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CME CREDIT

What primary care physicians should know about the toxicity of cancer chemotherapy

Many patients fear the side effects of cancer chemotherapy; interventions can reduce toxicity

The considerable toxicity of cytotoxic drugs used to treat cancer is well known—in fact, one of the main concerns that patients with cancer express is that chemotherapy will reduce their quality of life.

Symptomatic side effects such as emesis, hair loss, stomatitis, and neurotoxicity do reduce quality of life. However, organ-system effects that can be measured but are usually not evident to the patient (eg, bone marrow suppression, nephrotoxicity, liver function abnormalities) are potentially more serious.

For more than a decade, many investigators have been working to reduce the toxicity of chemotherapy while maintaining or improving its efficacy. Their efforts have resulted in new antineoplastic drugs that cause fewer side effects, and in the use of other drugs such as antiemetics and bone marrow colony-stimulating factors that counteract some of the side effects of chemotherapy. This article summarizes the side effects of cancer chemotherapy and how we are trying to reduce their incidence and impact.

ACUTE EMESIS

Emesis is the most common and distressing toxic effect of many chemotherapeutic agents. Cisplatin is the agent most often cited as causing severe emesis, but other drugs can also cause nausea and vomiting (eg, doxorubicin, carboplatin, dacarbazine, cyclophosphamide).

Carboplatin, a modified form of cisplatin, causes less emesis, nephrotoxicity, and neurotoxicity than its parent compound. Controlled clinical trials demonstrated that carboplatin is as effective as cisplatin in a number of types of cancer. However, it is less effective than cisplatin in at least one disease (germ cell tumors) and in general should not be used as initial treatment in this type of cancer. This illustrates the importance of conducting clinical trials before changing treatment patterns in an attempt to reduce side effects.

Antiemetic drugs

It is far easier to prevent chemotherapy-induced emesis than to treat it once it develops. Thus, standard practice is to give antiemetic agents prophylactically. The specific drugs used depend on the emetogenic potential of the chemotherapy.

Serotonin subtype 3 receptor antagonists have proved highly effective in preventing emesis caused by cisplatin and other cytotoxic agents in multiple clinical trials. Two of these agents—ondansetron and granisetron—are commercially available in the United States in both intravenous and oral formulations. The dosage varies, depending on the emetogenic

potential of the cytotoxic drug or drugs used.

Corticosteroids have also proved highly effective as antiemetic agents and work synergistically with the serotonin receptor inhibitors. Thus, in most situations in which a serotonin receptor antagonist is used, a corticosteroid (most often dexamethasone) is also included.

Prochlorperazine is often used as an antiemetic agent in less-emetogenic chemotherapeutic regimens. It can be given parenterally, orally (5 to 10 mg every 4 to 6 hours), or rectally (25 mg every 4 to 6 hours).

Anxiolytic agents are often given on the night before or the morning of chemotherapy or both, because anxiety often contributes strongly to chemotherapy-associated emesis. Anxiolysis may be particularly important in the first course of therapy, before a patient knows how he or she will tolerate the drugs.

DELAYED EMESIS

It is far easier to prevent chemotherapy-induced emesis than to treat it

The agents listed above can significantly reduce acute emesis (developing within the first 24 hours after chemotherapy) in most patients, even with the most emetogenic chemotherapy regimens such as those containing cisplatin.

Unfortunately, delayed emesis (developing more than 24 hours afterward) remains a problem in many patients. Although strategies such as continuing to give a serotonin receptor antagonist for several days have been tried, evidence is limited that any of them is particularly effective in reducing delayed emesis.

Severe delayed emesis is relatively uncommon with most standard chemotherapeutic regimens. However, when it occurs, it can profoundly affect quality of life and persist for many days.

ALOPECIA

Some cytotoxic agents cause alopecia, as cells involved in hair differentiation and growth have a high mitotic rate and are easily damaged.

For example, paclitaxel, used in an increasing number of malignant diseases, can cause rapid hair loss within 7 to 21 days after the initial treatment course. Some patients lose all their hair, including axillary and pubic hair, eyebrows, and eyelashes. It is important to warn patients of this possibility and assure them that their hair will grow back after the treatment is stopped.

No known method prevents hair loss effectively. For example, applying ice to the scalp may delay hair loss for a cycle, but at the cost of considerable discomfort to the patient. In addition, reducing the delivery of cytotoxic agents to the scalp might reduce their effectiveness against circulating tumor cells in this region, at least in theory.

Patients should have the opportunity to obtain a wig before starting chemotherapy, so they can be prepared for the impact of hair loss on their appearance. While hair loss is a concern for both sexes, it is particularly distressing for women. Many, if not most, insurance companies now pay for wigs for these patients.

BONE MARROW SUPPRESSION

Myelosuppression is a potentially serious complication of cytotoxic chemotherapy, as it can predispose patients to infections, bleeding, and anemia. Because bone marrow cells (especially granulocyte precursors) divide rapidly, they are particularly susceptible to many cancer chemotherapeutic agents. With most chemotherapeutic regimens, blood counts reach a nadir 7 to 15 days after drug delivery.

Although myelosuppression is very common, it is usually only a laboratory phenomenon that is documented through a complete blood count, and most patients do not experience any clinically relevant symptoms from it. The most common symptom is fatigue, which is often a result of multiple factors, including chemotherapy-induced anemia or neutropenia.

Granulocyte suppression

Fever, reflecting a systemic infection, may develop with severe granulocyte suppression (ie, a neutrophil count $< 1.0 \times 10^9$/L).

Antibiotics. Any fever ($\geq 38^\circ$C) that occurs with severe granulocyte suppression is clinically important even without any localiz-

ing signs or symptoms of infection and requires the prompt institution of a broad-spectrum antibiotic or antibiotics—within several hours. If possible, blood and body fluid cultures should be obtained before starting antibiotics.

The antibiotics can be discontinued when the neutrophil count increases again to a least 1.0×10^9/L if there are no localizing signs of infection or positive results on blood or body fluid cultures. If the patient has a documented bacterial infection (eg, in the urinary or respiratory tract), antibiotics should be continued to complete a standard treatment course (eg, 2 weeks).

Colony-stimulating factors. Two available drugs—granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF)—have proved effective when used prophylactically in reducing the severity of chemotherapy-induced neutropenia. They are also used to accelerate the rate of marrow recovery in patients who have already developed severe myelosuppression.

These agents are not routinely used in most chemotherapy programs, as the anticipated severity of myelosuppression does not justify their use. In addition, they must be given parenterally and are quite expensive. However, they can be useful adjuncts if severe myelosuppression makes it impossible to deliver adequate doses of chemotherapeutic agents.

STOMATITIS, MUCOSITIS, DIARRHEA

Because the mucosal cells of the gastrointestinal tract, mouth, and throat divide rapidly, several chemotherapeutic agents often damage them. Patients may complain of a sore throat, difficulty swallowing, significant pain, abdominal cramping, or diarrhea.

Treatment is principally symptomatic. Several commercially available drugs can reduce the severity of diarrhea. Patients with particularly severe symptoms may require intravenous hydration.

Analgesic agents, including narcotics, may be indicated in patients with significant stomatitis or mucositis. A viscous solution of 2% lidocaine HCL can provide local pain relief, as can kaolin-pectin and diphenhydramine mouthwashes. To reduce irritation, persons with stomatitis and mucositis should avoid acidic food.

Fever in a patient with severe stomatitis, mucositis, or diarrhea, particularly in the presence of neutropenia, is of concern because the damaged mucosa can allow gastrointestinal flora to enter the blood stream and lead to bacteremia. Broad-spectrum antibiotics should be started promptly.

OTHER TOXIC EFFECTS OF CHEMOTHERAPY

Peripheral neuropathy, characterized by numbness and tingling of the fingers and toes, occurs with some cytotoxic agents, including cisplatin and paclitaxel. The severity of this side effect is often related to the peak and cumulative doses. The likelihood of neuropathy increases with use of more than one neurotoxic agent.

There is no evidence that any drug can prevent peripheral neuropathy, but clinical investigation is ongoing in this area. Fortunately, in most circumstances, these symptoms gradually abate over several months after chemotherapy is stopped.

Hearing loss and tinnitus can occur with high doses of cisplatin. Although audiograms often document decreases in high-frequency hearing in persons receiving cisplatin, these abnormalities are rarely clinically relevant. Thus, because this test lacks clinical utility, most patients receiving cisplatin do not undergo routine audiograms.

Rare toxic effects include:

- Heart failure (induced by anthracyclines).
- Pulmonary dysfunction (with bleomycin)
- Hemorrhagic cystitis (ifosfamide, high-dose cyclophosphamide).
- Renal insufficiency (cisplatin, ifosfamide).
- Severe hypersensitivity reactions (paclitaxel). ■

SUGGESTED READING

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