

# Managing Hematologic Toxicities

Gerardo Capo, MD, and Roger Waltzman, MD

**C**hemotherapy is an essential tool in treating cancer. However, the toxicities of chemotherapeutic agents are numerous. The most common organ system to be affected is the bone marrow and, secondarily, peripheral blood cells [1]. The effect of these agents on each cell line is dependent upon that cell line's kinetics. Since red blood cells have a half-life of 120 days, the anemia that may result from myelosuppressive chemotherapy occurs much more slowly than the decrease in white blood cells or platelets, because their half-lives are 6–8 hours and 5–7 days, respectively [2]. Consequently, with chemotherapy, the latter two cell lines are suppressed earlier and often more severely. Most chemotherapeutic agents cause a white blood cell count nadir between days 5 and 14, with recovery by days 7–21 [3]. Some classes of chemotherapeutic agents cause slightly more delayed suppression of bone marrow cells and longer recoveries, especially the nitrosoureas and mitomycin, with myelosuppression occurring up to 4–5 weeks posttherapy [4].

The degree of cytopenia is affected not only by the particular agent used, the dose, and the cell-line kinetics but also by a host of factors involving the cellularity of the host marrow compartment: age (a younger patient has a more cellular and less fatty marrow than an elderly person, which typically results in greater tolerance to a particular chemotherapy dose); marrow reserve not affected by tumor infiltration; effects of previous chemotherapy or radiotherapy on the marrow; nutritional status; and the ability of the liver and kidneys to metabolize and/or excrete particular compounds [2]. Thus, anemia, neutropenia, and thrombocytopenia may be anticipated to some extent when administering chemotherapy, and treatment of these cytopenias must be tailored specifically based

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**Abstract** This overview of the hematologic toxicities of cancer chemotherapy addresses the frequency and clinical significance of neutropenia, anemia, and thrombocytopenia and attempts to provide evidence-based guidelines, based on clinical trials, for the use of cytokine growth factors and transfusion support. The current emphasis on high-dose and dose-dense chemotherapy increases the need for close attention to the amelioration of hematologic toxicities. The latter is highly dependent upon the appropriate and judicious use of cytokine support. Although these supportive agents may be relatively nontoxic, it is important to understand their potential side effects and to use them only when warranted by evidence-based studies.

on cell-line counts, comorbidities, and the clinical status of the individual patient.

## Anemia

Anemia has been reported in up to 44% of cancer patients, even before they have begun receiving chemotherapy [5, 6]. The mechanisms underlying cancer-related anemia include direct tumor infiltration of bone marrow; reduced levels of endogenous erythropoietin production [7]; an increase in inflammatory cytokines, such as tumor necrosis factor (TNF), that may directly inhibit erythropoiesis by curbing stored iron utilization [8]; and other contributory factors, such as nutritional deficiencies, hemorrhage, and hemolysis. Each patient should be evaluated fully and, if warranted, begin treatment for reversible causes of anemia prior to initiating a chemotherapy regimen, especially since the start of a chemotherapeutic regimen can cause the incidence of anemia to rise as high as 90% in some types of tumors [8, 9].

## TREATMENT OPTIONS

The main treatment options for anemia include blood transfusions, recombinant human erythropoietin (epoetin alfa [Epogen, Procrit]), darbepoetin alfa (Aranesp), and iron therapy (or a combination). Decisions regarding treatment must be tailored to each patient based on the degree of anemia, clinical status, and comorbidities. The

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National Cancer Institute (NCI) has created toxicity criteria that can be used to evaluate anemia. Grade 3 anemia (severe) and grade 4 anemia (life-threatening) are defined as hemoglobin values of 6.5–7.9 g/dL and less than 6.5 g/dL, respectively. Grade 1 anemia (mild) is defined as a hemoglobin level greater than 10.0 g/dL but less than normal, and grade 2 anemia (moderate) as a hemoglobin level between 8.0 and 10.0 g/dL. (The World Health Organization's criteria differ slightly, but only in regard to grades 1 and 2.) It is important to recognize that the NCI common toxicity criteria are strictly laboratory values and therefore fail to capture the clinical relevance of anemia, ie, associated symptomatology and quality of life (QOL).

It is critical to assess both laboratory values and the clinical status of the patient when deciding whether or not to initiate treatment, which treatment is most appropriate, and when it should be started. In the case of a patient with symptomatic anemia and decreased intravascular volume, crystalloids should be used first to increase intravascular volume [10]. Patients with continued symptoms or poor cardiac or respiratory function manifesting as dyspnea, cardiac failure, or angina require immediate transfusion of packed red blood cells. However, some authors warn against the regular use of blood transfusions for mild to moderate anemia because of the potential risks involved, including infection (cytomegalovirus infection, hepatitis, HIV, parasites), allergic responses, transfusion-associated lung injury, and alloimmunization, which may then result in reactions and difficulties with subsequent cross-matching [11–13]. In addition, there is evidence that the US blood-donor pool is shrinking, whereas its usage is rising [14]. Thus, blood transfusions should be reserved only for cases where they are absolutely necessary.

Prior to the advent of erythropoietin therapy, treatment for mild to moderate anemia was generally avoided; intervention was often withheld until the patient had severe symptoms or the hemoglobin concentration fell below 7–8 g/dL [15, 16]. Over the past decade, however, data have emerged showing that chemotherapy-induced anemia, even mild to moderate grades, can have an adverse impact on patients' QOL [17].

Several instruments, such as the Functional Assessment of Cancer Therapy–Fatigue, Linear Analog Self-Assessment (LASA), and Quality of Life Questionnaire Core 30 (QLQ-C30) scales, have been developed and validated to measure

QOL parameters objectively. The Fatigue Coalition has reported that up to 67% of patients receiving chemotherapy experienced fatigue (30% on a daily basis) and that 90% felt precluded from a “normal life” because of it; 75% of these patients changed their employment status, and 65% of patients had a caregiver who needed to take off from work at least 1 day per month [18]. A study using the Functional Assessment of Cancer Therapy–Anemia (FACT-An) scale, which contains questions related to fatigue and anemia, showed that patients with higher hemoglobin values report less fatigue and better QOL [19].

Erythropoietin is a naturally produced hematologic growth factor that is responsible for the proliferation, maturation, and differentiation of red blood cells. The availability of recombinant human erythropoietin, or epoetin alfa, has created a therapeutic option not only for patients with severe anemia but also for those with mild-to-moderate anemia. Epoetin alfa has been studied extensively in patients with renal failure, HIV, and cancer, and improvements in hemoglobin levels have been correlated with improvements in QOL [20–27].

The use of epoetin alfa in the cancer population began with a trial that included one group of patients receiving no chemotherapy that was randomized to receive epoetin alfa at 100 U/kg or placebo given subcutaneously (SC) three times weekly for 8 weeks and another group of patients receiving either cisplatin- or non-cisplatin-based chemotherapy who were randomized to receive either epoetin alfa at 150 U/kg or placebo SC three times weekly for 12 weeks [26]. This landmark trial demonstrated that the use of epoetin alfa therapy significantly increased hemoglobin values ( $P < 0.004$ ) and reduced transfusion requirements ( $P < 0.005$ ) by 12 weeks compared with placebo.

Following this registration trial, the use of epoetin alfa in patients receiving chemotherapy was then studied in three open-label community trials involving more than 7,000 patients in the United States [24, 25, 27]. The study by Glaspy et al [24] included 2,342 patients and dosed epoetin alfa by weight: 150 U/kg administered SC three times weekly, with a dosage increase to 300 U/kg three times weekly at the end of 2 months if there was an inadequate response. The study by Demetri et al [25] treated 2,370 patients with epoetin alfa using a fixed dose of 10,000 U SC three times weekly; at 1 month, the dose for non-responding patients was increased to 20,000 U SC three times

weekly. All patients were required to have a non-myeloid malignancy and be anemic (defined as a hemoglobin level < 11 g/dL in the Demetri study; not defined in the Glaspy study) at the time of registration. The Gabrilove trial [27] pioneered weekly dosing at 40,000 U of epoetin alfa, with an increase at 1 month to 60,000 U weekly for non-responding patients.

All three studies demonstrated an association between an increase in the hemoglobin value and improvement in QOL. These studies defined a hemoglobin response as an increase in hemoglobin level of at least 2 g/dL or attainment of an absolute hemoglobin concentration of 12 g/dL [25]. With regard to the effects of epoetin alfa on hemoglobin, a mean rise of 1.8–2 g/dL was noted compared with baseline. Approximately one half to two thirds of patients responded. All three studies demonstrated significant ( $P < 0.001$ ) decreases in the percentage of patients requiring transfusions and in the number of transfusions required per patient.

The investigators also found that the improvement in QOL parameters was significantly correlated ( $P < 0.001$ ) with an increase in hemoglobin concentration, the primary objective of the study, and was also independent of tumor response (assessed retrospectively in the Glaspy trial but prospectively in the Demetri study) [24, 25]. The Demetri study [25] was the first to demonstrate that hemoglobin and disease response are independent variables that affect QOL. Currently, once-weekly dosing of epoetin alfa in cancer patients is the community standard.

#### ASCO/ASH GUIDELINES

The American Society of Clinical Oncology (ASCO) and The American Society of Hematology (ASH) formed an independent panel of experts to assess the results of the major trials published between 1993 and 1999 on the use of epoetin alfa in anemic cancer patients [28]. Their objective was to address the indications and efficacy of epoetin alfa using evidence-based clinical practice guidelines in patients with cancer. Included in the evaluation were approximately 22 trials comprising 1,927 patients, of which 18 trials (1,698 patients) were randomized. Seven of the randomized trials (with a total of 853 patients) were placebo controlled and double blinded. Only two trials were restricted to hematologic malignancies; most trials, therefore, involved patients with solid tumors. The guidelines may be summarized as follows:

- Epoetin alfa is recommended for patients with chemotherapy-associated anemia and a hemoglobin concentration of less than 10 g/dL.

- In patients whose hemoglobin concentration is less than 12 g/dL but has never fallen below 10 g/dL, the decision of whether to treat immediately or wait until the hemoglobin level falls closer to 10 g/dL depends upon clinical circumstances.

- The recommended starting dose of epoetin alfa is 150 U/kg three times a week for at least 4 weeks, with a possible dose escalation to 300 U/kg three times weekly at 4 weeks in those not responding to the initial dose.

- An alternative dose of 40,000 U weekly may be considered, although supported by less strong evidence, with a dose escalation also considered after 4–8 weeks for non-responders.

- When the hemoglobin concentration nears 12 g/dL, the dose of epoetin alfa may be titrated to maintain this level or stopped and restarted when the hemoglobin level again falls to near 10 g/dL.

- Baseline and subsequent periodic monitoring of iron stores may be valuable in maximizing symptomatic improvement; however, there is no evidence to recommend exactly when this monitoring should be done.

- With regard to hematologic malignancies (myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia), the physician is advised to treat with chemotherapy and/or corticosteroids first and monitor changes in blood counts as a result of decreased tumor burden before considering epoetin alfa [28]. In all cases, if the hemoglobin concentration does not rise more than 1 g/dL by 8 weeks of therapy, the drug should be discontinued.

Darbepoetin alfa is a drug closely related to epoetin alfa, with five, rather than three, N-linked carbohydrate chains, which increase its maximum sialic acid content from 14 to 21. This, in turn, increases its molecular weight from 30,000 to 37,000 Da and confers a half-life of 33–48 hours when given SC, compared with 16–19 hours for epoetin alfa [29]. Thus, darbepoetin alfa's potential benefit over epoetin alfa is that it may be administered less frequently, and, indeed, this benefit has been shown to be true in the nephrology setting [30, 31].

Vansteenkiste et al [32] completed a phase III double-blind, placebo-controlled trial that randomized 320 lung cancer patients receiving platinum-based chemotherapy with hemoglobin values < 11 g/dL to undergo treatment with either

darbepoetin alfa (at a starting dose of 2.25  $\mu\text{g}/\text{kg}$  weekly) or the volume equivalent of placebo. If the hemoglobin concentration had not increased by 1.0 g/dL at week 6, the dosage of darbepoetin alfa was doubled to 4.5  $\mu\text{g}/\text{kg}$  per week and was continued at this level for the remainder of the study period of 2 weeks. The primary endpoint was the proportion of patients who received blood transfusions during the study period.

The results showed that patients receiving darbepoetin alfa required fewer transfusions than those receiving placebo (27% vs 52%;  $P < 0.001$ ). Investigators also found a significantly greater hematopoietic response (defined as either an increase in hemoglobin level of 2 g/dL or attainment of a hemoglobin value of 12 g/dL) in the darbepoetin alfa group than in the placebo group (66% vs 24%;  $P < 0.001$ ), as well as a greater than 25% improvement in fatigue scores (32% vs 19%;  $P < 0.019$ ).

Two studies addressed the issue of dosing darbepoetin alfa on an every-2-week schedule compared with weekly epoetin alfa in cancer patients [33, 34]. Glaspy and colleagues [33], in an open-label multicenter study, randomized 128 patients to receive darbepoetin alfa at one of four doses (3.0, 5.0, 7.0, and 9.0  $\mu\text{g}/\text{kg}$ ) every 2 weeks and compared these groups with patients receiving epoetin alfa at 40,000 U weekly. (The latter group received epoetin alfa at 60,000 U weekly if non-responsive, with the dose change at week 6, rather than week 4.) Treatment ended after 12 weeks, and the data were analyzed after 16 weeks. The results showed that the proportion of patients whose hemoglobin concentration rose by more than 2 g/dL was 66% in the group receiving darbepoetin alfa 3.0  $\mu\text{g}/\text{kg}$  and 84% in those given 5.0  $\mu\text{g}/\text{kg}$ , compared with 63% of patients in the weekly epoetin alfa group. The authors concluded that darbepoetin alfa given at a dosage of 3.0  $\mu\text{g}/\text{kg}$  every 2 weeks is comparable to weekly epoetin alfa—the community standard of care.

The most recently published study addressing every-two-week dosing of darbepoetin alfa compared with weekly epoetin alfa was also reported by Glaspy et al [34]: 127 patients were randomized to four different groups; three of the groups were “front-loaded” with darbepoetin alfa at 4.5  $\mu\text{g}/\text{kg}$  weekly for 4 weeks. Group 1 continued at this dose until the hemoglobin level reached 12 g/dL, at which time a maintenance dose of 1.5  $\mu\text{g}/\text{kg}$  weekly was used. Groups 2 and 3 were switched at week 5 to 2.25 and 3.0  $\mu\text{g}/\text{kg}$  weekly, respectively, for 8

additional weeks. Group 4 received 40,000 U of epoetin alfa weekly, and patients who had not achieved an increase in hemoglobin concentration greater than 1.0 g/dL received higher doses—60,000 U weekly—for the remaining 6 weeks. Efficacy endpoints assessed were changes in hemoglobin concentration, the proportion of patients achieving a hemoglobin response greater than 2 g/dL over baseline, and fatigue scores.

The authors concluded that, although the sample size of each group (30 patients) was too small to formally compare them, darbepoetin alfa can be administered safely using front-loading dosing regimens. Furthermore, it is conceivable that front-loading regimens may result in a larger proportion of treated patients achieving a desired hemoglobin response more quickly. Finally, and importantly, the authors concluded that the darbepoetin alfa-treated groups reported early improvements in fatigue, which were maintained throughout the study period.

### NCCN GUIDELINES

In October 2003, the National Comprehensive Cancer Network (NCCN) updated their guidelines for cancer treatment-related anemia [35]. The guidelines state that either epoetin alfa or darbepoetin alfa is an acceptable option when guidelines call for erythropoietin cytokine support. The guideline recommends considering darbepoetin alfa whenever the hemoglobin value is between 10 and 11 g/dL and strongly recommends it at hemoglobin levels below 10 g/dL. The NCCN guidelines suggest that darbepoetin alfa should be started at a dose of 2.25  $\mu\text{g}/\text{kg}$  weekly, with an increase up to 4.5  $\mu\text{g}/\text{kg}$  weekly at the end of 6 weeks of treatment if the hemoglobin level has not increased by more than 1 g/dL. An alternative dosing schedule of 3  $\mu\text{g}/\text{kg}$  or a fixed dose of 200  $\mu\text{g}$  every 2 weeks is commonly used, with increases to 5  $\mu\text{g}/\text{kg}$  or 300  $\mu\text{g}/\text{kg}$  every 2 weeks, respectively, in the absence of an appropriate response in hemoglobin. The recommendation for epoetin alfa (Table 1) is to begin at a dose of 40,000 U weekly or 10,000 U three times a week, with an increase at 4 weeks to 60,000 U weekly or 20,000 U three times weekly, respectively, if the desired response has not been achieved.

After achievement of a hemoglobin value greater than 12 g/dL, doses of either agent should be titrated to maintain this level, unless there is no improvement in symptoms. If the patient achieves no significant response in hemoglobin

**Table 1**  
Cytokine Therapy of Cancer- and Treatment-Related Anemia

AGENT	STARTING DOSE	FREQUENCY	DOSE ESCALATION	INDICATION FOR DOSE ESCALATION
Epoetin alfa	40,000 U	Once weekly	60,000 U once weekly	Hgb rise < 1 g/dL at 4 weeks
Epoetin alfa	10,000 U	Three times a week	20,000 U three times a week	Hgb rise < 1 g/dL at 4 weeks
Darbepoetin alfa	2.25 µg/kg	Once weekly	4.5 µg/kg	Hgb rise < 1 g/dL at 6 weeks

Hgb = hemoglobin

concentration by 8–12 weeks, then the drug should be discontinued. Regardless of the supportive drug chosen, iron supplementation is advised when the ferritin level is less than 100 ng/mL and the transferrin saturation is less than 20%.

Side effects reported with epoetin alfa and darbepoetin alfa include nausea, dyspnea, coughing, weakness, constipation, fever, and vomiting [22, 23, 36]. Thrombotic events were reported in 6.2% of patients on darbepoetin alfa, compared with 4.1% of patients on placebo, a statistically significant finding.

### Neutropenia

Neutropenia is the most common hematologic toxicity [4]. White blood cell nadirs generally occur 5–14 days following administration of chemotherapy and recover by days 7–21 [3]. The NCI neutropenia toxicity grading scale is as follows [37]:

*Grade 1 (mild):* absolute neutrophil count (ANC) between the lower limit of normal (LLN) and 1,500/mm<sup>3</sup> (LLN–1.5 × 10<sup>9</sup>/L).

*Grade 2 (moderate):* ANC between 1,000 and 1,500/mm<sup>3</sup> (1.0–1.5 × 10<sup>9</sup>/L).

*Grade 3 (severe):* ANC between 500 and 1,000/mm<sup>3</sup> (0.5–1.0 × 10<sup>9</sup>/L).

*Grade 4 (life-threatening):* ANC < 500/mm<sup>3</sup> (< 0.5 × 10<sup>9</sup>/L).

High-dose chemotherapy can extend the duration and deepen the nadir of the neutropenia, and the consequent risk of infection is directly related to both of these factors [2, 3]. The standard of care has been to treat patients with febrile neutropenia with broad-spectrum antibiotics [38]. Resolution of febrile neutropenia has been a common endpoint in trials of antimicrobial agents given to patients receiving chemotherapy, since recovery of the neutrophil count has been shown to be an important prognostic factor in patients with this complication [39].

Filgrastim (Neupogen) is a recombinant form of human granulocyte colony-stimulating factor (G-CSF), which, like its endogenous counterpart,

stimulates neutrophil proliferation, differentiation, and activation [40]. In 1991, the first phase III randomized, double-blind, placebo-controlled trial comparing the addition of filgrastim to each chemotherapy cycle versus chemotherapy alone in 207 patients was published [41]. The authors reported significant reductions in the incidence of febrile neutropenia, as well as in the incidence, duration, and severity of grade IV neutropenia and in the overall number of days of intravenous antibiotic use and hospitalizations. Trillet-Lenoir et al [42] showed similarly favorable results in their trial of 130 patients who were randomized to receive either filgrastim or placebo following the administration of combination chemotherapy. The results of this study showed significant decreases in the incidence of febrile neutropenia, need for antibiotic initiation, infection-related hospitalizations, and need for chemotherapy dose reduction secondary to leukopenia.

### ASCO GUIDELINES

In 1994, an ASCO panel of experts, upon review of pertinent information regarding hematoietic colony-stimulating factors (CSFs) and their use in conjunction with chemotherapy administration in clinical trials, created evidence-based clinical guidelines for the use of CSFs [43]. These guidelines, most recently updated in 2000 [44], recommend that primary prophylactic use of CSFs should be used when the anticipated frequency of febrile neutropenia exceeds 40% or in patients considered at high risk for febrile neutropenia or infection because of comorbidities (eg, extensive prior chemotherapy or pelvic radiotherapy, neutropenia existent prior to chemotherapy, or active infection). In the 1996 update, the ASCO panel recommended consideration of secondary prophylactic CSF administration in patients with one prior episode of febrile neutropenia, based on the results of a trial by Crawford et al [41] showing that patients with febrile neutropenia after one cycle of chemotherapy who subsequently crossed

over to receive open-label G-CSF had significantly fewer episodes of febrile neutropenia in subsequent cycles. However, the 2000 update reconsidered this recommendation because of a lack of evidence showing a reduction in disease-free or overall survival, even in the situation Crawford studied [44]. ASCO currently recommends, exclusive of curable tumors, considering dose reductions after the occurrence of febrile neutropenia with a prior cycle of chemotherapy.

Regarding afebrile patients with neutropenia after chemotherapy administration, the ASCO guidelines maintain that CSFs should not be used routinely. ASCO again considered whether the addition of CSFs to intravenous antibiotics (the standard of care) in patients who develop febrile neutropenia after chemotherapy had been shown to be of benefit since the last update. After reviewing six trials in which adult patients received either G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine, Prokine]) in addition to antibiotics after the development of febrile neutropenia [45–50], it was concluded that CSFs had not been shown to be of significant benefit, and ASCO recommended against their routine implementation in cases of uncomplicated febrile neutropenia, defined as fever of less than 10 days' duration; no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan dysfunction, or invasive fungal infection; and no uncontrolled malignancies [44]. Patients with complicated febrile neutropenia are considered to have a potentially poorer prognosis, and CSF use may be considered, although no data exist to support this.

The recommendations regarding hematologic malignancies, myelodysplastic syndromes, use of CSFs for progenitor cell transplantation, and their use in pediatric populations are beyond the scope of this review. We therefore refer readers to the ASCO guidelines, which address these topics in detail [44].

### **SIDE EFFECTS OF FILGRASTIM AND PEGFILGRASTIM**

The side-effect profile of filgrastim has included, most commonly, mild-to-moderate skeletal pain in 20%–25% of patients [40, 41]. Most patients respond well to non-narcotic oral analgesics, but some do require opiates for pain control. Allergic reactions have been reported on the initial and subsequent doses of filgrastim in fewer than 1 in 400

patients; skin, respiratory, and cardiovascular symptoms were reported as allergic manifestations, usually within 30 minutes of drug administration. Resolution of symptoms occurred rapidly in most patients after treatment with antihistamines and corticosteroids [40]. A similar side-effect profile was reported with pegfilgrastim (Neulasta), with 12% of patients acquiring adequate pain control with non-narcotic analgesics and 6% requiring narcotics for bone pain; in one study, no patient withdrew due to skeletal pain [51].

### **DOSE-DENSE CHEMOTHERAPY**

Dose-dense chemotherapy is emerging as an important new way of administering chemotherapy with the intention of increasing the cure rate of certain tumors by administering identical doses of chemotherapy at more rapid intervals with the use of growth factor support. This frequent dosing, generally every 2 weeks rather than every 3 weeks at standard doses of chemotherapy, would not be feasible without prophylactic growth factor support, because doses would likely be delayed secondary to neutropenia. Several studies have shown that using filgrastim or pegfilgrastim support allows the dose-dense regimen to proceed with rare interruptions.

One study looked at 807 elderly patients with non-Hodgkin's lymphoma who were randomized to receive either twice-weekly CHOP (cyclophosphamide, doxorubicin, Oncovin [vincristine], and prednisolone) (CHOP-14) or CHOP plus etoposide (CHOEP-14) or every-3-week CHOP (CHOP-21) or CHOEP (CHOEP-21) [52]. Patients treated with CHOP-14 or CHOEP-14 received filgrastim support starting from day 4 until recovery of neutrophils. Interestingly, complete response rates were 63.2% for CHOP-21, 69.6% for CHOEP-21, 77% for CHOP-14, and 73.2% for CHOEP-14. At 40 months' follow-up, time to treatment failure and overall survival were significantly better for patients receiving CHOP-14 than for those receiving CHOP-21 ( $P = 0.03$  and  $P = 0.04$ , respectively), and leukopenia occurred significantly less often with CHOP-14 than with CHOP-21. Similar favorable results were preliminarily reported in patients with Hodgkin's disease receiving twice-weekly ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine) chemotherapy plus pegfilgrastim support [53].

The dose-dense chemotherapy administration model has also been investigated in solid tumors.

## PEER VIEWPOINT

Commentary by A. Robert Turner, MD, FRCPC

Neutropenic sepsis, chemotherapy-associated anemia, and thrombocytopenic hemorrhage have become daily concerns for medical oncologists and hematologists caring for patients with solid tumors or hematologic malignancies. These toxicities can be life-threatening and can have significant impact on quality of life for our patients. Biomedical research has produced several hematopoietins that are physiological supplements or replacements for natural human hematopoietic growth factors. The growth factors are readily available and can be given in high dosage with few side effects. The main question is whether their high cost can be justified by their clinical effects.

In July 2000, the American Society of Clinical Oncology (ASCO) updated its 1994 guidelines and adopted a series of recommendations for the use of hematopoietic colony-stimulating factors based on current evidence [1]. These guidelines examined the evidence for the use of granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) and granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine, Prokine]) in oncology. There are several guidelines related to the treatment and prevention of neutropenic sepsis:

- Primary prophylaxis of febrile neutropenia cannot be justified unless the chemotherapy utilized produces febrile neutropenia in more than 40% of patients treated.
- Chemotherapy dose reduction, rather than the administration of leukopoietins, should be considered after febrile neutropenia has occurred, except in a setting of potentially curable treatment.
- Leukopoietins should not be routinely used as part of the treatment of uncomplicated fever and neutropenia (the duration of severe neutropenia can be decreased, but the clinical benefit is not clear).
- There is no evidence that the use of leukopoietins to increase chemotherapy dose intensity or adherence to chemotherapy dose schedules improves survival.
- Leukopoietins are recommended to help in the mobilization of peripheral blood hematopoietic stem cells, usually in combination with chemotherapy.
- Leukopoietins can be used in patients with acute myelogenous leukemia, myelodysplasia, or

acute lymphoblastic leukemia if hospitalization can be shortened enough to outweigh the costs of the growth factors.

### MY PERSONAL CLINICAL EXPERIENCE

The ASCO 2000 update of recommendations provides an excellent set of standards that must be integrated with clinical experience. Based upon my own experience, there are several uses of G-CSF or GM-CSF that I incorporate into my practice:

- Febrile neutropenia, in a patient who has received high-dose chemotherapy for a hematological malignancy, is a morbid disease. Anything that will shorten the period of leukopenia and help the patient survive to have sufficient neutrophils to fight off the sepsis is important.
- Dose intensity and schedule adherence are important in treating Hodgkin's disease [2] and aggressive non-Hodgkin's lymphomas.
- G-CSF, in combination with fludarabine and cytarabine, has been effective in the therapy of relapsed acute myelogenous leukemia [3].
- G-CSF in conjunction with recombinant human erythropoietin produces gratifying remission of leukopenia and anemia in myelodysplasia in the absence of blast excess.

### GUIDELINES FOR THE USE OF ERYTHROPOIETINS

In October 2002, ASCO and the American Society of Hematology (ASH) jointly published a review article on the use of erythropoietins (epoetin alfa [Epogen, Procrit] and darbepoetin alfa [Aranesp]) in patients with cancer [4]. This article, like the ASCO 2000 update of recommendations on the use of colony-stimulating factors, provides a firm basis for the use of erythropoietins in oncology. The guideline panel—speaking specifically to the use of epoetin alfa, since data on darbepoetin alfa were not mature enough at the time of publication of the recommendations—recommended the use of epoetin alfa in patients with chemotherapy-associated anemia. Good evidence from clinical trials supports the use of subcutaneous erythropoietin for a minimum of 4 weeks, and dose escalation should be considered for those patients not responding. The guidelines also say that treating beyond 8 weeks in the absence of response is not beneficial and that clinicians should avoid raising the hemoglobin level over 12 g/dL to minimize the risk of thrombotic complications.

These recommendations were based upon a

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P E E R V I E W P O I N T

benefit to the quality of life of patients. Erythropoietin therapy results in the need for fewer red-blood-cell (RBC) transfusions and a reduction in symptoms generally lumped together as “fatigue” [5]. Both results are important. Fatigue can be a devastating symptom for cancer patients, and the effects of erythropoietin therapy can be dramatic. It is not clear what mechanism causes the reduction in fatigue, but improved exercise tolerance, improved cognition, and reduced need for RBC transfusions all play a role. Erythropoietin therapy also may effect a reduction in tumor-cell hypoxia, and there have been some tantalizing suggestions of improved survival after erythropoietin therapy given in conjunction with chemotherapy.

No set of guidelines for the use of thrombopoietins has yet been developed. Simply put, there is no evidence justifying the use of thrombopoietins in oncology outside clinical trials. Their administration prior to and after high-dose chemotherapy may reduce the need for platelet transfusions, but there are little clinical trial data available that would allow for the development of guidelines.

The sophisticated use of RBC concentrates, platelet concentrates, and antibiotics is still the mainstay of the management of hematological toxicities. The science of transfusion medicine has progressed greatly in the past 20 years, and the products provided are generally safe from the risk of transfusion-transmitted disease as well as febrile/immunological reactions [6]. The broad-spectrum antibacterial and antifungal antibiotics now available lessen the need for leukopoietic support. Hematopoietic growth factors should be

used in concert with this important supportive treatment.

Hematological toxicities *can* be managed. Cytopenia-related deaths and hospitalization can be reduced, and our patients’ quality of life can be improved enough to remove hematological side effects from their list of concerns about chemotherapy.

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Citron et al [54] randomized 2,005 breast cancer patients to receive either sequential or concomitant chemotherapy with doxorubicin, cyclophosphamide, and paclitaxel in either a conventional 3-week or a dose-dense 2-week schedule. The patients receiving chemotherapy every 2 weeks were supported with filgrastim on days 3–10 of each cycle. At the first planned interim analysis, delays in treatment due to hematologic toxicity were significantly higher in patients on the 3-week schedule ( $P < 0.0001$ ), and grade 4 granulocytopenia was also more frequent in the 3-week schedule groups ( $P < 0.0001$ ). Disease-free and overall survival were significantly prolonged in the

dose-dense regimen groups, reconfirming the importance of investigating dose-dense regimens and the use of growth-factor supportive agents to ensure timely administration.

Pegfilgrastim’s molecular structure is identical to that of filgrastim but with the addition of a covalently bound polyethylene glycol molecule [55]. Its mechanism of action is the same as that of filgrastim, except that the molecular alteration renders pegfilgrastim a half-life of 15–80 hours [51], as opposed to filgrastim’s half-life of 3.5 hours after SC injection [40]. In contrast to filgrastim, pegfilgrastim exhibits a decreased renal clearance and a longer duration of circulation in the blood.

**Table 2**  
Cytokine Therapy of Cancer- and Treatment-Related Neutropenia

AGENT	STARTING DOSE ( $\mu\text{g}$ )	FREQUENCY	DURATION	INDICATION
Filgrastim	300	Once daily <sup>a</sup>	8–10 days or until ANC > 10,000/mm <sup>3</sup>	Body weight < 60 kg
Filgrastim	480	Once daily <sup>a</sup>	8–10 days or until ANC > 10,000/mm <sup>3</sup>	Body weight > 60 kg
Pegfilgrastim	6	1 dose per cycle of chemotherapy <sup>a</sup>	Single dose	In lieu of filgrastim at physician's discretion

<sup>a</sup> To provide optimal neutrophil recovery, initiate cytokine therapy 24–72 hours after chemotherapy.  
ANC = absolute neutrophil count

Consequently, a neutrophil-dependent clearance, in which the molecule must first bind to the neutrophil, becomes dominant [56], so the concentration of filgrastim decreases rapidly at the onset of neutrophil recovery following myelosuppressive chemotherapy [51]. It is in this fashion that the levels of pegfilgrastim are indirectly regulated by the amount of neutrophils in the blood. When appropriate, clinical use of this drug, with its once-per-cycle dosing, eradicates the need for up to 14 patient visits and injections per cycle associated with filgrastim, which translates into improved convenience and QOL for patients and a potential cost reduction.

Holmes et al [57] examined the efficacy of pegfilgrastim versus that of filgrastim in a multicenter, randomized, double-blind trial of 310 patients with stage II–IV breast cancer who received chemotherapy with docetaxel (Taxotere; 75 mg/m<sup>2</sup>) and doxorubicin (60 mg/m<sup>2</sup>) for a maximum of 4 cycles. Patients were randomized to two groups. The first received filgrastim 100  $\mu\text{g}/\text{kg}$  (per chemotherapy cycle) on day 2 of each chemotherapy cycle, with subsequent daily doses of placebo for up to 14 days or until the ANC reached  $10 \times 10^9/\text{L}$ . The second group received filgrastim 5  $\mu\text{g}/\text{kg}$  daily, also beginning on day 2 of each cycle and continuing up to 14 days or until the ANC reached  $10 \times 10^9/\text{L}$ . The results showed that pegfilgrastim and filgrastim were comparable with regard to duration of severe neutropenia and the depth of the neutrophil count nadir in all cycles. Moreover, febrile neutropenia occurred less frequently across all cycles in the pegfilgrastim group, compared with the filgrastim group.

Green and colleagues [58], in their study of 157 patients with breast cancer who also were randomized to receive either filgrastim or pegfilgrastim at a dosing schedule (Table 2) similar to those em-

ployed by Holmes et al [57], found the two drugs to be comparable in efficacy with regard to the incidence and duration of neutropenia, as well as median time to recovery to an ANC exceeding  $2.0 \times 10^9/\text{L}$  and in the rate of intravenous antibiotic usage.

### Thrombocytopenia

Thrombocytopenia also occurs due to chemotherapy, but its clinical significance in the treatment of solid tumors is uncommon [2]. Spontaneous bleeding rarely occurs when platelets are above 20,000/ $\mu\text{L}$ , and two studies have shown that the threshold for platelet transfusion could be safely decreased from 20,000/ $\mu\text{L}$  to 10,000/ $\mu\text{L}$  [59, 60]. For the patient with a bleeding diathesis, coagulation studies must be evaluated, because coagulation factor disorders may lead to excessive bleeding, particularly in the setting of thrombocytopenia [61]; moreover, other contributory causes, such as sepsis, hypersplenism, and certain medications (eg, aspirin), should be considered and corrected when appropriate. Thrombocytopenic patients who are bleeding should receive platelet transfusions. Common risks associated with red blood cell transfusions (see above) also apply for platelet transfusions (eg, infectious risks), and refractoriness to platelet transfusion due to development of antibodies can become a significant problem for patients who become dependent upon transfusions, although leukocyte filtration can decrease the incidence of this complication [61].

Chemotherapy-induced thrombocytopenia may occur in patients receiving high-dose chemotherapy, induction treatment for acute leukemia, multiple cycles of certain chemotherapeutic agents (eg, gemcitabine [Gemzar]), or concomitant administration of several therapeutic agents [62]. Two hematopoietic growth factors that accelerate

platelet recovery, interleukin-11 (IL-11, oprelvekin [Neumega]) and recombinant human thrombopoietin (rhTPO), have been developed to treat this complication [63, 64]. Oprelvekin promotes growth of hematopoietic stem cells, as well as megakaryocytic progenitor cells, although its primary function is to maintain female sterility [62, 65]. It was the first commercially available thrombocytopoietic cytokine [66].

Oprelvekin was tested in a randomized, placebo-controlled trial in 93 cancer patients who previously received platelet transfusions for severe chemotherapy-induced thrombocytopenia [65]. Patients received either placebo or oprelvekin on day 1 after chemotherapy administration for the cycle after which they had required the transfusion; subsequent cycles were without dose reduction. Although significantly fewer patients receiving oprelvekin required platelet transfusions, side effects of oprelvekin were remarkable and included fatigue, edema, and cardiovascular symptoms (atrial arrhythmia, palpitations, syncope). Moreover, there were no differences among treatment groups in the number of hospitalization days. A similarly designed study showed that a small cohort of breast cancer patients had a mean increase in platelet counts as the dose of oprelvekin was escalated [67]. One patient in the higher dose group experienced a cerebrovascular accident but subsequently recovered after discontinuation of oprelvekin therapy.

Thrombopoietin (TPO), also known as c-Mpl ligand, was developed with enthusiasm because of the relatively modest efficacy and poor side-effect profile of IL-11 and the increased lineage specificity of TPO [62, 66]. TPO directly increases the size and number of megakaryocytes. Two forms of TPO exist: recombinant TPO (rhTPO), which is identical to its endogenous counterpart, and PEG-rHuMGDF, in which TPO is conjugated to a polyethylene glycol moiety that increases its circulatory half-life, much like the molecular alteration of pegfilgrastim. Both molecules have been studied in clinical trials.

A randomized, double-blind, placebo-controlled study using PEG-rHuMGDF versus placebo was conducted in 53 patients with lung cancer who received carboplatin (Paraplatin) and paclitaxel [68]. The patients who received PEG-rHuMGDF had significantly higher median platelet count nadirs ( $111,000/\text{mm}^3$ ) and faster platelet count recoveries to baseline than the patients who received

placebo ( $188,000/\text{mm}^3$ ); neither group, however, required platelet transfusion.

A second study of 40 non-small-cell lung cancer patients receiving carboplatin at AUC 11 and paclitaxel  $175 \text{ mg}/\text{m}^2$  [69] showed that patients who received PEG-rHuMGDF and G-CSF had higher platelet count nadirs than did placebo-treated patients ( $89,000/\text{mm}^3$  vs  $27,000/\text{mm}^3$ ). Cytokine-supported patients required fewer platelet transfusions in the first two chemotherapy cycles, but thrombocytopenia became dose limiting in both groups in later cycles.

Basser and colleagues [70] examined the efficacy of PEG-rHuMGDF versus placebo in 68 patients with advanced cancer receiving carboplatin and cyclophosphamide. PEG-rHuMGDF was given after the second and subsequent cycles of chemotherapy. The platelet nadir was higher and the duration of grade 3 or 4 thrombocytopenia shorter in patients who received PEG-rHuMGDF; however, maintenance of dose intensity was possible only for a limited number of cycles, even in the cytokine-supported group. Of note, in all three studies, the non-hematologic side effects were comparable for the PEG-rHuMGDF and the placebo groups, with the exception of one patient who developed a diffuse, pruritic grade 2 maculopapular rash that resolved with antibiotic treatment and discontinuation of PEG-rHuMGDF [68].

## Conclusions

In this overview of the hematotoxicity of cancer chemotherapy, we have attempted to address the frequency and clinical significance of neutropenia, anemia, and thrombocytopenia with the goal of providing the reader with evidence-based guidelines, derived from rigorous clinical trials, for the use of cytokine growth factors and transfusion support. The appropriate use of high-dose chemotherapy, especially for recurrent hematologic malignancies, although a topic beyond the scope of this review, clearly increases the need for close attention to the amelioration of hematologic toxicities. Additionally, as discussed above, the use of dose-dense therapy in lymphoma and breast cancer may be increasing in practice and is highly dependent upon the appropriate and judicious use of cytokine support. Though these supportive agents may be relatively non-toxic, it is important to understand their potential side effects and to use them only when warranted by evidence-based studies.

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## PEER VIEW POINT

Commentary by Howard Ozer, MD, PhD and  
Shubham Pant, MD

Chemotherapy-induced hematopoietic toxicity is multifactorial in nature and has a significant effect on the treatment of cancer patients. Such toxicity often leads to postponement of chemotherapy cycles, decreases in dosage, and discomfort for the patient.

Anemia induced by chemotherapy is affected by the type of agents used, their schedule of administration, and their intensity. A cancer patient who presents with anemia should undergo a complete work-up, including iron studies, and treatment should be initiated for reversible causes of the anemia. The main treatment options are transfusions, erythropoietin (epoetin alfa [Epoen, Procrit]), and darbepoetin alfa (Aranesp). The use of transfusions as treatment for cancer-associated anemia has been decreasing due to concern about transfusion reactions, risk of infection, and the cost associated with transfusions.

### ERYTHROPOIETIN

Erythropoietin was first approved by the US Food and Drug Administration (FDA) in 1989 for anemia of chronic renal failure. Its use in cancer patients has been evaluated in several well-designed trials, with the endpoints being hemoglobin response (defined as an increase in hemoglobin level of at least 2 g/dL or attainment of an absolute hemoglobin concentration of 12 g/dL), decreased need for transfusions, and improvement in patients' quality of life. For a cancer patient, erythropoietin is recommended when the hemoglobin level falls to less than 10 g/dL, with transfusion as an option, depending upon the clinical presentation of the patient.

In this issue of *The Journal of Supportive Oncology*, Capo and Waltzman have reviewed the positive effect of erythropoietin on improvement in quality of life of cancer patients as measured by tools like EORTC QLQ-C30, which consists of 30 questions related to quality-of-life parameters like eating, dressing, nausea, constipation, etc, and others like the Linear Analog Self-Assessment (LASA) questionnaire. Conversely, the guidelines developed by the American Society of Clinical Oncology recommend further investigation due to the variety of assessment tools applied in different studies and the methodolog-

ical difficulties encountered in conducting some of these studies [1]. Studies utilizing a new tool, the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale, reported better quality of life and functional well-being in patients with hemoglobin levels higher than 12 g/dL [2].

However, large randomized trials have failed to show a benefit for erythropoietin in patients with hemoglobin levels between 10 and 12 g/dL. Use of erythropoietin in such patients and in patients who are at increased risk for complications of anemia, such as the elderly or those with coronary artery disease, should be based on clinical judgment.

The usual dosage of erythropoietin in the clinical setting is 40,000 U/week, based on ease of administration, although most of the clinical trials have employed (and shown a benefit with) a dosage schedule of 150 U/kg 3 times a week, as recommended in the FDA-approved package insert. Gabrilove et al [3] reported similar efficacy with weekly dosing of erythropoietin in a large, non-randomized, community-based trial. The dose of erythropoietin is escalated to 300 or 600 U/kg (when starting at 150 U/kg) or from 40,000 to 60,000 U if the increase in hemoglobin level is no greater than 1 g/dL by 4 weeks of treatment. If the hemoglobin value fails to rise by 1 g/dL by 8 weeks, the erythropoietin should be discontinued and other causes of anemia, such as tumor progression, should be investigated. Once the hemoglobin level is above 12 g/dL and the chemotherapy regimen has been concluded, the general view is that erythropoietin should be discontinued until the hemoglobin level falls. No large-scale study has reported a benefit from keeping the hemoglobin concentration above 12 g/dL.

### DARBEPOETIN ALFA VS ERYTHROPOIETIN

Darbepoetin alfa contains two additional carbohydrate chains, a total of 22 additional sialic acid residues, leading to an increase in half-life over that of erythropoietin. Anemic lung cancer patients receiving chemotherapy and darbepoetin alfa once weekly needed statistically fewer transfusions, were less fatigued, and had higher hemoglobin concentrations than patients who received placebo [4]. Darbepoetin alfa also has been evaluated on an every-2-week dosing schedule, compared with weekly dosing of erythropoietin. A dose of 3 µg/kg of darbepoetin alfa

Capo  
Waltzman

every 2 weeks was found to be as effective as erythropoietin 40,000 U/week, with no new side effects [5]. Trials of darbepoetin alfa given once every 3 weeks and once every 4 weeks are currently under way, but other than in abstract form, no large studies have yet been published.

Reported side effects of darbepoetin alfa are fever, nausea, and constipation in both the placebo and experimental treatment arms. Front-loading dosing of darbepoetin alfa also is being studied, with preliminary data indicating that its administration weekly for 4 weeks followed by a lower dose appears to be efficacious and may decrease the time to response relative to treatment with epoetin alfa [6].

#### MANAGEMENT OF NEUTROPENIA

Neutropenia is one of the most problematic hematologic toxicities and is associated with significant mortality and morbidity. Its severity is classified into four grades, with grade 4 representing an absolute neutrophil count  $< 500/\text{mm}^3$ . In patients receiving non-myelosuppressive therapy, the use of colony-stimulating factors (CSFs) for primary prophylaxis cannot be justified on the basis of cost savings. Current ASCO guidelines recommend primary prophylaxis for chemotherapy regimens with an expected incidence of febrile neutropenia of at least 40%, although rising costs in treating febrile neutropenia may result in lowering this threshold.

Primary prophylaxis also may permit completion of a chemotherapy regimen at full dose intensity in special circumstances, such as when comorbid conditions exist in patients who had prior chemotherapy or radiotherapy, and in treating the elderly (defined as 60 years of age and older). However, such prophylaxis has failed to demonstrate any benefit in overall survival [7].

For patients who have experienced a prior episode of febrile neutropenia, dose reduction, except in curable tumors such as germ-cell tumors, is a viable alternative to the use of CSFs. The principal reason for intervention with CSFs has been to avoid delays or modification in chemotherapy doses, but studies have failed to demonstrate disease-free or overall survival benefits in cases where the dose of chemotherapy was maintained and secondary prophylaxis was instituted. There have been no data to support the routine administration of CSFs in afebrile neutropenic patients, and the current standard of care is to observe such

patients closely and treat them with broad-spectrum antibiotics if they develop fever. The only advantage in administering CSFs has been a reduction in the duration of neutropenia by a day or two, but without other clinical benefits.

As mentioned by Capo and Waltzman, dose-dense therapy is currently under intense investigation, with the thought that more frequent administration of cytotoxic therapy would be a more efficient way of minimizing residual tumor burden than dose escalation. This has been demonstrated in a few randomized trials [8, 9], most of which revealed a statistically significant increase in survival with dose-dense regimens. One of the trials also randomized patients to receive dose-dense chemotherapy with and without granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine, Prokine]) but failed to demonstrate a difference in any clinically significant outcomes [10].

Pegfilgrastim (Neulasta) is produced by covalently binding a 20-kDa polyethylene glycol molecule to the *N*-terminus of filgrastim (Neupogen), extending its half-life to more than three times that of filgrastim. Two randomized, blinded trials in breast cancer comparing daily dosing of filgrastim to a one-time dose of pegfilgrastim concluded that one injection of pegfilgrastim provided neutrophil support with safety and efficacy similar to those provided by daily injection of filgrastim [11, 12]. The adverse effects were similar in both treatment groups, the most common being skeletal pain.

The main complication of chemotherapy-induced thrombocytopenia is hemorrhage. Currently, a platelet count of  $10,000/\text{mm}^3$  is the cut-off point to transfuse in the absence of clinical signs of bleeding. Hematopoietic growth factors that accelerate platelet recovery include interleukin-11 (oprelvekin [Neumega]) and thrombopoietin.

A long-acting form of recombinant human thrombopoietin called PEG-rHuMGDF has been tested in clinical trials. These studies have demonstrated an improvement in the platelet nadir, with platelet counts returning to baseline more rapidly after treatment with PEG-rHuMGDF than after treatment with placebo [13–15], but statistically significant benefits—decreased need for platelet transfusions or shorter hospital stays—still remain to be demonstrated in well-designed trials. The treatment side-effect profile in patients

receiving PEG-rHuMGDF was similar to that in patients given placebo.

In conclusion, the treatment of hematologic toxicities should be a combination of clinical correlation and evidence-based guidelines.

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