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Common complications and emergencies associated with cancer and its therapy

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■ **BACKGROUND** As the incidence of cancer rises and as physicians treat it more aggressively, more patients will experience complications of cancer or of its therapy.

■ **OBJECTIVE** To review the pathogenesis, diagnosis, and treatment of the superior vena cava syndrome, malignant pericardial effusions, the syndrome of inappropriate antidiuretic hormone secretion, hypercalcemia, the tumor lysis syndrome, seizures, spinal cord compression, obstructive uropathy, infections, febrile neutropenia, bleeding, thrombocytopenia, and coagulopathies in patients with cancer.

■ **SUMMARY** In general, the best treatment for most of the complications of cancer is to successfully treat the cancer itself; if this is not feasible, palliative measures should be taken. The complications of treatment are well known and should be treated promptly when they arise if they cannot be prevented.

■ **CONCLUSIONS** Although treating the complications associated with cancer cannot always prolong the patient's life, it frequently can improve the quality of life remaining. Therefore, physicians who care for patients with cancer should anticipate these complications and treat them promptly when they occur.

■ **INDEX TERMS:** NEOPLASMS; SUPERIOR VENA CAVA SYNDROME; PERICARDIAL EFFUSION; INAPPROPRIATE ADH SYNDROME; HYPERCALCEMIA; TUMOR LYSIS SYNDROME; SEIZURES; SPINAL CORD COMPRESSION; URETERAL OBSTRUCTION; INFECTION; NEUTROPENIA; FEVER; BLOOD COAGULATION DISORDERS
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THE INCIDENCE of cancer in the United States is increasing, and we are treating many forms of cancer more intensively than in the past. Therefore, more patients are at risk for oncologic emergencies and for the complications of cancer and its therapy. All physicians who care for patients with cancer should recognize these clinical situations when they develop, as appropriate medical management can improve both quality of life and survival for the affected patients.

SUPERIOR VENA CAVA SYNDROME

Symptoms, pathogenesis

Clinical features that characterize the superior vena cava (SVC) syndrome include dyspnea, cervicofacial edema, severe fatigue (due to decreased blood return to the heart), headache, altered mental status, and decreased vision. On physical examination, patients may have dilated veins over the thorax, neck, and face, upper-extremity edema, and Horner's syndrome.

SVC syndrome usually results from extrinsic compression of the

SVC and the veins it drains by a mediastinal mass, which is generally malignant and may be either a primary cancer or a metastatic lesion. The SVC is particularly vulnerable to obstruction because of its location, being surrounded by the mediastinum, sternum, right mainstem bronchus, and lymph nodes. A tumor of the lung or lymph nodes in this region can compress the thin-walled SVC and obstruct blood flow to the heart. Collateral circulation may or may not be a prominent feature of the process, depending on the rate at which the obstruction develops.

Thrombosis of the SVC has been noted at autopsy in as many as half of patients with SVC syndrome. If a patient's condition does not rapidly improve following the institution of antineoplastic treatment, a large clot may be the cause.

Although malignant diseases currently cause more than 95% of cases of SVC syndrome, as recently as 30 years ago tuberculosis and syphilis caused 40%. Thus, one should not assume that the SVC syndrome is always caused by malignant disease. In addition to tuberculosis and syphilis, other rare, benign causes include fibrosing mediastinitis, goiter, and aortic aneurysms.

Importantly, with the increasing use of semipermanent indwelling central venous catheters to provide venous access (eg, Hickman and Broviac catheters, subcutaneous portal devices), the incidence of nonmalignant causes of SVC syndrome has increased, and catheter-associated caval thrombosis is now a frequent cause of SVC syndrome.

Carcinoma of the lung causes 80% of cases of SVC syndrome, and lymphomas cause 15%. Approximately half of cases due to lung cancer are associated with small-cell lung cancer, principally because this cancer usually involves the central or perihilar areas of the lung.

Diagnosis of SVC syndrome

One generally suspects SVC syndrome on the basis of clinical signs and symptoms. The chest radiograph almost always reveals a mass, usually in the mediastinum and most often on the right side. Hilar adenopathy occurs in 50% of patients, and pleural effusions are observed in 25%. Additional diagnostic evaluation is generally not necessary. Venograms, although able to demonstrate the precise location of the obstruction, are relatively contraindicated due to the high venous pressure and the risk of excessive bleeding.

Management approaches

Considerable controversy exists as to how rapidly to initiate treatment of cancer-associated SVC syndrome. Until recently, this condition was considered a medical emergency, and treatment was initiated as soon as the clinical syndrome was recognized. Because SVC syndrome may be part of the presenting signs and symptoms of lymphoma or lung cancer, such patients may not have a histologic diagnosis of cancer when therapy is considered.

Biopsy in the upper chest area poses some risk when SVC syndrome is present because the central venous pressure is considerably elevated. One should initially attempt the least invasive procedure available to document the presence of cancer. Such procedures include cytologic study of sputum and bronchoscopy with washings and limited biopsies. One of these relatively noninvasive procedures can provide a diagnosis in approximately 60% of patients. If more tissue is required, a biopsy of the more superficial lymph nodes (where bleeding can be more easily controlled) should be performed first, if these nodes are suspected to be abnormal. Occasionally, mediastinoscopy or thoracotomy is required to confirm the presence of malignant disease.

In a patient with severe respiratory compromise or central nervous system dysfunction believed to be due to SVC syndrome, treatment may be initiated first, and a histologic diagnosis can be sought later when the patient's condition has stabilized.

Treatment of SVC syndrome focuses on the underlying cancer; radiation therapy is employed in most circumstances unless the tumor is known to be very sensitive to chemotherapy (eg, small-cell lung cancer). The total dose of radiation will depend on the tumor being treated; lymphomas are much more sensitive to radiation than lung cancer is. Seventy-five percent of patients will note symptomatic improvement within 3 to 4 days after the initiation of treatment, and 90% experience major relief by the end of the first week.

In the 10% of patients whose symptoms do not improve within the first week of therapy, one should suspect a clot and consider initiating anticoagulants or fibrinolytic agents. However, since the SVC syndrome responds to antineoplastic therapy in most patients, and a significant risk of bleeding exists in patients with a friable tumor mass under increased venous pressure, anticoagulants should not be employed routinely in all patients initially presenting with this disease process.

Diuretics may temporarily relieve symptoms of severe respiratory compromise. Steroids may be helpful in patients with lymphomas but are of limited usefulness in lung cancer.

MALIGNANT PERICARDIAL EFFUSIONS

Pericardial effusions may occur in a number of malignant diseases (eg, cancer of the breast or lung, melanoma, leukemia) through hematogenous spread or as a result of direct extension from an adjacent structure (eg, lung, lymph nodes). Patients may present with the sudden onset of dyspnea, orthopnea, cyanosis, and venous distension, although a malignant pericardial effusion can develop gradually and cause few symptoms. Other signs and symptoms of pericardial involvement include chest pain, cough, and hepatic engorgement from venous congestion.

In a patient with a known or suspected malignant disease, the differential diagnosis of a pericardial effusion includes bacterial or viral infection (including tuberculosis), trauma, uremia, collagen vascular disease, and radiation-induced injury. A pericardiocentesis should be performed in situations where the diagnosis is in doubt, particularly in an individual without previous documentation of metastatic disease. The fluid should be sent for cytologic analysis, culture, and staining for acid-fast organisms.

Radiation-induced pericarditis is often difficult to distinguish from pericardial involvement with cancer. A positive cytologic study helps establish the diagnosis, but a negative result does not rule out the presence of cancer. The presence of progressive disease in the lung is useful supplementary information, and a detailed history of the radiation exposure may allow an assessment of whether radiation injury is likely the cause of the patient's symptoms.

Cardiac tamponade

When the amount of fluid in the pericardium is sufficient to cause a decrease in the volume of blood reaching the ventricles, cardiac tamponade results. A decrease in cardiac output leads to tachycardia and peripheral vasoconstriction. A characteristic feature of cardiac tamponade is a fall in systolic pressure of more than 10 mm Hg with respiration (pulsus paradoxus).

The chest radiograph usually reveals cardiomegaly, and the heart contour frequently appears globular. Nonspecific changes on the electrocardiogram are the rule, although electrical alternans (al-

teration of both the P waves and QRS complexes) is often considered pathognomonic of cardiac tamponade. The echocardiogram is probably the most useful test for determining the presence and severity of both pericardial effusion and cardiac tamponade.

In a patient with severe cardiac compromise, immediate pericardiocentesis with removal of as little as 50 to 100 mL may be lifesaving. Usually, the pericardial fluid will rapidly return unless one employs other measures to prevent reaccumulation such as instillation of radioactive compounds, talc, antineoplastic agents, quinacrine, and tetracycline.

Although a "window" can be surgically created in the pericardium to permit the fluid to exit, scarring in the region frequently prevents necessary drainage. More aggressive surgery, including pericardiectomy, can rarely be recommended for most patients with advanced malignant diseases.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) results from an abnormal production of arginine vasopressin due to secretion from either the normal posterior pituitary gland or from the cancer itself. Hyponatremia, which can be severe, is the hallmark of SIADH and results both from loss of sodium in the urine and from renal water retention.

Malignant diseases are the most common cause of SIADH, although a number of other causes should be considered when a patient presents with this condition. These include pulmonary disorders such as tuberculosis and pneumonia and central nervous system disorders caused by trauma, infection, and tumors. As many as 10% of patients with small-cell lung cancer acquire SIADH during the course of their illness.

The signs and symptoms of SIADH result from the low serum sodium concentration and the corresponding hypo-osmolar state. Patients initially note fatigue, emesis, loss of appetite, and muscle aches. When the serum sodium concentration falls below 100 mEq/L, patients may have seizures or altered mentation, enter a coma, or die. Both the serum sodium concentration and its rate of fall influence the severity of symptoms.

One must consider a number of other possible causes of a low serum sodium concentration, including dysfunction of the heart, liver, thyroid, kid-

neys, or adrenal glands, severe emesis or diarrhea leading to excessive loss of sodium that cannot be compensated for by renal retention, and dilutional hyponatremia due to excessive water intake without adequate sodium intake. Of note, several chemotherapeutic agents, including cyclophosphamide and vincristine, commonly employed in small-cell lung cancer, can produce a clinical picture closely resembling malignancy-associated SIADH.

Therapeutic focus in cancer-related SIADH

Therapy for SIADH due to cancer should focus on treating the underlying malignant disease. Individuals with SIADH in association with small-cell lung cancer can experience rapid resolution of their electrolyte abnormalities following the initiation of chemotherapy. In patients with sodium levels below 128 mEq/L who have only mild symptoms (eg, fatigue, anorexia), moderate restriction of fluid intake (approximately 500 mL/day) may result in significant improvement.

When more severe symptoms are present, including seizures or significant changes in mental status, treatment should include infusion of either normal saline or 3% hypertonic saline to raise the serum sodium level. The serum sodium level should not be permitted to increase more rapidly than 1 mEq/L/hour, as more rapid rises can lead to central pontine myelinolysis.

In patients who do not respond to chemotherapy, demeclocycline can help. This agent causes dose-dependent, reversible, nephrogenic diabetes insipidus that counteracts the influence of vasopressin on the kidney. The dosage is 200 mg three times a day or 300 mg twice a day. Caution is advised in using this agent, since high doses are nephrotoxic.

HYPERCALCEMIA

Hypercalcemia is a common complication of malignant disease. As many as 10% of all patients with metastatic cancer experience this condition at some point during the course of their illness, and 20% of patients with cancer of the breast or lung do.

Pathogenesis

A number of documented or hypothesized pathogenic processes may be responsible. However, all mechanisms ultimately result in an increase in bone resorption. The direct infiltration of tumors into

bone and the secretion of humoral factors leading to an increase in calcium egress from bone are the two most important mechanisms of hypercalcemia in this patient population.

Clinical recognition

The severity of signs and symptoms of hypercalcemia is greatly influenced by the serum calcium concentration and its rate of increase, the presence of other metabolic abnormalities, and the extent of the patient's underlying debility from cancer. Calcium's effect on the concentrating function of the renal tubules commonly causes polydipsia and polyuria. Neurological symptoms can range from mild lethargy to confusion, stupor, or frank psychosis. Also observed are emesis, anorexia, obstipation, ileus, and abdominal pain.

Therapeutic strategies

Vigorous saline hydration is the mainstay of the initial treatment of hypercalcemia. This decreases proximal tubular reabsorption of calcium and increases calcium excretion. Individuals with severe hypercalcemia should receive a minimum of 5 to 7 L of saline over the first 24 hours. Furosemide is frequently added to the regimen to increase urinary calcium secretion by blocking reabsorption in the ascending loop of Henle. However, furosemide should not be given until any calcium-induced dehydration has been corrected by saline infusion, because the symptoms of hypercalcemia may worsen with any additional dehydration.

Although saline diuresis lowers the serum calcium concentration in most patients with hypercalcemia, the condition usually recurs fairly rapidly once the infusion is discontinued. Thus, agents that can block bone resorption are generally added to the regimen. The optimal drug for this purpose is not yet known, but a number of agents can control malignancy-associated hypercalcemia, at least temporarily. The most widely used drugs include the diphosphonates, gallium nitrate, calcitonin, and mithramycin.

Glucocorticoids can be helpful in hypercalcemia associated with myeloma, lymphoma, or breast cancer, but not with other cancers. Salmon calcitonin rapidly reduces serum calcium levels, but its effect is generally very short-lived, which seriously limits its usefulness.

Effective antineoplastic therapy is the most successful method to maintain normal serum calcium

levels. If such treatment exists for a given tumor, it should be instituted as soon as possible.

Hormonal therapy in breast cancer patients

Women with breast cancer may experience a worsening of existing hypercalcemia when hormonal therapy is started. This does not signify progression of the cancer, and continued treatment generally leads to an antitumor response. However, patients with breast cancer and hypercalcemia who are receiving hormonal therapy must be observed closely.

TUMOR LYSIS SYNDROME

One of the more dramatic events in clinical medicine, the tumor lysis syndrome most often occurs in patients with highly responsive malignant diseases when large tumor masses are present at the time of initiation of chemotherapy. However, the syndrome can also develop spontaneously in individuals with bulky tumors.

In this syndrome, the rapid killing and subsequent lysis of tumor cells overcome the kidney's ability to remove the intracellular material released. Lymphomas (particularly Burkitt's type) and leukemias are the tumors most frequently associated with the tumor lysis syndrome, although it has been noted in small-cell lung cancer and metastatic breast cancer.

Characteristic findings include hyperkalemia, hyperuricemia, and hyperphosphatemia with hypocalcemia. These abnormalities can lead to renal failure, cardiac arrhythmias, and death. A fatal outcome is particularly tragic, as the tumor lysis syndrome is usually the direct result of a highly successful initial course of chemotherapy.

Prevention is preferable to treatment of the established process. Patients at risk (ie, with bulky tumors that usually respond rapidly to systemic antineoplastic therapy) should undergo vigorous hydration before starting chemotherapy. Alkalinization of the urine will increase the solubility of uric acid and help prevent the syndrome. Similarly, allopurinol added to the regimen decreases the formation of uric acid. Patients at risk should be carefully monitored for approximately 1 to 2 days after the start of treatment. Frequent measurements of serum electrolytes (at least twice a day) will enable one to detect and correct metabolic abnormalities before they become life-threatening.

SEIZURES

In as many as 30% of patients with cancer metastatic to the brain, a seizure is the first manifestation. The development of seizures in this clinical setting is a cause for great concern. However, not all seizures observed in individuals with cancer result from metastatic disease. For example, patients with metabolic abnormalities, including SIADH, may also experience seizures.

Initially self-limiting, seizures developing in this clinical setting will recur if the underlying abnormality is not treated appropriately. Anticonvulsant therapy should be rapidly initiated when an individual with a known or suspected metastatic or primary malignant lesion in the central nervous system experiences a seizure. Dexamethasone, used to reduce any brain swelling from the cancer, is usually initiated in addition to phenytoin.

When seizures develop, a computed tomographic scan or magnetic resonance image of the brain should be obtained on an urgent basis, unless the patient has a known primary tumor or metastatic lesion in the brain. If the structural lesions are demonstrated, local radiation therapy should be started as soon as possible to prevent additional seizures or further neurological deterioration. Although radiation therapy has little impact on survival in this setting, it can provide great short-term palliative benefit.

SPINAL CORD COMPRESSION

Without question one of the most devastating complications of cancer, spinal cord compression can quickly make a highly functional patient essentially bed-bound and totally dependent on those around him or her for all normal daily activities. Even if spinal cord compression does not greatly alter the duration of survival, it can dramatically worsen an individual's quality of life.

Spinal cord compression is common: as many as 5% of patients with metastatic cancer have evidence of epidural metastasis at some point during their disease. Several malignant diseases, including cancers of the lung, breast, and prostate, are particularly likely to metastasize to the vertebral bodies.

Pathogenesis and symptoms

Symptoms of spinal cord compression result when a tumor impinges on the limited space avail-

able to the cord within the spinal column. Sixty percent of epidural metastases occur in the thoracic spine, and the remaining cases are divided equally between the lumbar and cervical spine and sacrum. Of interest and importance in the differential diagnosis of back pain, approximately 10% of patients with documented spinal cord compression, mostly patients with lymphomas, have no evidence of vertebral-body involvement with tumor. The mechanism of compression in this setting is usually growth of a tumor in the paravertebral space through the intravertebral foramen.

More than 90% of patients with spinal cord compression have localized back pain as the presenting symptom. The pain often becomes radicular as the compression worsens, spreading down into the muscle groups and cutaneous regions supplied by the involved nerves. One cannot overemphasize the importance of detecting spinal cord compression when back pain is still the only symptom. Treatment initiated at this stage gives the patient an excellent chance of preserving ambulatory function (approximately 90%). However, once a serious neurological defect develops, fewer than 10% of individuals regain significant function, despite the initiation and completion of the same treatment program. Therefore, physicians caring for patients with malignant diseases must have a high index of suspicion that back pain may represent the initial sign of spinal cord compression.

Diagnostic aids

In a patient with cancer who has back pain, plain bone films can help in the differential diagnosis. In one retrospective analysis, 60% of cancer patients who presented with localized back pain and radiographic evidence of vertebral-body metastasis had myelographic evidence of spinal cord compression, as did fully 90% of the patients who had abnormal bone radiographs and symptoms of radiculopathy.

Although myelography has been the traditional "gold standard" for documenting spinal cord compression, in many centers magnetic resonance imaging has replaced the older, invasive study as the diagnostic procedure of choice. One difficulty with myelography is that when a lumbar myelogram demonstrates complete cord block, one must then obtain a cervical myelogram to demonstrate the upper level of the block. This is critical to define the upper limit of the radiation therapy portals.

Drug therapy

Of the many reported approaches to the management of suspected or documented acute spinal cord compression, all use corticosteroid therapy as the cornerstone of initial treatment. One reasonable approach calls for the administration of 100 mg of dexamethasone, followed by 4 mg every 6 hours. If subsequent evaluation fails to confirm the presence of cord block, the steroids can be tapered rapidly. While somewhat controversial, this high-dose steroid regimen has the major advantage of rapidly reducing any tumor-induced edema that may be contributing to spinal cord dysfunction and injury. Once the patient's condition has improved or at least stabilized and definitive treatment with radiation or surgery is initiated, the steroids can be tapered fairly rapidly.

Radiation therapy

The optimal method of treating spinal cord compression has never been defined in carefully conducted, randomized controlled trials. However, retrospective reviews have strongly suggested that for most patients local external-beam radiation produces results equivalent to those of surgery (laminectomy) and causes less morbidity. However, several circumstances would make immediate surgery the treatment of choice. These include patients who have previously received radiation therapy to the area of the block or whose neurologic status deteriorates during or immediately following radiation therapy; patients with tumors known to be radioresistant (eg, renal cell carcinoma); patients without a documented diagnosis of metastatic cancer; and patients with either an unstable spine or in whom the compression is documented on radiographic evaluation to be due to bone in the epidural space.

OBSTRUCTIVE UROPATHY

The differential diagnosis of obstructive uropathy in a patient with cancer includes bilateral ureteral obstruction (or unilateral obstruction in a patient with only one functioning kidney) and obstruction of the bladder outlet. Cancers of the pelvic organs (ie, cervix, prostate, ovary, colon, uterus) are the malignant diseases most commonly associated with this syndrome. Obstruction may also result from extrinsic compression of the ureters by enlarged retroperitoneal lymph nodes, radiation fibrosis, and hemorrhage.

Renal ultrasonography is the simplest and least costly method to document obstructive uropathy. The size of the kidney, the extent of hydronephrosis, and the amount of residual renal cortex are extremely helpful in determining the potential for restoration of renal function. Computed tomography or retrograde pyelography may be required to determine the actual site of obstruction, which is often not well defined on renal ultrasonography. A renal nuclear scan provides limited information in this clinical setting, but may be useful in defining the remaining function of an obstructed kidney.

Immediate relief of the obstruction is appropriate if patients have symptoms due to renal obstruction (eg, pain) or if there is infection proximal to the obstruction. It is important to relieve obstruction to preserve and improve renal function, even if the patient has minimal or no symptoms, as kidneys that have been completely obstructed for even 30 to 60 days can regain function when the obstruction is relieved. Therefore, one should not ignore an asymptomatic hydronephrotic kidney simply because the obstruction is assumed to be chronic.

A retrograde ureteral stent can successfully relieve obstruction in approximately 50% of individuals with obstructive uropathy caused by cancer. The complications associated with stent placement include infection, migration of the stent into the bladder, and obstruction. Stents can remain in place for considerable periods of time, although most urologists suggest the catheters be changed every 2 to 6 months. The stent can be removed if antineoplastic therapy (eg, local radiation) subsequently relieves the obstruction.

INFECTIONS

Infections are extremely common in patients with cancer. Infections can result either from the neoplasm itself or from its treatment. Individuals with certain malignant diseases, particularly the lymphomas and leukemias, have an impaired immune status and are considerably more susceptible to a number of common and unusual bacterial, fungal, and viral infections. Patients with the more common solid tumors may acquire an infection proximal to an obstructive lesion (eg, post-obstructive pneumonia), or growth of a tumor may lead to breakdown of normal tissue barriers responsible for preventing infection (eg, ulceration of the skin by cutaneous metastatic lesions).

TABLE
EVALUATION AND THERAPY OF NEUTROPENIC FEVER IN A PATIENT RECEIVING CHEMOTHERAPY

Fever (temperature > 38°C) and granulocytes < $1.0 \times 10^9/L$
↓
Obtain specimens of blood, sputum, urine, and any suspicious lesions for culture
↓
Initiate empiric broad-spectrum antibiotics (include vancomycin if patient has an indwelling central venous catheter)
↓
Modify regimen when results of cultures are available
↓
Start amphotericin B empirically if fever does not resolve
↓
Reduce dose of chemotherapy in next course, or include granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor

NEUTROPENIC FEVER

Perhaps the most common oncologic emergency currently encountered is neutropenic fever. Before the introduction of broad-spectrum antibiotics, fever in severely granulocytopenic patients was associated with an extremely high mortality rate. For example, in a classic paper, Bodey et al observed that 70% of neutropenic patients with sepsis due to *Pseudomonas* died within 48 hours if appropriate antibiotics were not started soon after the fever was initially noted. It is now standard clinical practice to initiate broad-spectrum antibiotics immediately in a febrile neutropenic (granulocytes < $1.0 \times 10^9/L$) patient with cancer, even in the absence of any localizing signs of infection on physical examination or laboratory evaluation.

Patient education

As fever is an excellent warning sign of infection, severe neutropenia itself is not generally considered an indication for antibiotics. Individuals receiving cytotoxic chemotherapy that may suppress the bone marrow must always be warned that any fever experienced during the vulnerable time period after chemotherapy (generally 7 to 15 days) must be considered potentially life-threatening. Patients experiencing fever in this clinical setting must seek immediate medical attention. Certain medications, such as aspirin, acetaminophen, and steroids, may block an adequate febrile response. Thus, one should carefully follow up patients who take these

medications when neutropenia may result from the treatment program.

Caveats to antibiotic use

Appropriate cultures must be performed in a febrile neutropenic patient before the initiation of broad-spectrum antibiotics. The results of these cultures may lead to important modifications in the antibiotic regimen. An approach to managing neutropenic fever is shown in the *Table*.

Some controversy remains as to the optimal choice of antibiotics as empiric therapy in patients with fever and neutropenia. However, most authorities continue to recommend an aminoglycoside along with a broad-spectrum penicillin. This regimen will cover most important gram-positive and gram-negative organisms that may infect the patient in this clinical setting.

A particularly controversial point is whether vancomycin should be included in the initial antibiotic regimen. Many patients with cancer have indwelling central venous catheters for convenient venous access. As a result, the incidence of staphylococcal infections in this group has increased substantially. Unfortunately, many organisms are methicillin-resistant and susceptible only to vancomycin. Thus, one can reasonably consider adding this antibiotic to the empiric regimen for a febrile neutropenic patient who has an indwelling central venous catheter, pending the results of blood cultures. Vancomycin can be discontinued if cultures reveal no evidence of staphylococcal infection.

When to resort to amphotericin B

Unfortunately, many neutropenic patients remain febrile despite the institution of broad-spectrum antibiotics. In this setting, the standard clinical practice is to administer amphotericin B empirically to treat a suspected but undiagnosed fungal infection. Several autopsy series have confirmed a high incidence of local and disseminated fungal infections in individuals with cancer who died following a prolonged period of neutropenia. These infections are rarely diagnosed during life. Unfortunately, amphotericin B is associated with considerable side effects (fever, rigors, renal dysfunction, thrombocytopenia). However, the value of this agent in treating serious fungal infections is well documented, and until a less-toxic alternative with equal efficacy becomes available, the empiric use of amphotericin B in persistently febrile neutropenic

patients should be strongly considered.

Granulocyte transfusions

Granulocyte transfusions have an extremely limited role in the management of neutropenia, as studies have confirmed the extreme difficulty of delivering an adequate number of cells for a sufficiently long period of time to affect the clinical course. However, under rare circumstances, granulocyte transfusions may be lifesaving by allowing a patient with persistently positive blood cultures despite appropriate antibiotics to survive long enough to control the infection when his or her own granulocytes recover.

Colony-stimulating factors

The bone marrow colony-stimulating factors G-CSF (granulocyte colony-stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor) have far greater clinical utility than transfusions of white blood cells for both treating and preventing chemotherapy-induced neutropenia. While we are still gaining experience with these factors, it is possible to make several important generalizations about them. First, both agents (which are commercially available) appear to stimulate the bone marrow equally when used at the recommended doses. Second, both effectively shorten the duration of chemotherapy-induced neutropenia but cannot prevent it. Thus, patients receiving chemotherapeutic regimens that suppress the bone marrow will continue to be at risk, but for fewer days.

In general, the initial course of chemotherapy should probably be administered without a bone marrow colony-stimulating factor, as the severity of neutropenia caused by most chemotherapeutic regimens cannot be predicted in individual patients. If a patient experiences an unacceptable degree of marrow suppression with the first course of treatment (eg, nadir fever, granulocyte count < 1000/ μ L), subsequent courses may be delivered with the colony-stimulating factor. However, an alternative and far less costly approach would be to use lower doses of the antineoplastic agents.

BLEEDING, THROMBOCYTOPENIA, AND COAGULOPATHIES

Bleeding commonly occurs in patients with malignant diseases and may be due to a number of possible causes. In patients with structural lesions, bleeding may be the result of a tumor eroding into

normal structures (eg, hematuria from renal or bladder cancers, melena or guaiac-positive stools from gastrointestinal tumors). Patients with leukemias may present with bleeding due to severe thrombocytopenia or disseminated intravascular coagulation. The optimal treatment of these conditions must focus on the underlying malignant disease. However, transfusions with packed red cells or platelets are frequently required.

Thrombocytopenia is a common side effect of chemotherapeutic agents, particularly with multiple-drug chemotherapeutic regimens. Severe thrombocytopenia (platelets $< 10\,000/\mu\text{L}$) is uncommon except with the more intensive treatment programs (eg, therapy of acute leukemia, bone marrow transplantation). However, individual patients may experience unanticipated severe bone marrow suppression and thrombocytopenia leading to petechiae and, potentially, more serious bleeding, including bleeding from and into vital organs. Prophylactic platelet transfusions are generally not administered unless the platelet count falls to $10\,000$ to $20\,000/\mu\text{L}$. Patients with evidence of bleeding, including those with structural lesions due to the cancer, may need transfusion, even if the platelet count is higher. In addition, if a patient with severe thrombocytopenia requires an invasive procedure, it is appropriate to attempt to first increase the platelet count to at least $50\,000/\mu\text{L}$.

It had been hoped that the bone marrow colony-stimulating factors might prevent cancer- or treatment-induced thrombocytopenia. However, as predicted by their activity in experimental systems, neither G-CSF nor GM-CSF has any significant effects on the severity of chemotherapy-induced thrombocytopenia. Thus, as chemotherapeutic programs are intensified with the use of G-CSF and GM-CSF to prevent neutropenia, the severity of treatment-related thrombocytopenia will likely increase. However, we can reasonably hope and even anticipate that one or more of the newer colony-stimulating factors currently in clinical trials (eg, interleukin-3, interleukin-6, interleukin-11) or a combination of them may effectively stimulate platelet recovery after cytotoxic chemotherapy.

A number of investigators have examined the use of "peripheral precursor cells" after high doses of chemotherapy to accelerate platelet recovery. The precursor cells are harvested from the patient's own peripheral blood when the bone marrow is recovering from a previous course of high-dose chemother-

apy. The yield of these thrombopoietic cells can be enhanced by giving one of the colony-stimulating factors. The use of peripheral precursor cells, while quite appealing, has limited utility as it requires leukapheresis and is very expensive and labor-intensive. Thus, this strategy should only be used when there is convincing evidence that an intensive chemotherapeutic regimen is more effective than an alternative program that does not cause severe thrombocytopenia.

Subclinical and clinical abnormalities of coagulation commonly develop in patients with advanced malignant diseases, particularly cancers of the stomach, prostate, pancreas, lung, and breast. Several of these neoplasms can produce mucin, which presumably can enter the vascular compartment to initiate the coagulation cascade. Patients with acute leukemia, particularly acute promyelocytic leukemia, may actually present with a coagulopathy that can initially worsen when treatment is initiated as dying cells release procoagulant material. Patients with solid tumors may experience abnormal clot formation (eg, lower-extremity deep venous thrombosis, pulmonary emboli, arterial thrombosis) as an initial or later manifestation of their malignant disease.

As with other complications of cancer, the best treatment for cancer-associated coagulopathy is to successfully treat the underlying cancer. However, particular attention must be directed to the difficulties associated with such treatment (eg, risk of chemotherapy-induced thrombocytopenia). Experience with acute promyelocytic leukemia is an excellent example of this point. Before the recognition that disseminated intravascular coagulation worsened with the initiation of chemotherapy, acute promyelocytic leukemia was associated with a particularly poor prognosis. However, now that meticulous attention is given to the short-term bleeding risks in this patient population, the long-term survival for patients with acute promyelocytic leukemia equals or exceeds that of other subtypes of adult leukemia.

SUMMARY

If physicians are familiar with the common complications of cancer and of its treatment, they can attempt to prevent some of them and quickly treat the ones that cannot be prevented. Such an approach can often help patients with cancer live longer, and it certainly will help them feel better.

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