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Oncologic emergencies for the internist

ABSTRACT

Most cancer patients experience at least one emergency during the course of the disease. This paper reviews the diagnosis and treatment of tumor lysis syndrome, hypercalcemia of malignancy, superior vena cava syndrome, spinal cord compression, strokes and seizures, and treatment-related emergencies.

KEY POINTS

To prevent tumor lysis syndrome, patients at risk should be started on intravenous fluids and, if possible, allopurinol, several days before chemotherapy.

Hypercalcemia of malignancy is treated with hydration and with bisphosphonates. Diuresis with furosemide should be started only after the patient is adequately hydrated.

The new onset of back pain in a cancer patient is a red flag for spinal cord compression. Prompt treatment with corticosteroids and radiation therapy may preserve the patient's ability to walk.

In neutropenic fever, antibiotics must be started immediately, including a broad-spectrum antipseudomonal drug such as ceftazidime. Patients should also receive vancomycin to cover resistant gram-positive organisms if they have any of the following: severe mucositis, catheter infection, current quinolone prophylaxis, hypotension, or known colonization with resistant gram-positive organisms.

As more cancer patients undergo outpatient therapy, internists are being confronted more often with emergencies related to cancer or its treatment. Emergencies in cancer patients encompass virtually every major organ system. This article focuses on the common and critical complications of cancer that the general internist is most likely to see and can least afford to miss, specifically:

- Tumor lysis syndrome
- Hypercalcemia of malignancy
- Superior vena cava syndrome
- Spinal cord compression
- Strokes and seizures
- Treatment-related emergencies.

Overall, most cancer patients experience one of these complications at some point in the course of their disease.

TUMOR LYSIS SYNDROME

Tumor lysis syndrome is the set of metabolic abnormalities that results from acute destruction of neoplastic cells and release of their intracellular products into the circulation. The high rate of cell turnover overwhelms the body's normal homeostatic mechanisms for handling potassium, calcium, phosphorus, and uric acid, leading to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and uremia. These may be seen alone or in combination with one another.

Tumor lysis syndrome occurs with a variety of tumors, most commonly the hematologic malignancies. Hande and Garrow[1] found an incidence of tumor lysis syndrome of 42% among patients with high-grade non-Hodgkin lymphoma, although it was considered clinically significant in only 6%. The risk depends not only on the type of tumor, but also on the extent of disease, the type of treatment, and the patient's preexisting renal function (TABLE 1).[2]

Features of tumor lysis syndrome

Hyperuricemia. Catabolism of large amounts of both RNA and DNA causes uric acid levels to rise fairly quickly. Normally, uric acid remains in the ionized state in the body; however, increased levels can lead to urate precipitation in the distal tubule.[3] The result of precipitation is an overall decrease in renal function.

Hyperphosphatemia and hypocalcemia also result from the above process. Phosphate levels in neoplastic cells can be as much as four times higher than in normal cells.[4,5] The breakdown and release of phosphate is initially compensated for by increased renal excretion. However, as the concentration of phosphate increases, it combines with calcium and precipitates in the renal tubule as well as in the soft tissues. Consequently, hypocalcemia and renal failure develop.[6] Clinically, hypocalcemia can manifest as agitation, tetany, and bone pain.

Hyperkalemia is the most life-threatening problem in tumor lysis syndrome

Hyperkalemia is perhaps the most life-threatening derangement in tumor lysis syndrome. The sudden increase in potassium results in the well-defined clinical presentation of cardiac arrhythmias and death.

All the above metabolic derangements are made worse by preexisting renal insufficiency.

Treatment of tumor lysis syndrome

Prophylaxis is the first step in treatment (TABLE 2).[7] If a patient is found to be at high risk for tumor lysis syndrome, he or she should promptly be started on both intravenous fluid and allopurinol if there is no contraindication to it. Close observation during therapy is also essential, as transient, urgent hemodialysis may reverse the toxicity.

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia of malignancy occurs in approximately 10% to 20% of cancer patients,[8,9] most often with lung cancer, breast cancer, and the hematologic malignancies such as multiple myeloma and lymphoma.[10]

Features of hypercalcemia of malignancy

Symptoms vary depending on the degree of hypercalcemia and how quickly it develops. Acute symptoms include nausea, vomiting, constipation, polyuria, polydipsia, muscle weakness, acute renal insufficiency, and mental status changes. Chronic symptoms include kidney stones, bone pain, and depression.

Mechanisms of hypercalcemia of malignancy

Normally, calcium levels are maintained by the interaction of parathyroid hormone, calcitonin, and $1,25(OH)_2$-vitamin D. The disorders of calcium metabolism in malignancy usually represent an alteration in one of these pathways or extensive lytic bone lesions.

Parathyroid hormone-related peptide. The most common cause of hypercalcemia of malignancy, classically seen in squamous cell lung cancer, is a syndrome mediated by production of a parathyroid hormone-related peptide (PTHrP). Structurally similar to PTH at the amino acid terminus, PTHrP binds to parathyroid hormone receptors, mobilizes calcium from bones, and increases renal reabsorption of calcium. Evidence suggests that there might be some clinical utility to measuring PTHrP because significant elevations of PTHrP seem to correlate with poorer outcomes.[11–13]

Abnormal production of calcitriol (1,25-vitamin D). The deregulated conversion of

Hypercalcemic patients invariably are dehydrated

25-vitamin D to 1,25-vitamin D appears to be responsible for some of the hypercalcemia of malignancy seen in both Hodgkin lymphoma and non-Hodgkin lymphoma.[14,15] Thus, it is similar to the hypercalcemia associated with sarcoidosis and other granulomatous diseases.

Direct tumor invasion into bony structures. Individual tumor cells secrete a variety of mediators, including interleukin-1, interleukin-6, and tumor necrosis factor, that upregulate local osteoclastic activity, causing calcium to be released into the serum.[16]

Treatment of hypercalcemia of malignancy

Treatment must address these various mechanisms to be effective; ideally, the best way is by reducing or eliminating the causative malignancy.

Hydration. Patients with hypercalcemia of malignancy invariably present with some dehydration caused by calcium's effect on the kidney. Thus, appropriate management should begin with giving intravenous fluids to improve symptoms and to induce excretion of calcium. However, even with adequate hydration, most patients do not achieve an acceptable calcium level, and thus additional therapies are used to control the renal and skeletal mechanisms of hypercalcemia of malignancy.

Diuresis with furosemide increases renal excretion of calcium, but should be started only when the patient has been adequately hydrated—otherwise it will exacerbate the free water loss relative to the loss of sodium and calcium.

Bisphosphonates. Most experts recommend using bisphosphonates, most often pamidronate, to produce a sustained decrease in the calcium level by inhibiting osteoclastic activity and calcium resorption from bone.[17] Pamidronate is given intravenously in either a

60-mg or a 90-mg dose over at least 2 hours.[18] Approximately 60% of patients respond to a 60-mg dose and nearly 100% to a 90-mg dose.[19] Pamidronate usually takes approximately 12 to 48 hours to produce an initial response, and the response is sustained for an average of about 2 weeks.[20]

Calcitonin is frequently used in addition to bisphosphonates because it has a rapid onset of effect: within 2 to 4 hours of administration.[21] Its main drawbacks are hypersensitivity reactions and tachyphylaxis; the latter usually develops within 3 days.

Gallium nitrate and plicamycin are used infrequently because of their toxicity.

Steroids are frequently helpful in the short term, especially in sensitive tumors such as lymphoma and myeloma.

Dialysis remains an option for those who cannot tolerate a saline load.

SUPERIOR VENA CAVA SYNDROME

Superior vena cava syndrome is relatively rare, affecting 2.4% to 4.2% of lung cancer patients, who account for 65% of all cases.[22] Small cell lung cancer is the most frequent cause of the syndrome because it has a predilection for the central region of the lungs.[23] Lymphoma accounts for 8% of cases, and breast cancer and other mediastinal metastatic lesions account for 10%.[22]

Experts recommend pursuing a tissue diagnosis in superior vena cava syndrome

Of note: several nonmalignant diseases such as granulomatous and fibrosing mediastinitis, goiters, and aortic aneurysms can also cause superior vena cava syndrome.

Features of superior vena cava syndrome

Superior vena cava syndrome results from an increase in central venous pressure caused by vena caval obstruction. Typically this produces cough, dyspnea, and dysphagia combined with swelling and discoloration of the neck, face, or upper extremities. Depending on the site of the disease, both vocal cord paralysis and Horner syndrome (sinking in of the eyeball, ptosis of the upper eyelid, elevation of the lower lid, constriction of the pupil, narrowing of the palpebral fissure, and anhidrosis and flushing of the affected side of the face; caused by compression of sympathetic nerves) can occur.

Treatment of superior vena cava syndrome

Initial treatment consists of elevating the head of the bed and giving diuretics and corticosteroids. However, corticosteroids are more useful when the cause of the obstruction is lymphoma rather than lung cancer.

Chemotherapy and radiation therapy. Unless tracheal obstruction is present or impending, superior vena cava syndrome is not immediately life-threatening, and most experts recommend pursuing a tissue diagnosis so that specific treatment can be given for the primary tumor alongside treatment for the symptoms.[22]

Both primary chemotherapy and radiation are important components of therapy. In small cell lung cancer, Chan et al[24] found no difference in the response rate in patients who received chemotherapy compared with radiation therapy. The recurrence rate of superior vena cava syndrome depends on the type of tumor causing the obstruction. In large cell lymphoma the high risk of recurrence with chemotherapy resulted in a recommendation to use radiation therapy.[25]

Intravenous stenting can relieve symptoms, particularly dyspnea, for most patients.

Anticoagulation. Thrombus formation occurs in up to 50% of patients with superior vena cava syndrome. In a small study, Adelstein et al[26] attempted prophylaxis with full doses of heparin and warfarin but found it conferred no survival advantage when treated patients were compared with 10 historical controls. However, anticoagulation is still used for symptom relief regardless of effect on survival.

SPINAL CORD COMPRESSION

Spinal cord compression is not immediately life-threatening unless it involves level C3 or above, but it may lead to profound, permanent morbidity. Paraplegia or loss of sphincter control or both not only diminishes a patient's quality of life but also predisposes to further complications such as venous thrombosis, decubitus ulcers, and urinary obstruction.

Spinal cord compression occurs at some time in approximately 5% of all cancer patients,[27] most often in carcinomas of the prostate, lung, and breast.

Features of spinal cord compression

Pain is the primary symptom and is eventually reported in 96% of patients with spinal cord compression.[28] The pain may be acute or may gradually increase over weeks. Although the pain is similar to that of disc disease, one potential difference is that the pain of spinal cord compression can be increased in the supine position and decreased when upright.

Other signs and symptoms are weakness, sensory deficits, and autonomic dysfunction.

Diagnosis of spinal cord compression

It is often difficult to decide whether a patient with back pain should be thoroughly evaluated to exclude spinal cord compression, but a patient with known or suspected metastatic disease (especially tumor types with a tropism for bone) presenting with a new pain pattern or a neurologic deficit deserves meticulous evaluation.

Magnetic resonance imaging (MRI) without contrast is the best and most cost-effective test.[29]

MRI without contrast is the best test for spinal cord compression

Several nonmalignant conditions, such as osteoporotic compression fractures and spinal abscesses, may also cause spinal cord compression and must be diagnosed accurately, as their treatment and prognosis are markedly different.

Treatment of spinal cord compression

Neurologic compromise can be rapid; therefore, treatment must begin quickly after diagnosis.

Corticosteroids are a critical part of the initial management because they decrease edema that may compress vasculature or the nerves directly and lead to permanent injury. Although dosages are debated, the minimum is dexamethasone 10 mg (or an equivalent) by intravenous bolus followed by 4 mg intravenously every 6 hours.

Radiation therapy. Carcinomas of the prostate, lung, and breast are more predictably responsive to radiotherapy than are other types of tumors. However, a patient presenting with any type of malignant spinal cord compression should also seen urgently by a radiation oncologist.

Chemotherapy may be an option for extremely chemosensitive tumors such as pediatric neuroblastomas.

Surgery is the remaining option if a tissue diagnosis is needed, the area has previously received maximal irradiation, spinal stabilization is needed, or other treatments are not working.

STROKES AND SEIZURES

Strokes and seizures are common in cancer patients. Strokes occur in 7% of all cancer patients[30] and are equally split between hemorrhagic and thrombotic subtypes. Seizures occur in 2.7% of patients with cerebral metastases and in 1.8% of cancer patients without brain metastases.[31]

Initial treatment of strokes and seizures in cancer patients is the same as in patients without cancer. After initial stabilization, specific treatment of the tumor such as radiotherapy or steroids should be started. In addition, patients with thrombotic strokes might be considered candidates for antiplatelet, anticoagulation, or thrombolytic therapy.

Patients with cerebral metastasis without a history of seizure should be advised not to drive or engage in activities in which an unexpected seizure could harm them or others. Randomized studies have shown no benefit from prophylactic anticonvulsants,[32] with possible exceptions for melanoma brain metastases or leptomeningeal metastases.

TREATMENT-RELATED EMERGENCIES

Extravasation of chemotherapeutic drugs

Extravasation—leakage of chemotherapeutic drugs into the skin— results in pain, redness, swelling, and even necrosis. Its reported incidence ranges from 0.1% to 6.5% of chemotherapy infusions.[33] Although these reactions are usually seen in an oncologic setting, they are increasingly being seen in the primary care physician's office as more patients undergo home infusion therapy.

Occasionally, symptoms may develop hours or days after the initial insult. The delay can be caused by endocytolysis, in which a small amount of drug kills and lyses cells at the injection site and then moves on repeat-

edly to damage the surrounding tissues.

Extravasation is important because large areas of skin may break down, leading to poor cosmetic results, secondary infection, and contractures if the injury is over a joint.

The most common culprits are vesicants, which cause blisters when they contact skin. Anthracyclines (eg, doxorubicin and idarubicin) and vinca alkaloids (eg, vincristine and vinorelbine) are the most common vesicants used in clinical practice.

If the patient is complaining of pain or problems during vesicant infusion, the infusion should be stopped, the line aspirated to remove residual drug, and an antidote (if available) instilled through the line (TABLE 3).[33] If using a port, disconnect the infusion line; if using a temporary intravenous line, discontinue it. Compression of the site should be avoided as this may spread the remaining drug further out from the injection site. The use of heat, ice, and antidotes depends on the specific chemotherapeutic drug.

If a patient presents to an internist with pain at an injection site, with or without redness, shortly after a chemotherapy infusion, he or she should be referred to his or her treating oncologist urgently.

Neutropenic fever

Neutropenic fever is common, and if it is left untreated the mortality rate is 50%.[34]

Neutropenia is defined as a neutrophil count lower than 0.5×10^9/L (500/mm^3), or less than 1.0×10^9/L and expected to decline below 0.5 soon. A fever is defined as a single temperature of 38.3˚C (101.0˚F) or higher, or a temperature of 38.0˚C (100.4˚F) or higher lasting over 1 hour.

A complete fever workup should be completed, and then antibiotics should be started promptly. All patients should receive a broad-spectrum antipseudomonal drug such as ceftazidime. They also should receive vancomycin to cover resistant gram-positive organisms if any of the following is present: severe mucositis, catheter infection, current quinolone prophylaxis, hypotension, or known colonization with resistant gram-positive organisms. Often, despite a comprehensive search, the cause is never found; however, it is essential to start antibiotics immediately upon noting a neutropenic fever. Antibiotics should be continued until the absolute neutrophil count exceeds 0.5×10^9/L and the patient is afebrile.

It is important for the patient and all of his or her contacts to routinely wash their hands.

Stop the infusion if the patient complains of pain during vesicant infusion

Dehydration

Often overlooked, dehydration is a serious risk and is very common in cancer patients because of cachexia caused by the disease or its treat-

ment. Dehydration is associated with delirium in 30% of cancer patients and is linked to shorter survival.[35] Common treatment-related causes include emesis, diarrhea, and mucositis. For example, in some series of colon cancer patients,[36] approximately 50% required a change in treatment because of dehydration and 20% required intravenous fluids.

An internist can improve a patient's quality of life by providing supportive care with fluids, antiemetics, and antidiarrheal drugs and by communicating with the oncologist to discuss adverse effects that may require a change in treatment.

Anaphylaxis and capillary leak

Some systemic treatments such as interleukin-2 (IL-2) may cause severe hypotension, especially when given at high doses intravenously. The mechanism is decreased systemic vascular resistance and leakage out of vessels, leading to intravascular volume depletion. Some hypotension is seen in up to 70% of patients receiving IL-2 in high doses, and 3% experience life-threatening degrees of hypotension.[37] Close monitoring in an intensive care unit is wise before starting such high-dose therapy.

The treatment is to not give more IL-2 until the patient recovers and to provide supportive care with intravenous fluids and phenylephrine. IL-2 in low doses rarely causes such hypotension.

Hemorrhagic cystitis

Some chemotherapeutic drugs have toxic metabolites that are excreted by the kidney and can cause severe bladder hemorrhage. A common example is acrolein, which is formed by the metabolism of cyclophosphamide and ifosfamide.

Hemorrhagic cystitis is more common when urinary output is low, because low urine output increases the concentration of acrolein in the urine and the duration that the bladder mucosa is exposed to it. Therefore, hydrating the patient before chemotherapy is an important preventive measure. Another preventive measure is to give mesna during chemotherapy infusion.[38]

If hemorrhage is severe, exsanguination may result. Blood transfusions and a urology consult are essential. Continuous bladder infusions via a three-way catheter are commonly used to prevent bladder clots and also to flush out any remaining urothelial toxins. Measures as drastic as formaldehyde bladder infusions or cystectomy are rarely needed.

Dehydration is common and often overlooked in cancer patients

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