

Oncological emergencies

A. Cervantes & I. Chirivella

Department of Hematology and Medical Oncology, University Hospital Valencia, University of Valencia, Spain

Introduction

Cancer and its therapy may lead to urgent conditions. The care of cancer patients with emergency problems presents a challenge not only to medical oncologists but also to clinicians involved in emergency medicine. There are many kinds of problems for which cancer patients may require assistance in an emergency care facility. Cancer patients may often have complex medical problems in addition to the diagnosis of cancer, such as coronary heart disease, chronic obstructive pulmonary disease or diabetes mellitus. We can define an oncological emergency as an acute condition that is caused by cancer or its treatment, requiring rapid intervention to avoid death or severe permanent damage.

The initial approach to acutely ill cancer patients

Cancer patients presenting with acute emergencies should be approached in a similar way to those without cancer. However, staging of the tumor and response to current treatment, overall prognosis and patient and family wishes should be rapidly assessed in order to establish an appropriate treatment plan.

The first assessment should be quick and must include the main complaint or leading symptom, a focused history, baseline vital signs and a rapid overall physical examination.

A comprehensive assessment is essential for the majority of cancer patients with acute emergencies. Depending on the clinical picture, the acute event may be due to the tumor itself, to the treatment given to control the tumor or it may be related to a new or previously existing condition not related to cancer [1]. Emergencies in cancer patients may be classified into three different groups: (i) structural or obstructive emergencies caused by a space-occupying tumor, (ii) due to metabolic or hormonal problems and (iii) secondary to complications arising from treatment effects.

Structural and obstructive oncological emergencies

In this group we have to consider superior vena cava syndrome, pericardial tamponade, spinal cord compression, increased intracranial pressure, urinary obstruction, hemoptysis and airway obstruction.

Superior vena cava syndrome

Superior vena cava syndrome (SVCS) results from the partial or complete obstruction of blood flow through the superior vena cava vein to the right atrium, causing severe reduction in venous return from the head, neck and upper extremities. The obstruction may be due to compression, invasion, thrombosis or fibrosis of this vessel. Although this syndrome is still considered one of the classical oncological emergencies, it rarely causes an immediate life-threatening situation. Malignant tumors, such as lung cancer, lymphoma and metastatic tumors are responsible for >90% of all SVCS cases. Lung cancer, particularly small-cell and squamous-cell, accounts for almost 85% of all cases. Malignant lymphomas, mainly of non-Hodgkin histology, are the second cause. Although Hodgkin's disease usually involves the mediastinum, it rarely causes this syndrome. Other primary mediastinal tumors, like thymoma or germ cell tumors account for <2% of all malignant SVCS. Non-malignant causes are very exceptional and include retrosternal goitre, sarcoidosis, tuberculosis, mediastinal post-irradiation or idiopathic fibrosis. Another increasing cause of SVCS is the frequent use of long-term central venous catheters in patients with cancer [2].

As a result of a venous obstruction, there is a rise in intravenous pressure and collateral circulation often flows through the azygous system. Sudden obstruction, although very uncommon, is a real emergency that may induce a rapid increase in intracranial pressure, leading to brain edema. However, SVCS most often develops insidiously over several weeks, allowing some mechanisms of compensation. Patients may present with a series of symptoms and signs, such as neck and facial swelling, particularly around the eyes, dyspnea and cough. Head fullness and pressure sensation are common. Hoarseness, headaches, nasal congestion, epistaxis, hemoptysis, dizziness, dysphagia and syncope may also be present. Symptoms may get worse if the patient bends forward, stoops or lies down. Typical signs include venous distention in the neck and thoracic wall, facial edema and plethora, proptosis, stridor and arm edema.

The diagnosis of SVCS is mainly clinical. CT scan is the most useful radiographic study for imaging the mediastinum and for diagnosing SVC obstruction. CT may reveal the site of obstruction and collateral flow and is also able to differentiate extrinsic compression of the vein by tumor from intravascular thrombosis. Moreover, CT scan gives detailed information on the tumor mass and its relation to mediastinal

structures and may even help to guide a fine-needle aspiration biopsy if a histology diagnosis has not yet been obtained. Invasive procedures, like bronchoscopy, percutaneous needle biopsy, mediastinoscopy or even thoracotomy can be performed safely by an experienced clinician with very little risk of bleeding [3].

More than 50% of patients with SVCS become symptomatic before the diagnosis of cancer is made. On the other hand SVCS is rarely a life-threatening condition by itself. Therefore, empirical treatment with radiation before a tissue diagnosis of malignancy has been made, should never be done. The prognosis of patients with SVCS depends very much on the prognosis of the underlying disease. In cases of malignant lymphoma or small-cell lung cancer, considered as very chemosensitive diseases, the benefit of therapy is not compromised by the presence of SVCS [4]. The management of SVCS has shifted from empirical radiation, recommended for more than two decades, to a more methodical diagnostic evaluation. In fact emergency radiation before biopsy may preclude proper interpretation of the biopsy sample in >50% of cases. The only accepted exception to this may be those cases with impending airway obstruction or severe increase in intracranial pressure.

As initial measures, supplemental oxygen, diuretics, head elevation and corticoids may be useful in relieving symptoms, but as soon as the histology diagnosis is available, specific therapy for the underlying neoplastic disease should be initiated. Chemotherapy is the preferred treatment of malignant lymphoma or small-cell lung cancer. Most patients will experience a significant response with disappearance of all clinical manifestations of SVCS within 1 or 2 weeks. Radiotherapy remains the main option for patients having SVCS due to tumors insensitive to chemotherapy, such as recurrent disease of non-small-cell lung cancer. If a new patient with a non-small-cell lung cancer presents with SVCS, initial treatment may be chemotherapy. But if there is no objective response, radiotherapy should be given promptly. External beam radiation for SVCS is well tolerated and an improvement of symptoms is seen within a few weeks.

When SVCS is related to central venous catheters, catheter removal should be combined with anticoagulation to prevent embolization. In this setting, if SVCS is detected early, it can be successfully treated with fibrinolytic therapy without removing the catheter. Low doses of warfarin (1 mg/day) reduce the incidence of catheter-related thrombosis.

Superior vein caval stenting can also provide rapid symptomatic relief within a few days in most patients, although these stents must remain in place for the rest of the patient's life. Stenting may also be indicated in patients in whom chemotherapy or radiation has failed [5].

Pericardial tamponade

Pericardial tamponade occurs when pericardial fluid accumulates causing hemodynamic instability. In cancer patients, two mechanisms may lead to accumulation of excess fluid in the pericardial space: obstruction of lymphatic drainage or excess

fluid secretion from tumor nodules on pericardial surfaces. In almost half of cancer patients presenting with pericardial effusion, non-malignant causes, such as drug or radiation-induced pericarditis, hypothyroidism, uremia, infection or autoimmune disease, should also be considered. Two types of radiation-induced pericarditis have been well recognized: an acute, inflammatory and effusive pericarditis that occurs a few months after radiation has been given, and which usually resolves spontaneously, and a chronic, effusive pericarditis that may appear up to 20 years after radiation and is accompanied by a thickened pericardium and usually requires surgical removal [6].

Pericardial effusion is usually a late finding in patients already diagnosed with metastatic cancer. Two-thirds of patients are asymptomatic. In symptomatic patients, shortness of breath, chest pain, orthopnea and general weakness are the most common complaints. Physical examination may vary from normal to severe signs of hemodynamic collapse. Tachycardia, hypotension, jugular vein distention and edema may indicate diminished cardiac output. Two-dimensional echocardiography is the most useful test for diagnosing pericardial effusion and assessing its hemodynamic impact, that is, whether tamponade is present or not. Pericardial fluid should be examined cytologically to confirm neoplastic invasion.

Pericardiocentesis with the introduction of sclerosing agents like bleomycin or tetracycline, the creation of a pericardial window, complete pericardial stripping or systemic chemotherapy are effective treatments [7, 8]. Acute pericardial tamponade with life-threatening hemodynamic instability requires immediate drainage [9]. The other approaches are used to avoid a rapid relapse of pericardial effusion.

Spinal cord compression

Spinal cord compression is the first manifestation of cancer in ~10% of patients who present with this complication and will also occur during the disease course of 5–10% of all cancer patients. It should be considered a true oncological emergency. Delays in starting treatment may result in irreversible consequences, including paraplegia. In most cases spinal cord compression is caused by extradural metastases from tumors involving the spine. Bone metastases to thoracic, lumbar or cervical vertebrae may produce a cord injury when affecting the vertebral body or when the pedicle enlarges and compresses the underlying dura. Localized back pain and tenderness due to vertebral metastases are the most common and earliest symptom of spinal cord compression. It may be present even several months before compression is diagnosed or other neurological signs are present. Pain is due mainly to spinal involvement but after some time it may be caused by radicular traction due to cord compression and it has some special characteristics that should be recognized by the expert clinician. This pain may increase overnight, does not improve with commonly used analgesics and may get worse with recumbence or with maneuvers increasing pressure in the epidural space: such as coughing, sneezing or straining. What really differentiates this pain from disc disease is the fact that

cord compression pain gets worse when the patient is in the supine position.

Patients with cancer who develop back pain should be evaluated for spinal cord compression as soon as possible. Early diagnosis, before any muscle weakness occurs, is critical [10]. Eighty per cent of patients able to walk when a diagnosis is made will continue walking after treatment. However, only 10% of patients unable to walk at diagnosis will recover their ability to walk after therapy. An accurate history and physical examination are critical in diagnosing spinal cord compression. A thorough neurological examination may help in defining the area of the spine to be imaged. Motor, sensory and autonomic aspects should be carefully explored. Although some sensorial defects such as methameric hypoesthesia or autonomic abnormalities like urinary retention or constipation may be present, this indicates a late stage of damage and, most probably, irreversible paraplegia. Most patients with spinal cord compression have abnormalities on plain radiographs of the spine, such as bone erosion or pedicle loss, vertebral collapse or paraspinal soft tissue masses. However, magnetic resonance imaging (MRI) is the best method for assessing spinal cord compression. It defines the area of compression and it also helps in planning the radiation fields.

The aim of treatment of spinal cord compression is to relieve pain and to maintain or restore neurological function. If the suspicion is firm, dexamethasone should be given, although some controversy exists as to whether high doses (100 mg followed by 16 mg every 6 h) may have some advantage over lower doses (4 mg every 6 h). For most patients with spinal cord compression and a radiosensitive tumor, radiation therapy with dexamethasone is considered the standard treatment [11]. In some cases, surgical decompression plus other techniques to stabilize the spine may also help. Surgery may be indicated to obtain tissue for histological diagnosis when cord compression is the first manifestation of malignancy, in cases of radio-resistant tumors such as melanoma or clear-cell carcinoma, or if a fractured vertebra or a hemorrhage is the cause of cord compression. In some cases, when there is a single vertebra involved in patients without visceral metastases, a complete resection of the vertebral body may be indicated [12, 13].

Increased intracranial pressure

Increased intracranial pressure may be caused by brain metastases. Around a quarter of cancer patients will die with intracranial metastases. Lung, breast and melanoma are the most common tumors that metastasize to the brain. Clinical manifestations of brain metastasis are headache, nausea, vomiting, seizures, behavioral changes and sometimes focal neurological changes. This picture may not be different from intratumoral bleeding. Patients with melanoma, choriocarcinoma and clear-cell carcinoma of renal origin frequently present with bleeding. The tumor mass together with its surrounding edema may produce hydrocephalus and as the mass enlarges various herniation syndromes may occur depending on the location of the tumors within the cranium.

The patient with suspected brain herniation should be quickly assessed. After clinical assessment, the patient should have imaging studies of the brain. Although MRI is a better technique, the first study generally done is a CT scan. However, if the patient is unstable, CT may offer useful and more rapid information than MRI. If on clinical grounds, increased intracranial pressure is suspected, treatment should begin immediately, even before imaging documentation. Emergency treatments to prevent herniation are hyperventilation, mannitol and steroids. Mannitol is a hyperosmotic agent that is effective within minutes of its intravenous administration and may last for several hours. Steroids are administered to control vasogenic edema. Dexamethasone is given by a bolus intravenous injection of 16–40 mg, followed then by 40–100 mg per day. Its effect starts within hours and may last several days [14]. Once herniation has been controlled, a decision on the treatment of the brain metastases should be taken. If multiple nodules are seen, whole-brain irradiation is considered standard. 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 gynecological or urological tumors particularly cervical or prostatic carcinoma. Sometimes metastatic disease to the pelvis may produce urinary obstruction, leading to bilateral hydronephrosis and renal failure. A patient with flank pain with sudden anuria, sometimes alternating with polyuria and a progressive rise in serum creatinine should be suspected of having urinary obstruction. Renal ultrasound is the easiest way of detecting bilateral hydronephrosis. CT is often helpful in detecting the exact location of the obstruction, particularly if there is a retroperitoneal or pelvic mass.

Urinary obstruction associated with pain, infection or renal failure requires intervention. Ureteral stents may be placed with local anesthesia and may relieve the obstruction. If this is not possible, percutaneous nephrostomy is an alternative approach. After relief, polyuria may follow, increasing the risk of dehydration and electrolyte disturbances, particularly hypokalemia. Careful replacement of fluid and electrolytes is required.

Massive hemoptysis

Massive hemoptysis is defined as the expectoration of volumes ranging from one single episode of 100 ml to >600 ml of blood during 24–48 h. When respiratory difficulty occurs, hemoptysis should be treated urgently. Airway bleeding leading to life-threatening airway obstruction, aspiration, anemia or hypovolemic shock is also considered massive hemoptysis. In fact, fatal hemorrhage may present in one-third of patients with massive hemoptysis and the risk of death is directly associated with the amount of blood expectorated. The rate of hemoptysis, the amount of blood retained in the lungs

and the underlying pulmonary reserve are also well-recognized risk factors [15, 16].

Lung cancer accounts for a large proportion of patients having hemoptysis and up to 20% of cases of lung cancer will have hemoptysis at any time during its course. Endobronchial metastases from carcinoid tumors, breast, colon or kidney cancer, melanoma and sarcomas may also cause hemoptysis. Hemoptysis in cancer patients may also be caused by non-malignant conditions, such as fungal infections, or may be related to thrombocytopenia or other coagulation disorders. Thrombocytopenia or coagulation defects should be corrected to control hemoptysis.

The airway should be protected and intubation is recommended in patients with hemodynamic instability, severe dyspnea or hypoxia. They may require volume supplementation, oxygen, cough suppressants and correction of any coagulation disorder, if present. The site of bleeding must first be identified. The lesion should generally be treated with a surgical procedure, although neodymium–yttrium–garnet laser phototherapy has been used for palliative or curative treatment in patients with endobronchial tumors. Bronchial artery embolization may control brisk bleeding before a surgical procedure is performed, but is frequently associated with rebleeding. Radiotherapy may also inhibit hemoptysis by causing vascular thrombosis and necrosis of contributing vessels.

Acute airway obstruction

Acute airway obstruction involves the upper airways and may be caused by malignant or non-malignant conditions. This term refers to a blockage at the level of the main stem bronchi or above. It may result from intraluminal tumor growth or from extrinsic compression of the airway. Tumors that obstruct the upper airway by direct extension are primary tumors of the head and neck and lung. Non-malignant causes of airway obstruction are food or foreign body aspiration, airway edema or hemorrhage, tracheal stenosis and infections. Angioedema may also cause severe and life-threatening airway obstruction. Primary tumors of the lung are the most common cause of lower airway obstruction.

Dyspnea is frequently the only early symptom of airway obstruction. If dyspnea occurs on exercise, the airway diameter is decreased to 8 mm, but if dyspnea occurs at rest, the airway diameter is usually <5 mm and is related to the appearance of stridor. Stridor should be considered as a very unfavorable sign. For patients with upper airway obstruction, direct visualization via laryngoscopy or bronchoscopy should be performed, depending upon the location of the damage. In cases of lower airway obstruction, chest X-ray or CT scan may be diagnostic.

If the obstruction is proximal to the larynx, a tracheotomy may be life-saving. For more distal obstruction, particularly intrinsic lesions incompletely obstructing the airway, bronchoscopy with laser treatment, photodynamic therapy or stenting can produce immediate relief in some patients. External radiation or brachytherapy given together with steroids may also be useful in opening an obstructed airway. When extrinsic

compression is the main cause of obstruction, stent placement is the preferred method of palliation [17].

Metabolic emergencies

The most common metabolic emergencies in cancer patients are related to hypercalcemia, and inappropriate secretion of the antidiuretic hormone.

Hypercalcemia

Hypercalcemia is the most frequent paraneoplastic syndrome and a serious emergency leading to morbidity and mortality in cancer patients. Around 10% of advanced solid tumors, most often lung, breast, head and neck and renal cancer, as well as malignant lymphoma and myeloma may produce hypercalcemia. The main mechanisms by which cancer-related hypercalcemia may be produced are bone metastases, increased parathyroid hormone-related protein production and calcitriol secretion. But cancer patients may also develop hyperparathyroidism and other conditions that induce hypercalcemia in the general population of patients. In primary hyperparathyroidism, the intact parathyroid hormone (i-PTH) serum levels will be abnormally high.

Increased released of calcium from bone is the main factor contributing to hypercalcemia in cancer patients. Bone formation is suppressed and, at the same time, bone resorption is largely stimulated by the activation and proliferation of osteoclasts. In patients with malignancy-related hypercalcemia, i-PTH values will be very low. Bone metastases, which may cause hypercalcemia in some tumors with extensive bone involvement are common, notably in breast cancer, but in other similar situations, such as in prostate cancer, hypercalcemia is rarely seen. Bone resorption is not directly dependent on tumor cell invasion of bone, but is related to the production of several cytokines (tumor necrosis factor, lymphotoxin, endothelin, interleukin-1 and -6) that may stimulate osteoclast activity by mechanisms not always well defined, thereby inducing hypercalcemia.

PTH-related protein (PTH-rP) is a small peptide with eight of the first 13 amino acids homologous to PTH. Production of PTH-rP by tumor cells is the most common cause of hypercalcemia in cancer patients in the absence of bone metastases, particularly in those with squamous-cell carcinoma. It may also be present in breast, prostate or renal cancer or in patients with melanoma or neuroendocrine tumors. In this syndrome, serum calcitriol levels are not elevated.

Malignant lymphoma cells may produce a vitamin D derivative, known as calcitriol. This hormone can increase the gastrointestinal absorption of calcium, leading more frequently to hypercalciuria than to frank hypercalcemia. An elevated serum calcitriol level plus normal or slightly elevated serum phosphate and high urinary calcium, together with a suppressed serum i-PTH are commonly found in hypercalcemia associated with lymphoproliferative disorders.

The initial symptoms and signs of hypercalcemia, when serum calcium levels are >2.6 mmol/l, include fatigue,

malaise, anorexia, nausea, vomiting, confusion, bone pain, polydipsia, polyuria, constipation and weakness. If serum calcium rises above 3.5 mmol/l, neurological symptoms are more prevalent and patients may have confusion, sleepiness, lethargy and coma leading to death. Dehydration is a common finding of hypercalcemia and it is related to many factors. Among the most important are urine excretion of calcium leading to concentration defects in renal tubules, as well as vomiting and reduced fluid intake.

Before considering any therapy in patients with tumor-related hypercalcemia, there is a need to analyze whether therapy is indicated. Many times it is related to tumor progression, despite adequate therapy and in most neoplastic diseases, severe hypercalcemia is associated with a short survival time of several weeks to a few months. For this reason, intervention to reverse severe hypercalcemia should only be undertaken when the underlying malignant disease is likely to be controlled with appropriate therapy. In refractory patients or those with a very low possibility of getting any benefit from specific treatment, active therapy against hypercalcemia may not be appropriate. Depression of central nervous system function may occur and suffering may be reduced in a terminally ill patient.

Initial therapy of hypercalcemia should always include intravenous fluids and a biphosphonate. Dehydration is almost always present in patients with elevated calcium levels. Therefore, initial therapy should be directed to the reversal of dehydration by infusing a solution of normal saline at 100–300 ml/h. After 6–12 h of intensive hydration, serum calcium levels will fall by 20–40%. However, in patients with severe hypercalcemia, defined as more than 13 mg/dl, or presenting with neurological symptoms or renal failure secondary to high calcium levels, treatment with a biphosphonate should be started together with vigorous hydration. Biphosphonates, which are potent inhibitors of bone resorption, are very active and rapid in lowering serum calcium levels, with very few toxic effects. Zoledronate (4 mg) by intravenous infusion in half an hour, has been shown in a randomized trial to be more effective than pamidronate in the treatment of severe, acute hypercalcemia [18]. Treatment with corticoids, gallium nitrate or calcitonin is rarely used. However, in patients with lymphoma glucocorticoids may be useful.

Inappropriate secretion of antidiuretic hormone

The inappropriate secretion of the antidiuretic hormone (SIADH) should always be considered when a patient presents with hyponatremia. SIADH is due to the production of arginine vasopressin by the tumor cells. Hyponatremia is associated with plasma hyposmolarity and inappropriately high urinary osmolarity, together with a high level of excretion of urinary sodium without plasma volume depletion. Other causes of hyponatremia, such as renal failure, hypothyroidism or adrenal insufficiency, have to be excluded. Although SIADH may be caused by some drugs, such as antidepressants, angiotensin-converting enzyme inhibitors and anti-neoplastic agents such as cyclophosphamide, vincristin,

melphalan, cisplatin or vinorelbine, and even by some surgical procedures and benign lung diseases, the tumor most frequently associated with this syndrome is small-cell lung cancer. Hyponatremia confers a poor prognosis when associated with small-cell lung cancer.

Although most patients with SIADH are asymptomatic, the presence of clinical manifestations is directly related to the severity of hyponatremia. Early changes include anorexia, depression, irritability, lethargy, muscle cramps, weakness and behavioral changes. But when sodium plasma levels fall below 110 mEq/l, depressed deep tendon reflexes, pseudobulbar palsy, seizures and coma may appear.

If SIADH is caused by a tumor, optimal therapy is related to the treatment of the underlying malignancy. In the case of small-cell lung cancer, chemotherapy should be started as soon as possible to try to control the situation. If specific therapy is not available, or the tumor has developed resistance to chemotherapy, water restriction and the administration of demeclocycline should be considered.

Treatment-related emergencies

Cancer treatment may be responsible for some related problems, requiring urgent intervention. This is the case for tumor lysis syndrome, anaphylactic reactions related to chemotherapeutic agents and hemorrhagic cystitis.

Tumor lysis syndrome

Tumor lysis syndrome is caused by the destruction of a large number of actively proliferating tumor cells as a consequence of cancer chemotherapy. It is a well-recognized clinical entity in which a combination of several electrolyte disorders such as hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and lactic acidosis, can lead to acute renal failure. This syndrome was first described in patients with Burkitt's lymphoma who died a few days after receiving treatment with chemotherapy. The main cause of death in these patients was arrhythmia related to electrolyte disturbances, particularly hyperkalemia and renal failure.

For this reason a careful assessment of any fluid and electrolyte disturbance and prompt correction is essential to avoid serious complications of this syndrome. Tumor lysis syndrome is often observed in patients with very chemosensitive tumors and may appear after initiating chemotherapy in acute leukemia, Burkitt's and diffuse aggressive lymphoma. This syndrome is also rarely seen in patients with chronic lymphocytic leukemia, low-grade lymphomas or solid tumors. It has rarely been reported after treatment in ovarian, breast or small-cell lung cancer. In some patients with chronic lymphocytic leukemia receiving treatment with fludarabine or 2-chlorodeoxyadenosine, this syndrome may happen even 2 weeks after treatment.

Factors that contribute to the development of tumor lysis syndrome are the type of malignancy, how responsive the malignancy is to chemotherapy, the rapidity of cell turnover

and tumor burden. Pre-existing renal failure may also contribute. Pre-existing hyperuricemia and high pretreatment serum lactate dehydrogenase concentrations, especially if they are higher than 1500 U/l, tend to correlate with tumor burden in many hematological neoplasms and solid tumors. This is particularly true in aggressive lymphomas and may predict the occurrence of renal failure after chemotherapy.

Symptoms are non-specific and include nausea, vomiting, fatigue, weakness, myalgia and dark urine. Symptoms may progress in line with metabolic and electrolyte alterations and include muscle weakness, neuromuscular irritability, arrhythmias, seizures and sudden death. The metabolic abnormalities associated with tumor lysis syndrome are caused by the massive release of the cell contents and degradation products of destroyed neoplastic cells into the bloodstream. Effective chemotherapy induces the destruction of malignant cells and leads to increased serum uric acid levels from the turnover of nucleic acids. In the presence of an acid medium in the kidneys, uric acid precipitates, inducing renal failure. Moreover, lactic acidosis and dehydration may contribute to the precipitation of uric acid in renal tubules. As evidence for uric acid nephropathy, uric acid crystals are found in the urine.

Hyperphosphatemia is also caused by the release of intracellular phosphate by tumor cell lysis and produces a depression of serum calcium. Hypocalcemia leads to severe neuromuscular irritability and tetany. Calcium phosphate deposits in the kidneys and in this manner hyperphosphatemia may also contribute to renal failure. Potassium, as the main intracellular cation, is also liberated into the bloodstream when tumor cells are destroyed. Hyperkalemia adds a significant danger to tumor lysis syndrome, especially in the presence of renal failure, as life-threatening ventricular arrhythmias may occur.

The diagnosis of tumor lysis syndrome requires a high level of suspicion, because early symptoms are non-specific. Recognition of risks and prevention are key steps in its management. Routine uric acid and electrolyte measurements are indicated in patients with high tumor burden, particularly if they have acute leukemia or aggressive lymphomas, in which a rapid response to chemotherapy may be predicted. Prevention should include hydration with normal saline up to 3 l/m²/day, to induce a urinary output of at least 100 ml/h with or without diuretics. Oral sodium bicarbonate should be given to avoid acidic urine, if no contraindications, such as severe hypertension, are present. The xanthine oxidase inhibitor allopurinol (300 mg/day) is also recommended to prevent hyperuricemia. Rasburicase, a recently developed recombinant form of urate oxidase, is a very active drug in preventing the development of hyperuricemia in patients at high risk of having tumor lysis syndrome. It acts by catalyzing the enzymic oxidation of uric acid to allantoin, a metabolite that is five to ten times more soluble in urine than uric acid. This compound has been shown to be superior to allopurinol in the control of hyperuricemia in a randomized trial of pediatric patients with acute leukemia and lymphoma. In a series of 100 adult patients with aggressive lymphoma and a high risk of developing tumor lysis

syndrome, rasburicase was given at a dose of 0.20 mg/kg/day for 3–7 days, starting either the day before or the same day as chemotherapy. Most patients (95%) responded as soon as 4 h after the first dose of rasburicase and no patient had renal failure or major electrolyte disturbance during therapy [19].

When the patient presents with severe tumor lysis syndrome, an intensive care approach with continuous monitoring of hemodynamic, electrolyte and electrocardiographic changes should be initiated. Adequate hydration, rasburicase and sodium bicarbonate if acidosis is present, together with calcium and potassium correction and dialysis if renal failure occurs, are the key issues of management. Dialysis is recommended in the case of severe hyperphosphatemia (>10.2 mg/dl) with symptomatic hypocalcemia, persistent hyperkalemia, azotemia, hyperuricemia, oligo/anuria or refractory acidosis or volume overload.

Anaphylactic reactions related to chemotherapeutic agents

Anaphylactic reactions related to chemotherapeutic agents may sometimes create medical emergencies. Angioedema and urticaria are the most common manifestations of anaphylaxis and make up >90% of allergic reactions to drugs. Other frequent manifestations are abdominal pain, chest tightness, upper airway obstruction, bronchospasm and hypotension. Laryngeal edema followed by hypotension is the most frequent cause of death related to allergic reactions. The three main issues in treating anaphylactic reactions are early recognition, airway maintenance and hemodynamic support. The acute management of anaphylaxis in adults should start by removing the drug considered to be responsible. Immediate assessment of the airway and administration of epinephrine subcutaneously, depending on the severity, should follow. Intravenous fluids should be given, particularly in case of hypotension. Glucocorticoids and antihistamines may also be added. If resistant hypotension develops intensive care unit management will be required.

Many anticancer drugs may produce anaphylactic reactions. The most common are L-asparaginase, taxanes and platinum derivatives. L-asparaginase is an enzyme of bacterial origin used in the treatment of acute lymphoblastic leukemia. Anaphylactic reactions may occur in 10% of patients treated with this drug. Risk factors for adverse reactions are high dosage, previous exposure, intravenous administration and a personal history of allergy. Intramuscular administration is recommended because it is associated with a decreased incidence of anaphylactic reactions. Although reactions to L-asparaginase usually take place after the second week of treatment, they should be anticipated from the beginning of therapy.

When initially developed, taxanes (paclitaxel and docetaxel) induced major hypersensitivity reactions in almost 30% of treated patients and some minor reactions in around 40%. The major reactions were of anaphylactoid type. Reactions occurred more often when fast infusion rates and short infusion schedules were used. Most reactions happen in the first or

more unusually after the second course of treatment. Reactions start within 2–10 min of intravenous infusion and most of them resolve after 15–20 min of stopping the infusion. Most cases present with dyspnea, urticaria, angioedema, hypotension or bronchospasm. The most useful ways of preventing reactions are prolongation of infusion or the use of prophylactic medication. For instance, when paclitaxel was administered in a 96 h continuous infusion, no major reactions were observed, even without prophylactic measures. However, when 1-, 3- or 24-h infusions are to be used, prophylaxis with corticoids and antihistamines is indicated [20].

In recent years it has become increasingly appreciated that with prolonged use of carboplatin, there is a substantial risk of the development of hypersensitivity reactions. Although those reactions can be mild in severity, with limited skin rashes, more serious signs and symptoms, such as hypotension, intense anxiety, dyspnea or cardiovascular collapse may develop. Carboplatin reactions follow a heterogeneous course. Some events develop within minutes of initiation of the infusion, but others are first noted near the completion of intravenous administration or several hours to days after the drug has been delivered.

If the allergic episode is minor, carboplatin is generally continued. If the reaction develops during the infusion or while the patient is still in the clinic, intravenous diphenhydramine 50 mg is administered. If the reaction occurs after the patient has returned home, she should be advised to take diphenhydramine orally (25–50 mg every 4–6 h) if symptoms persist. With future courses, the patient is advised to take this medication at the onset of any signs or symptoms suggestive of a hypersensitivity reaction. If the reaction is of greater severity, the decision to continue or discontinue treatment with carboplatin must balance the potential for serious toxicity against the clinical benefit of the drug in the individual patient [21, 22].

Hemorrhagic cystitis

Hemorrhagic cystitis can be observed in patients receiving high doses or prolonged treatment with ifosfamide or cyclophosphamide. Both alkylating agents are metabolized to acrolein, a chemical agent with strong irritant properties that is excreted in the urine. Common symptoms may include dysuria, burning, frequency, gross hematuria, urgency and incontinence. The best way of managing this problem is prevention. Oral or intravenous hydration increases urinary flow and reduces 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 and it is very effective in preventing hemorrhagic cystitis.

However, when hemorrhagic cystitis occurs, a conservative approach with intensive hydration to stimulate urinary flow may be sufficient. If this therapy fails, irrigation with a formalin solution for 10 min may stop bleeding. In extreme cases when bleeding does not stop, surgical ligation or embolization of hypogastric arteries by interventional radiology

methods may be indicated. Sometimes, cystectomy may be required. External pelvic radiation plus brachytherapy to treat cervical cancer may cause hemorrhagic cystitis, particularly if radiation is given after removal of the uterus. This event may occur several years after radiation. Careful planning of radiation is the best way of avoiding this problem.

References

1. Yeung SJ, Escalante CP, et al. Oncologic emergencies. In Kufe DW (ed.): *Holland-Frei Cancer Medicine*, 6th edition. Hamilton, Canada: BC Decker 2003; 2659–2680.
2. Qanadi SD, Mesurole B, Sissakian JF et al. Implanted central venous catheter-related acute superior vena cava syndrome: management by metallic stent and endovascular repositioning of the catheter tip. *Eur Radiol* 2000; 10: 1329–1331.
3. Porte H, Metois D, Finzi L et al. Superior vena cava syndrome of malignant origin. Which surgical procedure for which diagnosis? *Eur J Cardiothorac Surg* 2000; 17: 384–388.
4. Wurschmidt F, Bunemann H, Heilman HP. Small cell lung cancer with or without superior vena cava syndrome: a multivariate analysis of prognostic factors in 408 cases. *Int J Radiat Oncol Biol Phys* 1995; 33: 77–82.
5. Yim CD, Sane SS, Bjarnason H. Superior vena cava stenting. *Radiol Clin North Am* 2000; 38: 409–424.
6. Maisch B, Ristic AD. Practical aspects of the management of pericardial disease. *Heart* 2003; 89: 1096–1103.
7. Liu G, Crump M, Gross PE et al. Prospective comparison of the sclerosing agents doxycycline and bleomycin for the primary management of malignant pericardial effusion and cardiac tamponade. *J Clin Oncol* 1996; 14: 3141–3147.
8. Colleoni M, Martinelli G, Beretta F et al. Intracavitary chemotherapy with thiotepa in malignant pericardial effusions: an active and well-tolerated regimen. *J Clin Oncol* 1998; 16: 2371–2376.
9. Allen KB, Faber LP, Warren WH et al. Pericardial effusion: sub-xiphoid pericardiostomy versus percutaneous catheter drainage. *Ann Thorac Surg* 1999; 67: 437–440.
10. Abrahm JL. Management of pain and spinal cord compression in patients with advanced cancer. *Ann Intern Med* 1999; 131: 37–46.
11. Loblaw DA, Laperriere NJ. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. *J Clin Oncol* 1998; 16: 1613–1624.
12. Klimo P, Schmidt MH. Surgical management of spinal metastases. *Oncologist* 2004; 9: 188–196.
13. Patchell R, Tibbs PA, Regine WF et al. A randomized trial of direct decompressive surgical resection in the treatment of spinal cord compression caused by metastasis. *J Clin Oncol* 2003; 21: 237s.
14. Weissman DE. Glucocorticoid treatment for brain metastases and epidural spinal cord compression: a review. *J Clin Oncol* 1988; 6: 543–551.
15. Jean-Baptiste E. Clinical assessment and management of massive hemoptysis. *Crit Care Med* 2001; 28: 1642–1647.
16. Jougon J, Ballester M, Delcambre F et al. Massive hemoptysis: what place for medical and surgical treatment? *Eur J Cardiothorac Surg* 2002; 2: 345–351.
17. Lee P, Kupeli E, Metha AC. Therapeutic bronchoscopy in lung cancer. Laser therapy, stents and photodynamic therapy. *Clin Chest Med* 2002; 23: 241–256.
18. Major P, Lortholary A, Hon J et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001; 19: 558–567.

19. Coiffier B, Mounier N, Bologna S et al. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: Results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. *J Clin Oncol* 2003; 21: 4402–4406.
20. Markman M, Kennedy A, Webster K et al. Paclitaxel-associated hypersensitivity reactions: experience of the Gynecologic Oncology Program of the Cleveland Clinic Cancer Center. *J Clin Oncol* 2000; 18: 102–105.
21. Markman M, Kennedy A, Webster K et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 1999; 17: 1141–1145.
22. Markman M, Zanotti K, Peterson G et al. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 2003; 21: 4611–4614.