multiple contiguous spinal levels)
- Estimated survival ≥ 3 months

Exclusion criteria:

- Radiosensitive tumors: lymphoma, leukaemia, multiple myeloma, germ-cell tumor
- Paraplegic >48 hr for study entry
- Only cauda or root compression
- Prior radiation (if study dose of 10 X; 3 Gy is contraindicated)

Indication:

Patients with metastatic epidural spinal cord compression treated

with direct (<24 h after randomisation) decompressive surgery plus postoperative radiotherapy retain the ability to walk for longer and regain the ability more often, than do patients treated with radiotherapy alone.

Malignant pericardial effusion/Tamponade

10-15% of all cancer patients have some degree of pericardial effusion. Clinical signs include jugular venous distension, pulses paradoxus, muffled heart sounds and poor cardiac output. Investigations include ECG, chest radiography and echocardiography. Urgent pericardiocentesis or creation of a pericardial window is the treatment of choice in these patients.

Superior Vena Cava (SVC) Obstruction

This usually results from malignant disease in the mediastinum causing extrinsic compression or invasion. It may also occur due to an iatrogenic complication, such as thrombosis around a central venous line. The characteristic features are facial swelling, chest pain and distension of the neck and chest wall veins. Right apical lung malignancies, followed by mediastinal lymphomas are the commonest causes of SVC obstruction. They account for 75% and 15% of all cases of SVC obstruction, respectively [13]. Palliative management includes chemotherapy, radiotherapy, corticosteroids and in some cases, intraluminal stenting.

Increased Intracranial Pressure

Increased intracranial pressure may be caused by brain metastases. Around a quarter of cancer patients die due to intracranial metastases. Lung, breast and melanoma are the most common tumors that metastasize to the brain [14]. Symptoms and signs suggestive of brain metastasis include headache, nausea, vomiting, seizures, behavioural changes and focal neurological deficits. The tumor mass together with its surrounding oedema may produce hydrocephalus and as the mass enlarges, herniation may occur depending on the location of the tumour within the cranium. Investigations include an MRI or a CT scan.

Emergency management to prevent herniation include hyperventilation, mannitoland steroids. Mannitol is a hyperosmotic agent that is effective within minutes of its intravenous administration and may last for several hours. Steriods are administered to control vasogenic oedema. Dexamethasone is given by a bolus intravenous injection of 16–40 mg, followed by 40–100 mg per day. Its effect starts within hours and may last several days [15]. Once herniation has been controlled, a decision on the treatment of the brain metastases should be taken. If multiplenodules are seen, whole-brain irradiation should be considered. However, for a single brain metastasis, surgery plus radiation should be considered. Radiosurgery may be indicated in patients having fewer than three metastases, each measuring<2 cm.

Urinary Obstruction

Urinary obstruction may occur in patients with gynaecological or urological tumors particularly cervical or prostatic carcinoma [14]. Occasionally, metastatic disease to the pelvis causes urinary obstruction, which may result in bilateral hydronephrosisand renal failure. Symptoms include, flank pain, sudden anuria, sometimes alternating with polyuria. A progressive rise inserum creatinine should make the clinician suspect urinary obstruction [14]. Investigations include, renal ultrasound and CT for detecting the location of the obstruction. Treatment includes insertion of ureteral stents under local anesthesia to relieve the obstruction. Percutaneous nephrostomy is another alternative.

Massive Hemoptysis

Lung cancer accounts for a large percentage of patients having hemoptysis 20% of cases of lung cancer usually have hemoptysis during the course of the disease [14]. Endobronchial metastases from carcinoid tumors, breast, colon or kidney cancer, melanoma and sarcomas may also cause hempoptysis. Malignancies of the lips, tongue, tonsils, larynx, throat and oesophagus may also result in hemoptysis, which may be moderate-to-massive in quantity.

Firstly, treatment involves airway patency. Intubation is recommended in patients with massive haemoptysis and hemodynamic instability. Other treatment measures include blood transfusion, oxygen, cough suppressants and correction of any coagulation disorder, if present [14].

Selective bronchialartery embolization may be required to control massive bleeding, and in some cases emergency lobectomy too may have to be contemplated. Radiotherapy may help to reduce bleeding by causingvascular thrombosis and necrosis of contributing vessels. In advanced diseased states it may be more appropriate to focus on palliative care and patient comfort while treating symptoms such as pain and hemoptysis. In such cases, symptomatic treatment may be more suitable in managing the patient and maintaining quality of life.

Treatment-related Emergencies

Anaphylactic reactions related to chemotherapeutic agents

Anaphylactic reactions related to chemotherapeutic agents may occasionally lead to medical emergencies. Angioedema andurticaria are the most common manifestations of anaphylaxis and constitute more than 90% of allergic reactions to drugs [14].

Other frequent manifestations of anaphylaxis include abdominal pain, chest tightness, upper airway obstruction, bronchospasm and hypotension. Laryngeal oedema followed by hypotension is the most frequentcause of death related to allergic reactions, if not diagnosed and treated promptly. Treatment includes intubation, administration of epinephrine, intravenous glucocorticoids and intravenous fluids. Early diagnosis is the key to reducing mortality in such cases.

5-FU associated coronary artery spasm

The common chemotherapeutic drug 5-fluorouracil (5-FU) used in the treatment of a number of solid tumors, including colorectal, breast, gastric, pancreatic, prostate, and bladder cancers are known to rarely cause angina pectoris, cardiac arrhythmias, myocardial infarction and sudden cardiac death. The probable reasons for these phenomena range from toxic and metabolic disturbances to coronary artery spasms. Some reportshave shown angiographically-proven spasmophilia of the coronary arteries and this has contributed to the understanding of angina pectoris occurring during treatment with 5-FU [16]. However, the exact mechanism of 5-FU cardiotoxicity is still unclear. *In vitro* studies by one group of researchers suggest that 5-FU causes direct vasoconstriction of vascular smooth muscle, which is mediated by the activation of protein kinase C (PKC) [17]. Studies have shown that the incidence of cardiotoxicity in patients treated with 5-FU ranged from 1.8% to 18% and it occurred in patients administered 5-FU either as a single agent or in combination with other chemotherapeutic agents [18].

doi:http://dx.doi.org/10.4172/lpma.1000102

Haemorrhagic cystitis

Hemorrhagic cystitis is usually seen in patients receiving high doses of ifosfamide or cyclophosphamide. These alkylating agents are metabolized to acrolein, which is a chemical agent with strong irritant properties, that isexcreted in the urine. Common symptoms may include dysuria, burning, frequency, gross hematuria, urgency and incontinence [14]. The best treatment in such cases is prevention. Oral or intravenous hydration increases urinary flow andreduces the contact of acrolein with the bladder mucosa.Mesna should always be administered with ifosfamide or with high-dose cyclophosphamide to detoxify acrolein and its metabolites in urine in order to prevent haemorrhagic cystitis. When hemorrhagic cystitis occurs, intensive hydration should be undertaken to increase urinary flow. If this therapy fails, irrigation witha formalin solution for 10 minutes may stop bleeding. In extreme cases when bleeding does not stop, surgical ligation or embolization of hypogastric arteries may be indicated [7]. Sometimes, cystectomy may berequired. In some cases, external pelvic irradiation in combination with brachytherapy, when given in the treatment of cervical cancer, has also been known to cause hemorrhagic cystitis.

Conclusion

There are many conditions related to malignancies and their treatment that can be life-threatening. However, early recognition and prompt management of these conditions help stabilize patients, there by facilitating them to further receive definitive oncological treatment which may either be curative or palliative. Hence, it can be concluded that a good knowledge of the above oncologic complications is imperative for early diagnosis and timely management, in order to help significantly reduce morbidity and also improve quality of life in these patients.

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