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Colony-Stimulating Factors for Febrile Neutropenia during Cancer Therapy

Charles L. Bennett, M.D., Ph.D., Benjamin Djulbegovic, M.D., Ph.D., LeAnn B. Norris, Pharm.D., and James O. Armitage, M.D.

South Carolina Center of Economic Excellence for Medication Safety and Efficacy and the Southern Network on Adverse Reactions (SONAR), South Carolina College of Pharmacy, University of South Carolina, Columbia; the Hollings Cancer Center, Medical University of South Carolina, Charleston; and the William Jennings Bryan Dorn Veterans Affairs Medical Center, Columbia — all in South Carolina (C.L.B., L.B.N.); Clinical and Translational Science Institute, Center for Evidence-based Medicine and Health Outcome Research, Department of Medicine, Morsani College of Medicine, University of South Florida, and Departments of Hematology and Health Outcomes and Behavior, H. Lee Moffitt Cancer Center and Research Institute — both in Tampa (B.D.); and University of Nebraska Omaha School of Medicine, Omaha (J.O.A.).

Abstract

A 55-year-old, previously healthy woman received a diagnosis of diffuse large-B-cell lymphoma after the evaluation of an enlarged left axillary lymph node obtained on biopsy. She had been asymptomatic except for the presence of enlarged axillary lymph nodes, which she had found while bathing. She was referred to an oncologist, who performed a staging evaluation. A complete blood count and test results for liver and renal function and serum lactate dehydrogenase were normal. Positron-emission tomography and computed tomography (PET-CT) identified enlarged lymph nodes with abnormal uptake in the left axilla, mediastinum, and retroperitoneum. Results on bone marrow biopsy were normal. The patient's oncologist recommends treatment with six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (CHOP-R) at 21-day intervals. Is the administration of prophylactic granulocyte colony-stimulating factor (G-CSF) with the first cycle of chemotherapy indicated?

The Clinical Problem

Cycling cells in the bone marrow are sensitive to some forms of chemotherapy, including DNA-damaging agents and agents that inhibit cell-cycle progression. Therefore, in patients who are treated with chemotherapy regimens that include such agents, normal hematopoietic cells undergo damage that is both immediate and cumulative. The most serious immediate consequence of chemotherapy is febrile neutropenia, which is defined as an absolute neutrophil count of less than 500 cells per cubic millimeter and a temperature of more than 38.5°C. Most standard-dose chemotherapy regimens are associated with 6 to 8 days of neutropenia.^{1–3} Data from the National Cancer Institute (NCI) suggest that more than 60,000 patients are admitted for the treatment of febrile neutropenia annually, or approximately 8 cases per 1000 patients receiving cancer chemotherapy.⁴

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Address reprint requests to Dr. Bennett at South Carolina College of Pharmacy, 715 Sumter St., Columbia, SC 29208, or at bennettc@sccp.sc.edu.

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Febrile neutropenia predisposes patients to serious infections and even death, particularly if severe neutropenia persists for longer than 10 to 14 days.^{4–6} In the study of NCI data, the in-hospital rate of death was 6.8%.⁴ In another analysis, the overall in-hospital rate of death was 9.5% (and 15.3% for patients with documented infection).⁶ The mean costs per hospitalization in these two studies were \$13,372 and \$19,110, respectively.^{4,6}

Pathophysiology and Effect of Therapy

When chemotherapy-induced leukopenia develops, endogenous cytokines, including interleukin-6 and tumor necrosis factor, are induced, which can result in fever, even in the absence of infection. However, the central concern in the patient with febrile neutropenia is the risk of infection.⁶ Numerous observations link the duration and degree of neutropenia with infection risk in patients with severe chronic neutropenia.⁷

Why is neutropenia associated with an increased risk of infection? The answer, although seemingly simple, is actually highly complex. Leukocytes, particularly neutrophils, are early responders to invading pathogens. Moreover, mucositis, which is another adverse effect of chemotherapy, disrupts the barrier function of the gut mucosa and permits microbial invasion. The skin, mouth, nasopharynx, and gut have complex spectra of microbial organisms, which may be altered by cancer and its treatment, the use of antibiotics, and other factors. For example, patients undergoing hematopoietic stem-cell transplantation have a reduced diversity of gut flora, with the emergence of relatively dominant species associated with invasive disease. Thus, the risk of bacterial invasion is related not only to the absolute neutrophil count but also to aspects of the immune system and organisms that it defends against. Strategies to minimize the adverse effects of febrile neutropenia focus on the use of colony-stimulating factors (CSFs) to reduce the duration and severity of neutropenia, empirical therapy with antibiotics even in the absence of confirmed infection, or both.

Growth factors support the survival and differentiation of hematopoietic cells (Fig. 1). The use of granulocyte–macrophage CSF (GM-CSF) supports the survival and proliferation of several target cells (i.e., neutrophils, eosinophils, basophils, monocytes, and dendritic cells) in culture and activates most of these types of mature cells, whereas the stimulatory effect of G-CSF is primarily on neutrophils.⁸ Plasma G-CSF levels are controlled in large part by the absolute neutrophil count.^{8,9} Studies using radiolabeled ligand have shown specific G-CSF binding on all neutrophils (mean, 260 receptors per cell), on most promyelocytes (94%, with 200 receptors per cell), and on early and more mature stem cells (mean, 60 receptors per cell).

G-CSF supports the survival and stimulates the proliferation of neutrophil progenitors, promotes differentiation of these cells into mature neutrophils, causes premature release of neutrophils from the marrow, and enhances phagocytic capacity, the generation of superoxide anions, and the killing of bacteria by these cells. G-CSF administration causes toxic granulation of neutrophils, reflecting heightened functionality and shifts toward more immature white-cell precursors. G-CSF also synergizes with other hematopoietic growth factors, such as erythropoietin and stem-cell factor.

Clinical Evidence

Shortly after complementary DNA sequences for G-CSF and GM-CSF were identified in 1985 and 1986, recombinant proteins were developed and rapidly entered clinical testing.^{10–12} Four CSFs have received regulatory approval to date: G-CSF (filgrastim and lenograstim); pegylated G-CSF (pegfilgrastim), in which the addition of polyethylene glycol increases the half-life of the agent; yeast-derived GM-CSF (sargramostim); and GMCSF

derived from *Escherichia coli* (molgramostim).⁸ Since filgrastim and pegfilgrastim are the principal CSF products in current clinical use, they are the focus of this article.

Filgrastim was approved by the Food and Drug Administration (FDA) in 1991 on the basis of a phase 3 trial involving 211 patients with small-cell lung cancer who were receiving cyclophosphamide, doxorubicin, and etoposide and were randomly assigned to receive either filgrastim or placebo.¹⁰ Over all cycles, the incidence of febrile neutropenia was 76% in the placebo group versus 40% in the filgrastim group ($P<0.001$), and the median duration of grade 4 neutropenia (<500 cells per cubic millimeter) was 6 days in the placebo group versus 3 days in the filgrastim group.¹⁰

FDA approval of pegfilgrastim in 2002 was based on a phase 3 trial of pegfilgrastim versus filgrastim involving 928 patients with metastatic breast cancer who were receiving doxorubicin and docetaxel.¹³ The mean duration of grade 4 neutropenia in cycle 1 was 1.8 days in the pegfilgrastim group and 1.6 days in the filgrastim group. A trend toward a lower incidence of febrile neutropenia was noted across all cycles in the pegfilgrastim group, as compared with the filgrastim group (13% vs. 20%). Several meta-analyses indicated that primary prophylaxis with G-CSF (i.e., G-CSF administered immediately after cycle 1 of chemotherapy) reduced the risk of febrile neutropenia by 50% in patients with solid tumors, without affecting the rates of tumor response, infection-related death, early-treatment-related death, or overall survival.^{14–17}

Clinical Use

Both filgrastim and pegfilgrastim are most often administered prophylactically after chemotherapy regimens that are associated with a high incidence of febrile neutropenia (Table 1). For regimens associated with a low or intermediate risk of febrile neutropenia (i.e., $<20\%$), these agents are often not administered unless the patient is more than 65 years of age, has a major coexisting illness (e.g., renal, hepatic, or cardiac dysfunction) or a preexisting condition (e.g., infection, open wound, or recent surgery), or has compromised marrow reserve from previous chemotherapy or radiation therapy. Some patients who do not receive primary prophylaxis will not have recovery of adequate granulocyte counts (i.e., 1000 to 1500 cells per cubic millimeter) in time to receive the next cycle of chemotherapy on schedule. In these patients, the use of filgrastim or pegfilgrastim in subsequent cycles facilitates treatment on the planned schedule.

Filgrastim is administered at a dose of 5 μg per kilogram of body weight daily by means of subcutaneous injection and is continued until the white-cell count recovers to near-normal levels.¹⁸ The duration of therapy is contingent on the myelosuppressive potential of the chemotherapy agents used. Premature discontinuation of filgrastim therapy, before the nadir of the white-cell count has been reached, should be avoided. Filgrastim should be discontinued if a very high white-cell count occurs ($>100,000$ cells per cubic millimeter). Pegfilgrastim is administered as a one-time dose of 6 mg subcutaneously for each cycle of chemotherapy.¹⁹

According to current recommendations, filgrastim should be administered starting 24 to 72 hours after the completion of chemotherapy, and pegfilgrastim should be administered once, 24 hours after the completion of chemotherapy.^{18,19} For convenience, some physicians begin treatment on the day that chemotherapy is completed, since phase 2 clinical trials have shown this approach to be safe and effective. However, we, as well as most practitioners, begin treatment 24 hours after the completion of chemotherapy.^{20,21} One randomized trial showed that pegfilgrastim administration 3 days after completion of CHOP-R rather than 1

day after completion was associated with a reduced incidence of leukopenia, a reduced rate of antibiotic therapy for apparent infection, and improved survival.²²

When filgrastim is used, clinical guidelines recommend monitoring of the complete blood count twice a week, with continued monitoring until the absolute neutrophil count reaches 2000 to 3000 cells per cubic millimeter. Blood counts are typically not monitored in patients receiving pegfilgrastim, since the administration of the drug is not dependent on the recovery of the white-cell count. In the outpatient setting, pegfilgrastim is more commonly used for reasons of convenience, but even in outpatients receiving filgrastim, white-cell counts are often not closely monitored.

Either filgrastim or pegfilgrastim is frequently used to facilitate the administration of chemotherapy in full or escalated doses. The rationale relies on the assumption that the dose intensity should not be compromised in patients in whom cancer therapy is designed to be curative (e.g., patients with estrogen-receptor-negative breast cancer or non-Hodgkin's lymphoma), in whom the receipt of a full dose of chemotherapy may have increased efficacy.²³ The use of CSF support is particularly important for delivery of dose-dense chemotherapy in women with estrogen-receptor-negative, node-positive breast cancer.²⁴ However, in other patients, dose escalation of standard chemotherapy regimens has not improved survival.¹ Therefore, dose reduction without the prophylactic use of filgrastim or pegfilgrastim is a feasible and generally preferred option, particularly in patients receiving palliative care.¹⁻³

CSFs are used in patients with a number of other conditions. The drugs are routinely administered for the mobilization of peripheral-blood progenitor cells (PBPCs), often with chemotherapy, so that the recovered PBPCs can be reinfused to shorten the duration of neutropenia after cytoreduction. CSFs are also administered after chemotherapy in patients with acute leukemia or after the transplantation of autologous peripheral-blood cells, since the use of these drugs decreases the duration of neutropenia and rates of hospitalization and antibiotic use. However, CSFs are not administered after allogeneic stem-cell transplantation because of increased risks of severe graft-versus-host disease, transplantation-related death, and death from other causes.²⁵

If the goal of administering CSFs is a reduction in the risks of fever and infection, prophylactic antibiotics might also achieve this goal. For patients with hematologic cancers, many of whom have disease-related or therapy-related impairment in immunity, antibiotic prophylaxis is frequently administered after chemotherapy. Studies have shown associations between antibiotic prophylaxis and reductions in the rates of febrile episodes, probable infection, hospitalization for infection, and even death.²⁶⁻²⁸ However, concern about the induction of microbial resistance makes this approach controversial. The only NCI-sponsored cooperative group clinical trial comparing the effectiveness of prophylactic antibiotics with that of G-CSF was terminated before the enrollment of a single patient because of a lack of funding.²⁹

Filgrastim and pegfilgrastim are both expensive. The current Medicare reimbursement for one 6-mg vial of pegfilgrastim is \$2,838.³⁰ Filgrastim is available in 300-mg and 480-mg vials, which are reimbursed at \$268 and \$427, respectively.³⁰ For a patient weighing 70 kg, the daily dose of filgrastim would be 350 mg. Thus, the cost of one dose of pegfilgrastim (sufficient for a single cycle of chemotherapy) is roughly the equivalent of 10 days of treatment with filgrastim (which may or may not be sufficient for a single cycle of chemotherapy, depending on the duration of neutropenia).

Adverse Effects

Injection-site discomfort is common with CSF preparations, as are constitutional symptoms such as fever, malaise, and influenza-like symptoms. A relatively common and sometimes severe adverse event is bone pain, which develops in 10 to 30% of patients who receive these agents. Non-narcotic analgesics usually control this symptom.^{18,19}

The administration of G-CSF or pegylated G-CSF after chemotherapy is rarely associated with acute myeloid leukemia or the myelodysplastic syndrome.^{31–33} A meta-analysis of 25 phase 3 clinical trials involving 12,812 patients receiving chemotherapy identified acute myeloid leukemia or the myelodysplastic syndrome in 22 control patients versus 43 patients receiving G-CSF (relative risk, 1.92; absolute risk, 0.41 percentage points; $P < 0.05$ for both comparisons).³⁴ Acute myeloid leukemia or the myelodysplastic syndrome after breast-cancer chemotherapy was more common in patients who were treated with G-CSF, in an overview analysis of clinical trials from the National Surgical Adjuvant Breast and Bowel Project and Medicare's Surveillance, Epidemiology, and End Results databases (risk ratio, 2.14 and 2.38, respectively; $P < 0.05$).^{32,33} Intensive evaluation by the U.S. Center for International Blood and Marrow Transplant Research, the German National Registry of Blood Stem Cell Donors, and the European Group for Blood and Marrow Transplantation has not identified an increased risk of acute myeloid leukemia among more than 43,000 peripheral-blood donors who underwent stimulation with G-CSF.^{35–37}

Rare cases of splenic rupture have been reported in patients who received G-CSF, GM-CSF, or pegylated G-CSF, including 10 patients with chronic neutropenia or cancer and 5 healthy donors of peripheral-blood stem cells.³⁸

Areas of Uncertainty

In 2012, the American Board of Internal Medicine Foundation's Choosing Wisely initiative identified key tests or procedures commonly used in medicine whose necessity was not supported by high-level evidence and that were associated with wide practice variation and inappropriate use. The American Society of Clinical Oncology (ASCO) identified the use of G-CSF as one of five key opportunities to improve care and reduce costs.³⁹ The recommendation was to avoid the use of G-CSF or pegylated G-CSF for primary prophylaxis in patients undergoing cancer therapy if the risk of chemotherapy-induced febrile neutropenia is less than 20%. In practice, wide variation from guideline standards results in extensive use of these agents when the risk of febrile neutropenia is less than 20% and there are no additional risk factors (e.g., an age of >65 years or the presence of coexisting illness).^{40–42} As an example, in a study of 2728 patients with cancer in western Washington State, CSF prophylaxis was used in 54% of patients at high risk for febrile neutropenia, in 24% of those at intermediate risk, and in 15% of those at low risk, with substantial variation according to study center.⁴² A particularly important area of uncertainty that is highlighted by these findings is an absence of tools (risk models) that reliably predict the risk of febrile neutropenia in individual patients.

An emerging clinical area involves biologic products that are similar to G-CSF and pegylated G-CSF (biosimilar products), which are less costly than filgrastim or pegfilgrastim.⁴³ Two biosimilar G-CSFs have been introduced in the European Union.⁴⁴ Clinical evidence from a meta-analysis indicated that one of these agents is similar to filgrastim with respect to rates of febrile neutropenia.⁴⁵

Guidelines

Clinical guidelines from ASCO and the National Comprehensive Cancer Network in the United States and from the European Organization for Research and Treatment of Cancer are quite similar in many respects. All three sets of guidelines recommend that CSFs be administered prophylactically if the risk of febrile neutropenia is greater than 20% and if equally effective treatments that do not require CSF support are unavailable.¹⁻³ For patients receiving chemotherapeutic regimens who have an intermediate risk of febrile neutropenia (10 to 20%), the guidelines emphasize the importance of considering the patient's age and coexisting illnesses.¹⁻³ Additional factors supporting the use of CSFs include previous cytotoxic or radiation therapy, preexisting tumor-related neutropenia or bone marrow involvement, reduced performance status, reduced nutritional status, advanced cancer, impaired renal function, infection, the presence of open sores, and hepatic dysfunction.

Guidelines recommend against administering CSFs in patients who are receiving concomitant radiation therapy with chemotherapy or who have had documented periods of afebrile neutropenia.¹⁻³ Clinical guidelines support the use of CSFs in patients with febrile neutropenia who are at high risk for infection-associated complications or who have factors predictive of a poor outcome.¹⁻³ Among the differences in recommendations in the three sets of guidelines, the U.S. guidelines broadly apply to myeloid growth factors G-CSF, pegylated G-CSF, and GM-CSF, whereas the European guidelines do not include GM-CSF.

Recommendations

The administration of G-CSF or pegylated G-CSF in a patient being treated for cancer depends on several factors, including the chosen chemotherapy regimen, coexisting illnesses, performance status, and complicating factors, such as hepatic or renal dysfunction (which can adversely affect the pharmacokinetics of many chemotherapy regimens). The patient described in the vignette is relatively young, was previously healthy without coexisting illnesses, and has a good performance status. She is scheduled to receive CHOP-R at 21-day intervals, the most widely used regimen in the United States for treating diffuse large-B-cell lymphoma. As noted in Table 1, this regimen is associated with a low-to-intermediate risk of febrile neutropenia (20%). Considering this patient's relatively young age, good performance status, absence of coexisting illnesses, normal renal and liver function, and absence of bone marrow involvement, we would not recommend administering G-CSF or pegylated G-CSF with the first treatment cycle.

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Figure 1. Use of Hematopoietic Growth Factors in the Survival and Differentiation of Hematopoietic Cells

Blood-cell development progresses from a hematopoietic stem cell (HSC) through sequential stages of differentiation, ultimately giving rise to the individual mature cell types found in the circulation, including platelets, erythrocytes, monocytes, neutrophils, eosinophils, basophils, T cells, natural killer (NK) cells, and B cells. Cytokines and growth factors that support the survival, proliferation, or differentiation of each type of cell are shown. The highlighted sequence shows the differentiation pathway for granulocytes (neutrophils, eosinophils, and basophils). Granulocyte–macrophage colony-stimulating factor (GM-CSF) supports the differentiation of common myeloid progenitors (CMP) into

common granulocyte–monocyte progenitors (GM). Granulocyte colony-stimulating factor (G-CSF) supports the differentiation of committed granulocyte progenitors (GP) into mature granulocytes. BCP denotes B-cell progenitor, CLP common lymphoid progenitor, EP erythrocyte progenitor, EPO erythropoietin, IL interleukin, M-CSF macrophage colony-stimulating factor, MEP megakaryocyte–erythrocyte progenitor, MkP megakaryocyte progenitor, MP monocyte progenitor, NKP natural-killer-cell progenitor, SCF stem-cell factor, TCP T-cell progenitor, TNK T-cell–natural-killer-cell progenitor, and TPO thrombopoietin.⁸

Table 1

Risk of Febrile Neutropenia, According to the Type of Cancer and Chemotherapy Regimen.*

Risk of Neutropenia and Type of Cancer	Chemotherapy Regimen
High risk (>20%)	
Bladder cancer	MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) for neoadjuvant or adjuvant therapy and metastatic disease
Breast cancer	Docetaxel and trastuzumab for metastatic or relapsed disease Dose-dense ACT (doxorubicin, cyclophosphamide, and paclitaxel) for adjuvant therapy [†] Doxorubicin and paclitaxel for metastatic or relapsed disease Doxorubicin and docetaxel for metastatic or relapsed disease TAC (docetaxel, doxorubicin, and cyclophosphamide) for adjuvant therapy
Esophageal and gastric cancer	Docetaxel, cisplatin, and fluorouracil
Hodgkin's lymphoma	BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) [‡]
Kidney cancer	Doxorubicin and gemcitabine
Non-Hodgkin's lymphoma	CFAR (cyclophosphamide, fludarabine, alemtuzumab, and rituximab) for chronic lymphocytic leukemia with del(17p) and relapsed or refractory disease ICE (ifosfamide, carboplatin, and etoposide) for diffuse large-B-cell lymphoma, peripheral T-cell lymphomas, and second-line or salvage therapy RICE (rituximab, ifosfamide, carboplatin, and etoposide) CHOP-14 (cyclophosphamide, doxorubicin, vincristine, and prednisone) with or without rituximab [‡] MINE (mesna, ifosfamide, novantrone, and etoposide) for diffuse large-B-cell lymphoma, peripheral T-cell lymphomas, second-line therapy, and refractory disease DHAP (dexamethasone, cisplatin, and cytarabine) for diffuse large-B-cell lymphoma, peripheral T-cell lymphomas, and second-line therapy ESHAP (etoposide, methylprednisolone, cisplatin, and cytarabine) for diffuse large-B-cell lymphoma, peripheral T-cell lymphomas, second-line therapy, and recurrent disease HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) plus rituximab
Melanoma	Dacarbazine-based combination (dacarbazine, cisplatin, and vinblastine) for advanced, metastatic, or recurrent disease Dacarbazine-based combination (dacarbazine, cisplatin, and vinblastine) plus interleukin-2 and interferon alfa for advanced, metastatic, or recurrent disease
Multiple myeloma	Modified HyperCVAD
Myelodysplastic syndromes	Rabbit antithymocyte globulin and cyclosporine Decitabine
Ovarian cancer	Topotecan, paclitaxel, or docetaxel
Sarcoma	MAID (mesna, doxorubicin, ifosfamide, and dacarbazine) or doxorubicin
Small-cell lung cancer	Topotecan

Risk of Neutropenia and Type of Cancer	Chemotherapy Regimen
Testicular cancer	VeIP (vinblastine, ifosfamide, and cisplatin) VIP (etoposide, ifosfamide, and cisplatin) BEP (bleomycin, etoposide, and cisplatin) [‡] TIP (paclitaxel, ifosfamide, and cisplatin)
Intermediate risk (10–20%)	
Occult primary adenocarcinoma	Gemcitabine and docetaxel
Breast cancer	Docetaxel every 21 days Epirubicin for adjuvant therapy Epirubicin plus sequential cyclophosphamide, methotrexate, and fluorouracil for adjuvant therapy CMF classic (cyclophosphamide, methotrexate, and fluorouracil) for adjuvant therapy AC (doxorubicin and cyclophosphamide) plus sequential docetaxel for adjuvant therapy (during docetaxel portion only) AC plus sequential docetaxel and trastuzumab for adjuvant therapy FEC (fluorouracil, epirubicin, and cyclophosphamide) plus sequential docetaxel Paclitaxel every 21 days for metastatic or relapsed disease Vinblastine for metastatic or relapsed disease
Cervical cancer	Cisplatin and topotecan for recurrent or metastatic disease Topotecan for recurrent or metastatic disease Irinotecan for recurrent or metastatic disease
Colorectal cancer	FOLFOX (fluorouracil, leucovorin, and oxaliplatin)
Esophageal and gastric cancer	Irinotecan and cisplatin Epirubicin, cisplatin, and fluorouracil Epirubicin, cisplatin, and capecitabine
Hodgkin's lymphoma	ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) [‡] Stanford V (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, and prednisone) [‡]
Non-Hodgkin's lymphoma	EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) for AIDS-related disease, Burkitt's lymphoma, and recurrent disease EPOCH plus intrathecal chemotherapy for AIDS-related disease, diffuse large-B-cell lymphoma, and recurrent disease ACOD (modified CHOP: doxorubicin, cyclophosphamide, vincristine, and prednisone) GDP (gemcitabine, dexamethasone, and cisplatin) for diffuse large-B-cell lymphoma, peripheral T-cell lymphomas, and second-line therapy GDP plus rituximab for diffuse large-B-cell lymphoma and second-line therapy FM (fludarabine and mitoxantrone) CHOP plus rituximab, including regimens with pegylated liposomal doxorubicin or mitoxantrone substituted for doxorubicin
Non-small-cell lung cancer	Cisplatin and paclitaxel for adjuvant therapy and advanced or metastatic disease Cisplatin and vinorelbine for adjuvant therapy and advanced or metastatic disease

Risk of Neutropenia and Type of Cancer	Chemotherapy Regimen
	Cisplatin and docetaxel for adjuvant therapy and advanced or metastatic disease Cisplatin and irinotecan for advanced or metastatic disease Cisplatin and etoposide for adjuvant therapy and advanced or metastatic disease Carboplatin and paclitaxel for adjuvant therapy and advanced or metastatic disease [§] Docetaxel for advanced or metastatic disease
Ovarian cancer	Carboplatin and docetaxel
Prostate cancer	Cabazitaxel [¶]
Small-cell lung cancer	Etoposide and carboplatin
Testicular cancer	Etoposide and cisplatin
Uterine cancer	Docetaxel for uterine sarcoma and advanced or metastatic disease

* Data are from the National Comprehensive Cancer Network (www.nccn.org/professionals/physician_gls/f_guidelines.asp#site). AIDS denotes acquired immunodeficiency syndrome.

[†] In general, dose-dense regimens such as this require growth-factor support for chemotherapy administration.

[‡] The use of granulocyte colony-stimulating factors with bleomycin-containing regimens may increase the risk of pulmonary toxicity.

[§] This combination is recommended if the carboplatin dose has an area under the receiver-operating-characteristic curve (AUC) of more than 6 or if the patient is of Japanese ancestry.

[¶] The published results for cabazitaxel have shown a rate of febrile neutropenia of 8%, and deaths from neutropenia have been reported. Primary prophylaxis with granulocyte colony-stimulating factors should be considered in patients with high-risk clinical features.