

2000 Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Clinical Practice Guidelines

By Howard Ozer, James O. Armitage, Charles L. Bennett, Jeffrey Crawford, George D. Demetri, Philip A. Pizzo, Charles A. Schiffer, Thomas J. Smith, George Somlo, James C. Wade, James L. Wade III, Rodger J. Winn, Antoinette J. Wozniak, and Mark R. Somerfield for the American Society of Clinical Oncology Growth Factors Expert Panel

THE AMERICAN Society of Clinical Oncology (ASCO) published evidence-based clinical practice guidelines for the use of hematopoietic colony-stimulating factors (CSFs) in 1994. ASCO guidelines are updated on a regular basis by a Review Committee of the original expert panel. The CSF guidelines were updated by the full expert panel in 2000.

For the 2000 update, an update committee, composed of members from the full panel and selected ad hoc members, was formed to complete the review and analysis of data published since 1994. Computerized literature searches of MEDLINE and CancerLit were performed. The key phrases granulocyte-macrophage colony-stimulating factors, granulocyte colony-stimulating factors, and clinical trials were used in searches of the published English-language literature from 1994 to 1999.

The Update Committee had two face-to-face meetings to consider the evidence for each of the 1996 recommendations. The guideline was circulated in draft form to the update committee and to the full expert panel for review and

approval. Each guideline from the 1996 update is listed below, followed by the 2000 update, and the 2000 recommendation.

SUMMARY OF RELEVANT BACKGROUND DATA

Myelotoxicity of Standard Chemotherapy Regimens

To determine the need for primary administration of colony-stimulating factors (CSFs), one must decide whether the risk of neutropenia associated with a particular chemotherapy regimen warrants CSF use. Table 1 lists a number of the commonly used chemotherapies usually given without CSF support (except when indicated) and the reported rates of neutropenia, fever, and sepsis. Table 1 is an updated version of Table 3 of the original CSF guidelines published in 1994. Many new chemotherapeutic agents, including the taxanes, topoisomerase-1 inhibitors, and vinorelbine, have been used as part of regimens in the 1990s. Whenever possible, large clinical trials are referenced as well as studies that represent current trends in treatment (eg, 3-hour instead of 24-hour paclitaxel administration).

As before, these trials focus on the results of overall treatment rather than on hematologic and infectious side effects. As a consequence, these data suffer from differences in the definition of infectious complications as well as from underreporting of febrile episodes. Despite these limitations, few of these common chemotherapy regimens produce significant complications related to neutropenia. It should be noted that when chemotherapy is given for treatment of relapsed or refractory disease, it is more likely to produce neutropenia (eg, topotecan in relapsed small-cell carcinoma of the lung).

Impact of CSFs on Economics of Febrile Neutropenia

The routine use of CSFs for primary prophylaxis cannot be justified on the basis of cost savings with any routine chemotherapy. Cost analyses have shown that CSFs save money when the risk of febrile neutropenia (FN) is greater than 40%,^{35,36} but no routine regimens have rates greater than 15%. This analysis was sometimes confused with the initial CSF guideline that used a 40% rate of FN as a *clinical*

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**The American Society of Clinical Oncology considers adherence to these guidelines to be voluntary. The ultimate determination regarding their application is to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative and novel therapies for this symptom in which better treatment is of paramount importance. In that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.*

Address reprint requests to American Society of Clinical Oncology, 1900 Duke St, Suite 200, Alexandria, VA 22314; email guidelines@asco.org.

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threshold for use of CSFs, based on the observed rate of neutropenia seen in the initial randomized trials used for Food and Drug Administration licensing in the United States.

The economic models used costs of hospitalization for FN of \$10,000; if the costs were much lower, as with early-discharge models or outpatient treatment models, the rate of FN would have to be much higher to offset the costs of using CSFs. Alternatively, CSFs could be justified if they cost substantially less. The use of CSFs at a much lower dose (eg, 2 $\mu\text{g}/\text{kg}$ instead of 5 $\mu\text{g}/\text{kg}$), which is promising but needs confirmation,³⁷ would lower the cost.

For secondary prophylaxis, the rate of FN could be 40% and could justify use of CSF, but dose modification would be a medically acceptable alternative because no major clinical benefit of maintaining delivery of previously toxic levels of chemotherapy with CSF use has been shown. A recent decision analysis model showed acceptable cost-effectiveness of CSFs to maintain dose-intensity in adjuvant therapy for breast cancer,³⁸ but CSFs are rarely needed for four cycles of doxorubicin and cyclophosphamide, and no benefit has been found to date even for escalated doses of doxorubicin³⁹ with CSF support.

A major advance would be a model to predict who will develop FN, so that CSF use could be restricted to that group. At present, it is not possible to predict who will develop FN and who would therefore benefit from prophylaxis with CSFs. Current models are promising but need prospective validation. Some possible predictors include a high risk of FN of 49% (23 of 47 patients) if the absolute lymphocyte count is less than 700/ mm^3 , compared with 11% (seven of 65 patients) if the absolute lymphocyte count is greater than 700/ mm^3 .⁴⁰ Similarly, others have proposed that the risk of FN is higher in adjuvant breast cancer chemotherapy if the hemoglobin or absolute neutrophil count (ANC) falls during the first cycle of chemotherapy.³⁶

SPECIFIC GUIDELINES

1. Guidelines for Primary Prophylactic CSF Administration

Definition of the Problem

Neutropenia and infection are major dose-limiting side effects of chemotherapy. The risk of initial infection and subsequent complications are directly related to the depth and duration of neutropenia.⁴¹ The magnitude of neutropenia depends on the intensity of the chemotherapy regimen. In addition, a number of host- and disease-related factors that are only partially characterized may also influence the risks of neutropenia in the patient receiving chemothera-

py.⁴²⁻⁴⁴ Because fever may be the first and only manifestation of infection, it has been standard practice for all patients who present with fever in the setting of neutropenia to receive broad-spectrum antibiotics.⁴² Usually this has been accompanied by hospitalization, although certain favorable subgroups of patients may possibly be treated as outpatients.⁴⁵ Traditionally, patients have remained hospitalized, on antibiotic therapy, until fever and any sign of active infection have resolved and the ANC has recovered.

Clinical Outcomes

In current practice, infectious mortality resulting from FN is low, and the incidence of FN with common chemotherapy regimens (with the exception of AIDS-related malignancies) seldom exceeds 25% to 40% in chemotherapy-naïve patients (Table 1). However, the average length of hospitalization for FN can exceed 1 week,^{21,43,46,47} during which time patients undergo numerous diagnostic procedures and intravenous (IV) antibiotic support with the attendant potential complications of such therapy. In addition to the impact on quality of life for the patient, episodes of FN may result in subsequent chemotherapy delays or dose reductions. Avoiding the occurrence of FN by use of a CSF might therefore be expected to enhance patient quality of life, reduce hospital costs, and improve chemotherapy delivery. Nonetheless, the incidence of FN depends entirely on the dose-intensity of the chemotherapy regimen, on the prior history of the patient population, and on the presence or absence of other comorbid conditions. Although it is now well established that primary prophylaxis with a CSF can reduce the incidence of FN by as much as 50%,⁴⁸⁻⁵³ in the absence of benefits in survival or response, such reductions can only have a significant impact on patient outcomes when improved clinical outcomes justify the costs of CSF administration. By design, primary prophylaxis results in unnecessary treatment of at least 50% of patients who would not have experienced FN on standard chemotherapy regimens, thus further hampering any cost benefit of CSF prophylaxis.

Alternative Approaches

Alternative approaches for avoiding an initial episode of FN remain limited. Prophylactic antibiotics continue to be used, particularly with high-dose chemotherapy regimens in hematologic malignancies,⁴⁸ but a positive clinical impact has not been universally documented.⁴⁹ Moreover, there is serious concern regarding the emergence of resistant microorganisms when prophylactic antibiotics are administered. Accordingly, the Infectious Disease Society of America does not recommend routine antibiotic prophylaxis, especially with fluoroquinolones.⁵⁴ Other strategies have in-

Table 1. Incidence of Hematologic and Infectious Toxicities Associated With Selected Chemotherapy Regimens

Cancer Histology (ref)	Stage and Prior Therapy	Regimen	No. of Patients	Leukopenia* (grade 4) (%)	Neutropenia* (grade 4) (%)	Febrile Neutropenia (%)	Fever† (grade \geq 2) (%)	Infection‡ (grade \geq 3) (%)	Infectious Death (%)
Adult AML ¹	Newly diagnosed	Ara-C/DNR	163	93	—	—	37 (no infection)	64	12
AIDS-related:									
Kaposi's Sarcoma ^{2,3}	Advanced	ABV	31	—	—	6	—	61	—
		Lipo Dox	34	—	35 (3+4)	—	—	24	—
		VP-16	41	—	—	7	—	17	—
NHL ^{4,5}	Intermediate- and high-grade, untreated	CHOP \pm GM-CSF	30	—	—	80-82	—	—	13
Bladder ⁶⁻⁸	Advanced, no prior systemic therapy	m-BACOD (modified) \pm GM-CSF M-VAC	198 126	— 24	22-36 (all cycles)	—	—	—	— 3
Breast ⁹⁻¹³	Adjuvant	CBDCA/Pac ITP (+ G-CSF) CAF	36 30 1572	— — 21 (arm 1) 1 (arm 2)	47 40	— 17 4 (arm 1)	— — —	1 pt — —	— — 1 pt
Colorectal ¹⁴⁻¹⁶	Adjuvant advanced	5-FU/LV/L 5-FU/LV	1492 116	0.3 24-34 (3+4)	— 50-67 (3+4) 11 (all cycles) 79 (all doses)	— 2-4 38 23	5.5 — — —	2.4 15-23 (any grade) 16 —	0 1 pt each arm — — 1 pt 1 pt each dose
Germ cell ^{17,18}	Advanced relapsed	CPT-11 PEB	189 77	— 16	22 (3+4)	3	— —	— 3	1 pt 0
Head/neck ^{19,20}	Recurrent; metastatic	VelP 5-FU/CBDCA	124 86	— 2.3	— 1.2	73	—	—	— 1.2
Lung ²¹⁻²⁶	Extensive SCLC, no prior treatment	CBDCA/Pac CDDP/VP-16	41 159	5 14	— 38	—	—	—	1 pt \leq 6 (all toxic deaths)
	Newly diagnosed SCLC	CAV CAE	156 102	28 —	52 98 (1st cycle)	— 57 (1st cycle)	— 61	16 13.3 (culture +; all cycles)	\leq 4 (all toxic deaths) 2.9
	Recurrent Advanced NSCLC, no prior treatment	Topo CDDP/VNR	107 206	— —	69 (38% cycles) 59	77 (all cycles) 10	— —	— —	4 pt 2 pt
		CBDCA/Pac CDDP/Gem	49 48	30 (all doses) (all cycles) 0	— 6	— 0	— —	— 0	— 0

Table 1. (Continued)

Cancer Histology (ref)	Stage and Prior Therapy	Regimen	No. of Patients	Leukopenia* (grade 4) (%)	Neutropenia* (grade 4) (%)	Febrile Neutropenia (%)	Fever† (grade ≥ 2) (%)	Infection‡ (grade ≥ 3) (%)	Infectious Death (%)
Lymphoma ^{27,28}	Relapsed HD; prior RT only	MOPP	123	17	22	—	3 (no infection)	13	1
	Relapsed HD; prior RT only	ABVD	115	3	3	—	5 (no infection)	2	0
	Intermediate-, high-grade NHL; no prior treatment	CHOP	216	25	22	—	—	5 (≥ grade 4)	1
Multiple myeloma ^{29,30}	Untreated	VAD	169	—	—	—	—	—	2 pts
	Recurrent	VAD	29	1,700/μL median	—	—	40	27.6	—
	Suboptimal, stage III, IV	CDDP/Pac	184	—	78	—	<1	—	2.2 (all toxic deaths)
Ovary ³¹⁻³³	Salvage	CBDCA/Pac	39	—	20 (all cycles)	3 pts (all doses)	—	—	—
	Advanced, untreated	Topo	452	32	81	26	—	—	—
	Advanced, untreated	AD	186	32	38	—	—	—	0
Sarcoma ³⁴	Advanced, untreated	MAID	188	86	79	—	—	—	3.5

NOTE: See cited publications for information regarding chemotherapy agents, doses, and schedules.

Abbreviations: —, no information; Ara-C, cytarabine; DNR, daunorubicin; ABV, doxorubicin, bleomycin, vinblastine, lipo Dox, liposomal doxorubicin; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; m-BACOD, bleomycin, cyclophosphamide, doxorubicin, vincristine, dexamethasone, methotrexate; M-VAC, methotrexate, vinblastine, doxorubicin, cisplatin; CBDCA/Pac, carboplatin, paclitaxel; ITP, ifosfamide, paclitaxel, cisplatin; CAF, cyclophosphamide, doxorubicin, fluorouracil; AC, doxorubicin, cyclophosphamide; Pac, paclitaxel; Doc, docetaxel; AT, doxorubicin, paclitaxel; 5-FU/LV/L, fluorouracil, leucovorin, levamisole; CPT-11, irinotecan; PEB, cisplatin, etoposide, bleomycin; Velp, vinblastine, ifosfamide, cisplatin; CDDP/VP-16, cisplatin, etoposide; CAV, cyclophosphamide, doxorubicin, vincristine; CAE, cyclophosphamide, doxorubicin, etoposide; Topo, topotecan; CDDP/VNR, cisplatin, vinorelbine; CDDP/Gem, cisplatin, gemcitabine; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; VAD, vincristine, doxorubicin, dexamethasone; AD, doxorubicin, dacarbazine; MAID, mesna, doxorubicin, ifosfamide, dacarbazine.

*Grade 4 leukopenia: WBC count < 1,000/μL; grade 4 neutropenia: absolute neutrophil count < 500/μL.

†Common toxicity criteria fever ≥ grade 2: ≥ 38.1°C (≥ 100.5°F).

‡Infection ≥ grade 3: systemic infection requiring hospitalization.

volved initial chemotherapy dose reduction or the use of an alternative, less myelosuppressive chemotherapy regimen in the high-risk patient. The introduction of novel chemotherapy and biologic agents or combinations in the 6-year period since the American Society of Clinical Oncology (ASCO) guidelines were first published has not resulted in an increase in the incidence of FN for initial therapy of any malignancy.

General Circumstances

1996 Recommendation. Primary administration of CSFs was shown to reduce the incidence of FN by approximately 50% in the three major randomized trials in adults in which the incidence of FN was greater than 40% in the control group. The value of primary CSF administration has not been clearly established in less myelosuppressive regimens, and the cost benefit of primary versus secondary administration for the majority of initial chemotherapy regimens is unproven. It is recommended that primary administration of CSFs be reserved for patients expected to experience levels of FN that are at least comparable to or greater than those seen in control patients in these randomized trials, ie, an expected incidence $\geq 40\%$. Thus, for previously untreated patients receiving most chemotherapy regimens, primary administration of CSFs cannot be recommended.

2000 Update. Routine use of CSFs for primary prophylaxis of FN for any common disease in previously untreated patients is not justified by the existing data. CSFs have had a disappointingly small impact to date on disease-free and overall survival.^{50,51} It was anticipated that CSF use might result in an improved cure rate, particularly for chemosensitive tumors such as non-Hodgkin's lymphoma (NHL), small-cell lung cancer, testicular cancer, and breast cancer. For the most part, either this has not been tested adequately or no impact has been found.

In several of the trials that initially described a reduction in the incidence of FN (with no impact on survival), the regimens created excess FN and are considered too toxic without significantly improved anticancer efficacy to justify current routine clinical use.^{52,53} For example, in the largest trial of CSFs in metastatic small-cell lung cancer, the rate of FN was 40% for the control arm⁴⁵; a rate of 10% or less would be expected with current regimens. This topic has recently been reviewed in detail.^{50,51}

Similar initial data in NHL also suggested the potential for lessened FN despite increased dose-intensity.⁵⁵ However, the increase of approximately 10% in dose-intensity has not resulted in an increase of either disease-free or overall survival, either because the benefit is too small (< 5%) or because this degree of increased dose-intensity does

not convey a survival advantage, even in this very chemosensitive tumor. As indicated in Table 1, however, CSFs may permit completion of chemotherapy in patients with special circumstances, such as those with AIDS-related NHL or the elderly, but they still do not provide a benefit in clinical outcome, such as improved survival. Similar comments apply to patients undergoing treatment for Hodgkin's disease.^{50,51} Although CSFs may allow completion of therapy in patients with special circumstances and may reduce the duration and severity of neutropenia in this setting, significant differences in delivered dose-intensity, hospitalizations, infections, and survival have not been determined in this population.

Phase II and III data in testicular and nonseminomatous germ cell tumors also demonstrate no difference in overall or disease-free survival.⁵² CSF use allowed completion of a full six cycles of chemotherapy, with fewer toxic deaths among the high-risk group of patients, but again with no impact on overall survival.⁵³ This suggests that those patients may be considered under the heading of "Special Circumstances" and may thus benefit from CSF use by exception.

In the setting of breast cancer, there are, to date, no prospective, multicenter randomized data demonstrating an improvement in disease-free or overall survival by increasing the dose of doxorubicin beyond $60 \text{ mg/m}^2 \times 4$ ⁵⁵ or by applying dose-intensive chemotherapy.⁵⁶⁻⁵⁹ One must await further maturation of data from already-completed and ongoing randomized trials in order to better assess the effect of high-dose chemotherapy on outcome. There are no direct data supporting a benefit for maintaining dose-intensity.

The available data indicate that, with a sufficiently high incidence of FN ($\geq 40\%$), there is strong evidence for the primary administration of CSFs to reduce hospitalization for antibiotic administration. Cost-effectiveness modeling also suggests that, depending on local cost factors, CSF administration may provide therapeutic savings if the expected incidence of FN is at least 40%, but only in high-risk patients or those requiring prolonged hospitalizations sufficient to exceed 10 to 14 days of CSF administration. In patients receiving more typical routine initial chemotherapy (the vast majority of newly diagnosed patients), CSF use for primary treatment cannot be recommended on either clinical or economic grounds. Primary administration of CSFs should be reserved for only those patients who are considered at high risk for FN due to special circumstances. Even in this patient population, the treating physician should be aware that the data are primarily modest for improved clinical outcomes (complications of FN) or economic benefit and that, because there are no data demonstrating an improvement in response or survival, dose reduction and

schedule modification remain acceptable alternatives to the increased cost incurred by use of CSFs.

2000 Recommendation. No change.

Special Circumstances

1996 Recommendation. Clinicians may occasionally be faced with patients who might benefit from relatively nonmyelosuppressive chemotherapy but who have potential risk factors for FN or infection because of bone marrow compromise or comorbidity. It is possible that primary CSF administration may be exceptionally warranted in patients at higher risk for chemotherapy-induced infectious complications, even though the data supporting such use are not conclusive. Such risk factors might include the following: pre-existing neutropenia due to disease, extensive prior chemotherapy, or previous irradiation to the pelvis or other areas containing large amounts of bone marrow; a history of recurrent FN while receiving earlier chemotherapy of similar or lesser dose-intensity; or conditions potentially enhancing the risk of serious infection, eg, poor performance status and more advanced cancer, decreased immune function, open wounds, or already-active tissue infections. This is not meant to be an all-inclusive list; it is anticipated that, depending on the unique features of the clinical situation, there will be instances when the administration of a CSF will be appropriate outside of uses recommended in other guidelines.

2000 Recommendation. No change.

2. Guidelines for Secondary Prophylactic CSF Administration

Definition of Problem

The rationale for secondary CSF administration in patients with a prior episode of FN is two-fold. It may direct the use of the CSF to a more restricted subset of patients who are most likely to benefit from CSF support. In addition, such a strategy can prevent the use of a CSF in many patients who might not need CSF support at all but who would nevertheless experience the inconvenience and cost of CSF support.

Clinical Outcomes

In providing secondary administration of a CSF, there is the expectation that subsequent neutropenic complication of chemotherapy may be circumvented. In addition, secondary administration may allow chemotherapy dose maintenance, which is important if it improves overall survival, disease-free survival, quality of life, toxicity, or cost-effectiveness.

Alternative Approaches

The principle alternative to intervention with a CSF has been chemotherapy dose modifications.

1996 Recommendation. There is evidence that CSF administration can decrease the probability of FN in subsequent cycles of chemotherapy after a documented occurrence in an earlier cycle. Even if FN has not occurred, the use of CSFs may be considered if prolonged neutropenia is causing excessive dose reduction or a delay in chemotherapy. However, in the absence of clinical data supporting maintenance of chemotherapy dose-intensity, physicians should consider chemotherapy dose reduction as an alternative to the use of CSFs.

2000 Update. The data supporting the use of CSFs for secondary prophylaxis are derived from the small-cell lung cancer trial by Crawford et al.²¹ This trial enrolled 199 patients with metastatic small-cell lung cancer, 102 of whom were treated with cyclophosphamide, doxorubicin, and etoposide and 97 of whom were treated with cyclophosphamide, doxorubicin, and etoposide followed by CSFs. Those patients in the control arm who developed neutropenic fever were allowed to receive open-label CSF as prophylaxis against infection for subsequent cycles of chemotherapy. Those patients who were treated with open-label CSF in this part of the study had a shorter duration of neutropenia (6 days in cycle 1 and 2.5 days in cycle 2 with CSF) and a reduction in the rate of fever with neutropenia (100% during cycle 1 and 23% during cycle 2), despite receiving the same doses of chemotherapy for both cycles. For patients on the placebo arm who did not develop neutropenic fever on cycle 1, and who continued on placebo, the duration of neutropenia was similar to that in cycle 1. Patients who remained on placebo had a continuing low rate of FN (5%) that was even lower than that of patients who crossed over and were receiving CSF. Thus, the results of this one study provide some evidence of improved incidence of FN in patients with a prior episode of FN.

2000 Recommendation. In the setting of many tumors exclusive of curable tumors (eg, germ cell tumors), dose reduction after an episode of severe neutropenia should be considered as a primary therapeutic option. No published regimens have demonstrated disease-free or overall survival benefits when the dose of chemotherapy was maintained and secondary prophylaxis was instituted. In the absence of clinical data or other compelling reasons to maintain chemotherapy dose-intensity, physicians should consider chemotherapy dose reduction after neutropenic fever or severe or prolonged neutropenia after the previous cycle of treatment.

3. Guidelines for CSF Therapy

Definition of the Problem

Patients with neutropenia are predisposed to infection because of the absence of granulocytes, the disruption of the integumentary, mucosal, and mucociliary barriers, and because of the inherent microbial flora shifts that accompany severe illness and antimicrobial usage.^{42,60} CSFs were licensed to reduce the likelihood of patients developing fever and neutropenia. A 1994 survey of CSF use found that 34% of physicians surveyed would administer a CSF to afebrile patients diagnosed with neutropenia.⁶¹ Seventy-three percent of surveyed physicians would use CSFs in conjunction with IV antimicrobial agents after the onset of fever and neutropenia. Some physicians have initiated a CSF later in the infection course when the patient has failed to show clinical improvement or when the cause of the infection is associated with a poor outcome (ie, invasive fungal infection, antibiotic-resistant bacteria).

Clinical Outcomes

The goals of therapeutic intervention with the CSFs are to reduce the incidence of infectious episodes and infection-related morbidity and mortality. This improvement in supportive care could potentially enhance a patient's quality of life by reducing the incidence and duration of hospitalization and antibiotic use, but the cost and toxicity of CSF therapy should be considered in all treatment decisions.

Alternative Approaches

The traditional alternative to prophylactic or therapeutic CSF administration has been to manage patients with neutropenia by monitoring temperature and ANC and by initiating empiric, broad-spectrum antibiotics if fever develops.^{54,62} Patients with neutropenia and fever have often been hospitalized for empiric antibiotic therapy until infection and neutropenia have resolved completely. This approach has been very successful, with a low incidence of infection-related mortality. Recent studies of infection risk have now defined lower-risk patients who may be suitable for outpatient or home antibiotic therapy.^{44,45,63}

A. Afebrile Patients

1996 Recommendation. Data are inadequate in regard to whether patients with neutropenia but no fever will benefit clinically from the initiation of a CSF at the time neutropenia is diagnosed; intervention with a CSF in afebrile neutropenic patients is not recommended.

2000 Update. Two small studies using CSFs in patients who were afebrile but neutropenic were reviewed in the 1994 version of the ASCO recommendations for the use of

hematopoietic CSFs.^{64,65} These studies failed to show clinical benefit, and despite being randomized, both included significant study design defects. A large randomized study has subsequently been reported.⁶⁶ This trial assessed the effect of granulocyte CSF (G-CSF) treatment on severe, chemotherapy-induced neutropenia in afebrile adults with cancer. All 138 patients had solid tumors or lymphoma and were randomized to receive CSF or placebo. The time to neutrophil recovery of more than 500/ μ L was 2 days shorter for G-CSF-treated patients (2 v 4 days), but this statistical difference was not accompanied by any apparent clinical benefit. The need for hospitalization, the number of days in the hospital, the number of days of parenteral antibiotic treatment, and the number of culture-positive infections were not reduced. The neutropenia in these patients was profound but short. Recent clinical data do not show clinical benefit for the routine uses of CSFs in afebrile patients at the time that neutropenia is diagnosed.

2000 Recommendation. Current evidence supports the recommendation that CSFs should not be routinely used for patients with neutropenia who are afebrile. The strength of this recommendation has increased with the trial reported in 1997.⁶⁶

B. Febrile Patients

1996 Recommendation. For the majority of patients with FN, the available data do not clearly support the routine initiation of CSFs as adjuncts to antibiotic therapy. However, certain FN patients may have prognostic factors that are predictive of clinical deterioration, such as pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), or fungal infection. The use of CSFs together with antibiotics may be reasonable in such high-risk patients, even though the benefits of administration under these circumstances have not been definitively proven.

2000 Update. Eight prospective, randomized, controlled trials have been completed evaluating G-CSF, granulocyte-macrophage CSF (GM-CSF), or both as adjunct therapy for patients with chemotherapy-induced fever and neutropenia.⁶⁷⁻⁷⁴ Six of these trials were placebo-controlled, four were double blind, and six provide strong evidence regarding clinical benefit (Table 2).

The largest trial was a study conducted in Australia and evaluated patients with fever and neutropenia who had received chemotherapy for treatment of solid tumors, lymphoma, or acute lymphoblastic leukemia (ALL).⁶⁷ Study participants were treated with IV antibiotics and then randomized to receive G-CSF 12 μ g/kg/d or placebo. The results of this trial were reviewed as part of the evidence included in the 1994 ASCO CSFs guideline.⁷⁵ The duration of neutropenia (ANC < 500/ μ L) was 1 day shorter for

Table 2. CSF Therapy of Fever and Neutropenia: Results of Randomized Trials

	Solid Tumor, NHL, ALL ⁶⁷ (n = 216)		Pediatric ⁶⁸ (n = 186)		Hematologic & Solid Tumor ⁶⁹ (n = 134)		Solid Tumors, Leukemia, Lymphoma ⁷⁰ (n = 100)		Solid Tumor, NHL ⁷¹ (n = 121)		Solid Tumors ⁷² (n = 68)		Pediatric ALL, Solid Tumor ⁷³ (n = 58)		Solid Tumors, NHL, ALL ⁷⁴ (n = 30)	
	Filgrastim		Filgrastim		Molgramostim		Molgramostim		Filgrastim & Molgramostim		Molgramostim		Molgramostim		Regramostim	
	G-CSF 12 μg/kg/d/sq	Placebo	G-CSF 5 μg/kg/d/IV	Placebo	GM-CSF 5 μg/kg/d/sq	Placebo	GM-CSF 250 μg/m ² /d	Control	G-CSF 5 μg/kg/d	GM-CSF 5 μg/kg/d	Placebo	GM-CSF 5 μg/kg/d	Placebo	GM-CSF 5 μg/kg/d/IV	Placebo	GM-CSF Placebo
Fever*	3	3	2	3	4	3	4	4	1	2	2	2	2	2.1	2	1.5
ANC* < 500/μL	3†	4	3†	5	7	4	7	8	2†	2†	3	3†	4	4.5	6	6.3
Antibiotic therapy*	-	-	5†	6	7	5	7	7	-	-	-	5	6	7†	8.5	10.8
Hospitalization*	8	8	5†	7	-	6	-	-	5†	5†	7	6	7	9	10	-
Infectious mortality, %	7	3	-	-	2	-	2	6	5	2.5	2.5	0	1	0	0	3

*Median duration in days.

†Statistically significant, p < .05.

‡Dash (-) indicates that no data were reported.

G-CSF recipients, but there was no clinical improvement in days of fever, duration of antibiotic therapy, or hospitalization. The beneficial effect of G-CSF on neutrophil recovery was most evident among patients with solid tumors who were more than 10 days from completion of chemotherapy when they became febrile. There was a suggestion that there were fewer protracted hospital admissions among G-CSF-treated patients.

Similar clinical results have been reported by four other studies conducted among adult patients.^{69-71,74} The largest of these studies evaluated 134 patients with solid tumors and hematologic malignancies.⁶⁹ Patients were randomly assigned to receive GM-CSF at a dose of 5 μg/kg/d or placebo. GM-CSF administration was not associated with a statistically significant decrease in the duration of hospitalization. Quality-of-life indicators, including limitation of mobility, emotional distress, and decreased energy, were reported more frequently among GM-CSF recipients than among those who received placebo. The trial from Spain enrolled 121 patients and used a three-arm design with both G-CSF and GM-CSF.⁷¹ CSF-treated patients had a statistically significant decrease in the duration of neutropenia (ANC < 500/μL) and the duration of hospitalization. There was a slight trend toward increased infection-related mortality among G-CSF recipients. The trial conducted in Houston enrolled 100 patients and compared GM-CSF recipients to untreated control subjects.⁷⁰ This trial included a subset analysis, which reported that those patients with pneumonia, cellulitis, abscess, or sinusitis had improved response rates (100% v 59%) when antibiotic therapy was combined with GM-CSF.

The group from France performed a randomized, unblinded trial of 68 adult patients with fever and neutropenia.⁷² GM-CSF treatment reduced the median duration of neutropenia (ANC < 500/μL), days of antibiotic therapy, and duration of hospitalization by 1 to 1.5 days. The greatest benefit for GM-CSF therapy was seen for patients who had received chemotherapy that was considered to have less than a 15% risk of inducing fever during the neutropenic period.

Studies among pediatric patients have shown some clinical benefit. The largest pediatric trial enrolled 186 patients with leukemia, lymphoma, and solid tumors.⁶⁸ Patients were randomized to receive G-CSF at 5 μg/kg/d or placebo. G-CSF therapy reduced the median hospital stay by 2 days (5 v 7 days) and the duration of antibiotic therapy by 1 day. G-CSF therapy seemed to benefit three subgroups: (1) patients with ALL or those not receiving dose-intensive, alkylating agent-based regimens; (2) patients with early onset of fever (< 10 days) after chemotherapy completion;

and (3) those without documented septicemia or focal infection.

A second pediatric trial failed to show a decrease in the duration of neutropenia, but the duration of hospitalization was shorter for GM-CSF recipients.⁷³ In all eight adjuvant studies, the infection-associated mortality was low and unaffected by CSF therapy.

Cost analysis was performed for three of the randomized trials.^{68,69,71} The pediatric trial was a prospective analysis that included costs of hospital bed days, antimicrobial agents, blood products, parenteral nutrition, and G-CSF. The median total cost per episode of fever and neutropenia was more expensive for placebo-treated patients than for G-CSF-treated patients (\$5,169 v \$4,147), but this difference was not statistically significant. The relative hospital room costs and antimicrobial charges were significantly lower for the CSF recipients.⁶⁸ In contrast, the cost analysis performed for the other two trials reported trends toward decreased cost for placebo recipients rather than for CSF-treated patients.^{69,71}

A group from the Netherlands has developed a "Markov-type" economic model that calculates all relevant direct costs and savings of CSF therapy.³⁶ Savings associated with CSFs in this study were highly dependent on the probability of the occurrence of fever and neutropenia. This probability differs among malignancies, treatment modalities, health conditions of the patients, disease status at time of therapy, and institutional policies regarding antibiotic discontinuation and hospitalization. This model found savings only with the administration of CSFs to patients with a high risk of complicated infections.

There is some variability in outcomes among the eight published trials. These discrepancies are likely secondary to differences in patient characteristics, study design, sample size, and data analysis, as well as possible clinical differences between G-CSF and GM-CSF in this therapeutic setting. Institutional policies regarding the timing of antibiotic discontinuation or need for hospitalization may also have hampered the ability of a CSF to influence these clinical parameters. The timing of antibiotic discontinuation remains controversial. The Infectious Diseases Society of America clinical guideline recommends that antibiotics be continued for at least 7 days and until all clinical and microbiologic signs of infection have resolved and the ANC is more than 500/ μL .⁵⁴ The National Comprehensive Cancer Network (NCCN) clinical guideline recommends that the duration of antibiotic treatment be individualized but be based on neutrophil recovery, specific site of infection and pathogen, and the status of the patient's underlying disease. The NCCN guideline recommends as little as 4 days of

antibiotic therapy for some patients with an uncomplicated infection and a sustained neutrophil recovery ($\text{ANC} > 1,000/\mu\text{L}$). Recommendations that support shorter duration of antibiotic treatment, or that report success with outpatient therapy of uncomplicated episodes of fever and neutropenia, suggest a lesser chance that CSFs will be beneficial when used in low-risk patients.

Conversely, subset analysis in several of the adjunctive therapy studies suggested that certain groups of patients could benefit from adjunctive CSF therapy, but these conclusions are inconsistent. The pediatric trial reported enhanced benefit for patients with ALL or those patients who did not receive dose-intensive alkylating treatment regimens, for patients with early-onset fever (< 10 days from chemotherapy), and for patients without a documented infection site.⁶⁸ The Australian study reported benefit only for patients with solid tumors who developed fever more than 10 days after completing their chemotherapy.⁶⁷ The study from Houston reported that CSFs improved outcomes primarily for patients with documented pneumonia, cellulitis, abscess, or sinusitis.⁷⁰ The group from France reported maximum benefit from CSFs for patients receiving chemotherapy associated with a low risk of fever and neutropenia. These reported differences cannot be reconciled; they likely represent the difficulties inherent in subset analysis of small patient groups and would need to be confirmed in larger patient trials.

The risk of serious infection and poor outcome depends on the duration of profound ($\text{ANC} < 100/\mu\text{L}$) neutropenia, the degree of the therapy-induced mucosal and mucociliary barrier damage, and the specific infection pathogen (ie, invasive yeast and molds, antibiotic-resistant bacteria).⁴² Patients with these higher-risk characteristics are those who theoretically could benefit from adjunct CSF therapy, as indicated by data published in abstract form only.⁷⁶ Continued study is required to determine whether such high-risk patients can be prospectively identified and whether CSF therapy will reduce mortality, hospitalization time, and infection-associated morbidity and treatment expense.

2000 Recommendation. The collective results of the eight trials⁶⁷⁻⁷⁴ provide strong and consistent support for the recommendation that CSFs should not be routinely used as adjunct therapy for the treatment of uncomplicated fever and neutropenia. Uncomplicated fever and neutropenia are defined as follows: fever of ≤ 10 days in duration; no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan dysfunction, or invasive fungal infection; and no uncontrolled malignancies. The eight trials have consistently shown a decrease in the duration of neutropenia of less than 500/ μL , but clinical benefit has not

consistently accompanied the decreased duration of neutropenia.

Certain patients with fever and neutropenia are at higher risk for infection-associated complications and have prognostic factors that are predictive of poor clinical outcome. The use of a CSF for such high-risk patients may be considered, but the benefits of a CSF in these circumstances have not been proven. These factors include profound ($\text{ANC} < 100/\mu\text{L}$) neutropenia, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), and invasive fungal infection. Age greater than 65 years and posttreatment lymphopenia may also be high-risk factors but have not been consistently confirmed by multicenter trials.

4. Guidelines for Use of CSFs to Increase Chemotherapy Dose-Intensity

Definition of Problem

In preclinical systems, there is substantial evidence for a steep dose-response curve for many antineoplastic agents. However, clinical evidence for a dose response beyond those doses used in standard chemotherapy regimens has been variable and limited. Most clinical evidence for the importance of chemotherapy dose has been of two types. The first of these is derived from retrospective analyses of delivered dose or dose-intensity, usually as a fraction of that specified by the protocol. While intriguing, these analyses cannot definitively prove that drug dose is directly related to therapeutic effect; the alternative possibility is that toxicity leading to dose reduction acts as a marker of patients with poor prognoses and that higher doses of chemotherapy over and above that which can be delivered under normal circumstances are of no benefit. The second type of evidence comes from the retrospective analysis of published data in which regimens are allocated a dose-intensity score compared with some standard regimen. These analyses are prone to bias because of differences between protocols with respect to patient characteristics or supportive care.

In addition to the retrospective reviews of dose-intensity, there have been examples of prospective studies in which patients have been intentionally assigned lower-than-standard chemotherapy doses; the results suggest decreased disease control and worsened survival compared with those achieved with conventional doses. A few randomized clinical trials also indicate that dose-intensity greater than that of conventional therapy but less than that requiring progenitor-cell support improves disease control. One of these randomized trials in small-cell lung cancer demonstrated that dose intensification of ifosfamide/carboplatin/etoposide/vincristine to a 3-week rather than a 4-week regimen

was not associated with increased FN or sepsis but did improve survival significantly.⁷⁷ In this trial with a 2×2 factorial design, no benefit was achieved in reduction of myelosuppressive complications by the addition of GM-CSF. Collectively, both the randomized and retrospective analyses have generated interest in using the CSFs to support increased chemotherapy delivery rather than to reduce the toxicity of standard regimens.

Clinical Outcomes

It has been hoped that administration of a CSF in support of chemotherapy can result in improved chemotherapy dose-intensity and consequent increases in response rates and duration of response.

Alternative Approaches

The principal alternative to providing higher chemotherapy dose-intensity with CSF support has been the administration of standard-dose chemotherapy with dose modification for neutropenic and other toxicities.

1996 Recommendation. Outside of clinical research trials, there is little justification for the use of CSFs to increase chemotherapy dose-intensity. In settings in which clinical research demonstrates that dose-intensity therapy not requiring progenitor-cell support produces improvement in disease control, CSFs should be used when these therapies are expected to produce significant rates of FN (eg, in $\geq 40\%$ of patients).

2000 Update. Several studies have demonstrated the possibility of achieving a modest to moderate increase in dose-intensity using CSFs as an adjunct to higher-dose chemotherapy.^{76,78-84} Unfortunately, the number of randomized, multicenter clinical trials in nonhematologic malignancies that have demonstrated a survival benefit for patients receiving higher-dose therapy remains extremely limited,⁸⁵ and increased toxicity is frequent. In the absence of a greater number of positive randomized trials in specific settings, this treatment approach must be approached cautiously. In the vast majority of trials to date, increased dose-intensity has not been demonstrated to improve overall survival.

2000 Recommendation. In the absence of more trials demonstrating a favorable effect on overall survival, disease-free survival, quality of life, or toxicity, there is no justification for the use of CSFs to increase chemotherapy dose-intensity or schedule or both outside of a clinical trial. This application of CSF use remains the domain of appropriately designed clinical investigation.

5. Guidelines for Use of CSFs as Adjuncts to Progenitor-Cell Transplantation

Definition of Problem

The major complications of high-dose chemotherapy supported by autologous bone marrow transplantation (BMT) or peripheral-blood progenitor cell (PBPC) transplantation are disease recurrence, infection, the need for RBC and platelet transfusions, delayed or incomplete engraftment, organ damage from the ablative regimen, prolonged hospitalization, and the high cost of treatment. These same problems, plus graft-versus-host disease (GvHD) and graft rejection, are also present in patients undergoing allogeneic BMT.

Clinical Outcomes

CSFs have been administered after both autologous and allogeneic BMT in anticipation of reducing the severity of infectious complications and thereby decreasing hospitalization time, reducing costs, and improving quality of life. Use of the CSFs to mobilize PBPCs into the circulation for collection is expected to enhance progenitor numbers, lessen the frequency, duration, and cost of leukopheresis procedures, and potentially speed hematologic recovery after transplantation of the CSF-mobilized cells.

Alternative Approaches

The primary alternatives to administration of CSFs after cytoreduction and PBPC transplantation have been monitoring of temperature and ANC, initiation of antibiotic therapy if a fever develops, and continuation of hospitalization until satisfactory resolution of infection and neutropenia. Before CSFs were used to increase PBPC numbers, these cells were collected without CSF-assisted mobilization, either by performing multiple leukophereses in steady state or by using high doses of chemotherapy alone to force progenitor cells into the blood for collection.

1996 Recommendation. CSFs can successfully shorten the period of neutropenia and reduce infectious complications in patients undergoing high-dose cytotoxic therapy with autologous BMT. CSFs are effective in mobilizing autologous PBPCs for transplantation, and autologous PBPC transplantation has been shown to lead to earlier hematopoietic recovery than autologous BMT.^{86,87} Trials have demonstrated the value of CSF administration after high-dose chemotherapy and PBPC transplantation.⁸⁸⁻⁹⁰ Available data suggest clinical benefits after allogeneic BMT, and routine primary CSF administration in this setting seems warranted.⁹¹ CSFs can also be used to mobilize donor PBPC for allogeneic transplantation.⁹²⁻⁹⁵ There also may be a role for the CSFs in assisting in the

recovery of patients who experience delayed or inadequate neutrophil engraftment after PBPC transplantation. CSFs can be routinely recommended as adjuncts to allogeneic and autologous PBPC transplantation, both for mobilization of PBPCs and as a means to speed hematopoietic reconstitution after BMT or PBPC transplantation. Administration of a CSF in cases of engraftment failure is warranted.

2000 Update. PBPCs may be less contaminated than bone marrow collections with tumor cells, although the mobilization process may lead to migration of tumor contaminants into the peripheral circulation; the clinical significance of such phenomena is controversial.⁹⁶⁻⁹⁸ Increasingly, CSF-mobilized PBPCs procured from healthy donors are used in the setting of allogeneic transplantation, providing faster hematopoietic recovery, similar to the autologous setting.⁹⁹ One major concern regarding the use of donor-derived, mobilized PBPCs is the theoretical potential for an increased incidence and/or severity of GvHD. Preliminary data suggest no such adverse effect regarding acute GvHD and the possible increase in the incidence/severity of chronic GvHD; an ongoing multi-institutional, randomized, prospective study is currently assessing GvHD-related complications after donor-derived, CSF-mobilized PBPC transplantation versus BMT.¹⁰⁰⁻¹⁰² CSFs, when administered shortly after reinfusion of PBPCs and at least within 5 days after autologous PBPC reinfusion, shorten the duration of neutropenia. The optimal timing is still under investigation.^{103,104} CSFs, when administered after PBPC reinfusion, accelerate neutrophil recovery and lower costs after allogeneic BMT and after reinfusion of autologous PBPCs.^{105,106} The therapeutic role of G-CSF in the treatment of relapsed acute and chronic leukemias after allogeneic BMT requires confirmation.¹⁰⁷

2000 Recommendation. CSFs are recommended to help mobilize PBPCs and after PBPC infusion. Mobilized PBPCs have largely replaced bone marrow-derived cells for use in autologous transplantation. Side effects associated with mobilization and subsequent apheresis are usually limited and include constitutional symptoms and a decrease in platelets and other hematopoietic elements, especially after mobilization with combinations of chemotherapeutic agents and a CSF. The optimal dose of CSFs and chemotherapeutic agents is the subject of ongoing investigations, but a higher (10 $\mu\text{g}/\text{kg}/\text{d}$) dose of G-CSF in the setting of mobilization may yield greater content of CD34⁺ progenitor cells in the PBPC product, as documented in patients with hematologic malignancies and in patients with rheumatoid arthritis.^{88,108} Although the optimal method of mobilization needs further investigation, especially in heavily pretreated patients, administration of G-CSF, either alone or in combination with GM-CSF, or after the use of

chemotherapeutic agents, generates PBPCs, leading to rapid hematopoietic recovery, shorter hospitalization, and possibly reduced costs.^{87,109-111} Further investigations are necessary to assess the potential risks, especially that of secondary hematologic malignancies associated with the use of combining chemotherapeutic agents and CSFs.¹¹² The role of CSF-mobilized donor bone marrow in the autologous transplant setting is also under assessment.¹¹³

6. Guidelines for Use of CSFs in Patients With Acute Leukemia and Myelodysplastic Syndromes

Definition of Problem

Essentially all patients with acute leukemia receiving induction therapy, and most such patients receiving intensive, postremission consolidation therapy, develop fevers that require hospitalization and IV antibiotics until neutrophil recovery occurs. Although morbidity and death from hemorrhage can occur in patients with associated coagulopathy or those with alloimmunization and refractoriness to platelet transfusion, infectious complications remain the major supportive care problem in the treatment of patients with acute leukemia. This is particularly true in older patients, in whom infectious deaths represent a major cause of failure to achieve complete remission. In patients who survive, complications of infections can compromise the ability to safely deliver postremission or subsequent therapy. In particular, fungal infections, which frequently occur later in the course of treatment, are difficult to treat and result in greater morbidity and mortality. Pulmonary and hepatic fungal infections and renal damage associated with amphotericin-B therapy can preclude administration of potentially curative postremission consolidation with chemotherapy or BMT. In patients with myelodysplastic syndromes (MDS) and chronic neutropenia, infection remains a major cause of morbidity and mortality, with the rate of infection directly related to the degree of neutropenia.

Data have been generated showing that the CSFs have the potential to alter cell-cycle kinetics in patients with acute myeloid leukemia (AML) such that drug sensitivity to S-phase-specific agents such as cytarabine could be enhanced. These *in vitro* data suggest that the CSFs have the potential to increase the effectiveness of treatment if administered before and/or concurrently with chemotherapy as leukemic cell "priming" agents.

Clinical Outcomes

Because of the underlying disease and the intensity of the chemotherapy administered for AML, CSF use will not eliminate severe neutropenia, but it may shorten the duration of neutropenia. Theoretically, CSF administration

could decrease the incidence of serious bacterial infections and fungal infections, minimize time spent on empiric therapy with amphotericin-B, reduce hospitalization time, increase the likelihood of achieving an initial complete remission, and promote delivery of subsequent therapy more safely and cheaply. Although reduced infectious mortality remains the most important potential consequence of postchemotherapy CSF administration, this is a difficult end point to evaluate with statistical confidence because of the effectiveness of current antibiotic and antifungal therapies. It is important to place such comparisons in clinical perspective, as results that are statistically significant but clinically insignificant do not help decision makers. Use of CSFs as primers for chemotherapy might enhance response rates and disease-free survival. In patients with MDS, a reduction in the number and severity of neutropenic infections and improvements in quality of life would be envisioned.

The potential for adverse effects with CSF administration in patients with myeloid malignancies also exists. Because most myeloid leukemia cells express receptors for the CSFs, postchemotherapy stimulation of leukemia growth has been a concern. Similar anxiety has arisen regarding CSF administration in patients with MDS, in whom conversion to overt leukemia is a natural feature of the disease. In patients undergoing CSF priming, it is conceivable that the CSF might prevent chemotherapy-induced apoptosis of leukemia cells. Therefore, randomized comparisons of complete response rate must be performed, with particular emphasis on differences in treatment failure caused by persistence of drug-resistant leukemia. Because CSF-primed patients receive chemotherapy and CSFs concurrently, stimulation of normal hematopoietic precursors with increased cytotoxicity against these elements might actually result in more prolonged marrow aplasia. Lastly, it is current practice to administer amphotericin-B to neutropenic patients receiving antibiotics who have persistent fever or other constitutional symptoms. If such side effects occur after CSF administration, it is possible that more, rather than fewer, patients will receive amphotericin-B or other changes in antibiotics, not because of infectious problems, but because of CSF-induced toxicity. In view of all these issues, it is essential that randomized trials be double-blinded with a placebo administered in the control arm.

Alternative Approaches

At this time, standard support after induction chemotherapy for leukemia consists of careful monitoring for infection and empiric institutions of antibiotics and antifungal agents in febrile patients. There is still controversy about the value of prophylaxis with oral antibiotics and antifungal agents.

Neutropenic patients with MDS are conventionally provided antibiotic support in response to fever or infection.

A. AML

1996 Recommendation. Primary administration of a CSF can be used after completion of induction chemotherapy in patients 55 years of age or older. Although there are fewer data, it is likely that the results showing shortening of the duration of neutropenia may apply to younger patients as well. CSFs given either before and/or concurrently with chemotherapy for priming effects still cannot be recommended outside of a clinical trial.

2000 Update. PRIMARY CSF ADMINISTRATION AFTER INDUCTION CHEMOTHERAPY FOR AML. Multiple, placebo-controlled, randomized studies¹¹⁴⁻¹²² have been conducted to evaluate the use of either GM-CSF or G-CSF begun after completion of induction therapy in newly diagnosed adult patients with AML. Most, but not all, of the trials enrolled predominantly older patients with AML. Although there are modest differences in design among the studies, the overall conclusions are remarkably similar and are as follows: (1) The addition of the CSFs decreased the time to recovery to 500 neutrophils/mm³ by 2 to 6 days. These studies did not use standard definitions of the duration of neutropenia, which perhaps accounts for the differences in magnitude of the effect. (2) Except for one study whose findings were discrepant from the others,¹¹⁴ there was no benefit from the use of CSFs in terms of improvement of complete response rates. Alternatively, there was no evidence of stimulation of leukemia growth and enhanced drug resistance after the use of CSFs, except in one small study in which a lower complete response rate in the group of patients receiving GM-CSF may have been related to maldistribution of other prognostic factors.¹²¹ (3) Most, but not all, studies showed statistically significant reductions in the duration of hospitalization and antibiotic use in patients receiving CSFs. The CSFs did not significantly prolong hospitalization in any of the studies.¹²³ (4) Except for one small study, CSF use had no effect on patient survival.¹¹⁵ Further analysis of this study suggested that clinical benefits were restricted to a subpopulation of patients who required two courses of induction therapy.¹²⁴ (5) In some studies, the CSF was not begun until marrow aplasia was demonstrated on bone marrow biopsy after the completion of chemotherapy^{115,118}; functionally, this resulted in a 2- to 3-day gap between the end of chemotherapy and the initiation of the CSF. In other studies, however, the CSF was begun the day after completion of chemotherapy with no requirement for marrow biopsy assessment.^{116,117,120} The results seem to be identical using these two approaches, and it would seem that it is not necessary to routinely perform bone marrow biopsies before

initiation of the CSF. However, since the results were similar using the two approaches, one could infer that delaying the start of the CSF for 2 to 3 days does not reduce the effect and could result in some cost savings. It should be emphasized that these different schedules have not been directly compared in randomized trials. (6) CSF use had no effect on platelet or RBC transfusion requirements. (7) Comparative studies have not been done, but the overall results suggest similar effects for G-CSF and GM-CSF. (8) Overall, during intensive chemotherapy for adult AML patients, clinical benefits included a shortening of hospital stays and cost savings of \$2,230 and \$2,310 in two studies and an increase in costs of \$120 in a third study.^{123,125,126}

CSF PRIMING OF LEUKEMIA CELLS IN PATIENTS WITH AML. In vitro studies have suggested that the CSFs have the potential to alter cell-cycle kinetics such that cytotoxicity from cell-cycle-specific agents, such as cytarabine, could be enhanced.¹²⁷ Four prospective randomized trials have evaluated this approach by using GM-CSF begun before the initiation of chemotherapy: three trials included patients receiving initial induction therapy,^{119-121,127} and the other included patients receiving high-dose cytarabine therapy for AML in first relapse.¹²⁸ An additional small trial evaluated the effect of G-CSF begun 2 days before induction chemotherapy in patients with relapsed or refractory AML.¹²⁹ There was no improvement in any study in response rate, response duration, or overall survival in patients receiving a CSF before and during their induction chemotherapy.

CONSOLIDATION THERAPY FOR PATIENTS WITH AML IN COMPLETE REMISSION. Postremission chemotherapy is routinely administered to patients with AML in an attempt to increase the fraction of long-term, disease-free survival in younger patients. In most centers, this chemotherapy is administered either in the outpatient setting or during a brief hospital admission after which the patient is discharged to the outpatient setting. Two large randomized trials evaluated the role of G-CSF given after completion of relatively standard consolidation therapy^{117,130} to such patients. Both demonstrated marked decreases in the duration of severe neutropenia, with elimination of severe neutropenia in a subfraction of patients. This was associated with a decreased rate of infection requiring antibiotic therapy. There was no effect on complete response duration or overall patient survival. Similarly, shortening of the duration of neutropenia compared with a prior cohort treated without G-CSF was noted in a study evaluating intensive consolidation chemotherapy with a less standard, investigational regimen.¹³⁰

2000 Recommendation. CSF use can be considered in this setting if benefits in terms of possible shortening of hospitalization outweigh the costs of CSF use. Several

studies have shown that CSF administration can produce modest decreases in the duration of neutropenia when begun shortly after completion of the initial days of chemotherapy of the initial or repeat induction. Beneficial effects on end points such as duration of hospitalization and incidence of severe infections have been variable and modest, although patients 55 years of age or older are most likely to benefit from CSF use. No study has yet demonstrated significant improvement in complete response rates or long-term outcome. Thus, while there seems to be minimal risk associated with the use of CSFs in this situation, the choice of whether or not to use the CSF is likely to be determined by cost considerations. In a nutshell, the cost of the cytokine must be balanced against any possible shortening of hospitalization associated with the slightly more rapid marrow recovery, as, for example, in patients 55 years of age or older. It is not known from the published data whether the CSFs significantly accelerate recovery to ANC of 100 to 200/mm³. In most patients, regenerating counts of this level are sufficient to protect against infection so as to permit safe discharge of patients from hospital.

There is no evidence that CSFs given either before or concurrently with chemotherapy for *priming effects* are of benefit, and their use in this fashion cannot be recommended outside the setting of the clinical trial.

There seems to be more profound shortening of the duration of neutropenia after *consolidation chemotherapy* for patients with AML in remission. Although the randomized studies did not address this issue, it is likely that this will be associated with decreased rates of hospitalization and possibly shorter durations of hospitalization in such patients. No benefit has been demonstrated in terms of prolongation of complete response duration or overall survival; however, the available evidence indicates that the CSFs can be recommended after the completion of consolidation chemotherapy.

B. MDS

1996 Recommendation. CSFs can increase the ANC in neutropenic patients with MDS. Data supporting the routine, long-term, continuous use of CSFs in these patients are lacking. Intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infection.

2000 Update. Morbidity and death from infection as a consequence of chronic, severe neutropenia are common in patients with MDS. CSFs can increase the level of circulating neutrophils in patients with MDS, with clinical improvement of infections in some such patients.^{131,132} The ANC declines when the CSF is discontinued. These observations were confirmed in a randomized trial comparing

G-CSF and a policy of best supportive care in patients with MDS.¹³³ Although the overall rate of transformation to frank AML was similar in the two groups, overall survival was shorter in the G-CSF recipients with refractory anemia and excess blasts. There is no clear-cut explanation for this observation, but prolonged or continuous treatment with G-CSF cannot be recommended in patients with MDS. Ongoing trials are evaluating whether the addition of G-CSF to erythropoietin increases the response rate compared with erythropoietin alone.

2000 Recommendation. No change.

C. ALL (Note. This topic is new to the guideline.)

Evidence-Based Review. Using study designs similar to those for patients with AML, six studies,¹³⁴⁻¹³⁹ of which five were prospectively randomized trials,¹³⁴⁻¹³⁸ evaluated the effect of G-CSF in both adults and children receiving initial induction and postremission therapy for ALL. A major difference from AML, however, is that after multi-drug therapy given for the first 3 to 6 days of each treatment course, most protocols for patients with ALL have additional therapy, usually corticosteroid/antimetabolite-based, given either intermittently or continuously. Thus, in contrast to AML studies, some of the ALL studies administered G-CSF concurrently with some chemotherapeutic drugs. In addition, the regimens used in these studies were more heterogeneous than those in the AML studies, and although most of the studies started the G-CSF shortly after the completion of the first few days of chemotherapy, the largest study in children¹³⁵ and a smaller study in adults¹³⁶ did not begin G-CSF/placebo until day 30 of initial induction therapy.

Nonetheless, most of the findings were similar. Although three of the trials were relatively small (< 40 patients/arm)¹³⁶⁻¹³⁸ and not all trials were double-blinded and placebo-controlled, they all demonstrated shortening of the duration of neutropenia (generally defined as recovery to > 1,000 neutrophils/mm³) after both the first and second courses of induction chemotherapy. The largest studies in adults¹³⁴ and children^{135,140} showed reductions in the duration of neutropenia of 6, 8, and 5 days. The effect on other clinical parameters, such as the incidence of severe infections or FN, the frequency and duration of hospitalization, and the ability to deliver the regimens on time, were variable. In the large (198 patients) trial in adults conducted by Cancer and Leukemia Group B, there was a trend toward a higher complete response rate in patients receiving G-CSF, particularly in patients more than 60 years old.¹³⁴ Given the very high complete response rate in children with ALL, the trials were not designed to detect further improvements in this parameter. The largest pediatric trial (164

patients), conducted at St Jude's Children's Research Hospital (Memphis, TN), did demonstrate shorter median hospital stays and fewer documented infections, although the overall requirement for hospitalization was not decreased and the overall costs were \$2,497 higher.¹³⁵ There was no improvement in disease-free or overall survival associated with the use of G-CSF in any of the five randomized trials.

2000 Recommendation. The data are sufficient to recommend G-CSF administration begun after completion of the first few days of chemotherapy of the initial induction or first postremission course, thus shortening the duration of neutropenia of less than 1,000/mm³ by approximately 1 week. Effects on the incidence and duration of hospitalization and the acquisition of serious infections are less consistent. Although there was a trend for improved complete response rates in one large study,¹³⁴ particularly in older adults, there was no prolongation of disease-free or overall survival in any of the trials. G-CSF can be given together with the continued corticosteroid/antimetabolite therapy, which is a feature of many ALL regimens, without evidence that such concurrent therapy prolongs the myelosuppressive effects of the chemotherapy. As in AML, it is not known from the published data whether the CSFs significantly accelerate recovery to ANC's of 100 to 200/mm³. In most patients, regenerating counts of this level are sufficient to protect against infection so as to permit safe discharge of patients from the hospital. The use of G-CSF for children with ALL was associated with small benefits in days of antibiotic use or in-hospital days, although a small amount of additional costs was incurred, after the costs of the CSFs were taken into consideration. Cost estimates of CSFs for adults with ALL have not been reported.

D. Leukemia in Relapse (Note. This topic is new to the guideline.)

Evidence-Based Review. There have been few randomized studies in patients treated in relapse for AML or ALL. One of the earliest studies of CSFs evaluated a heterogeneous group of patients with relapsed leukemia and demonstrated faster neutrophil recovery in patients receiving G-CSF after completion of chemotherapy.¹⁴¹ In patients with relapsed ALL, a small study suggested more rapid neutrophil recovery compared with historical controls, with no effect on infectious morbidity or response rate.¹⁴²

2000 Recommendation. The available data are not sufficient to recommend either for or against the use of CSFs in patients with refractory or relapsed ALL. Few controlled studies have evaluated CSFs in patients with relapsed or refractory acute leukemia. The available data suggest shortening of the duration of neutropenia but are inadequate to

comment on any effects on infectious complications and, in particular, on whether there may be an adverse effect on response rates in some patients with myeloid malignancies because of a stimulatory effect on leukemia growth in a situation in which there is less of a guarantee that chemotherapy will produce sufficient cytoreduction. Therefore, there is no evidence that CSFs are of important benefit in patients with refractory or relapsed myeloid leukemia, and they should be used judiciously or not at all in such patients.

7. Guidelines for Use of CSFs in Patients Receiving Concurrent Chemotherapy and Irradiation

Definition of Problem

In theory, adding chemotherapeutic agents such as cisplatin and fluorouracil to high-dose radiation therapy can kill tumor cells outside a radiation field, and these agents can also act as radiation sensitizers within the field.^{143,144} In clinical practice, concurrent chemotherapy and radiation therapy may be important in the treatment of some malignancies; the clinical evidence has been most persuasive in patients with esophageal cancer, demonstrating better local control and survival with combined chemoradiotherapy.¹⁴⁵⁻¹⁴⁷ In patients with lung cancer, randomized studies have suggested that combination chemotherapy in addition to high-dose radiation results in improved survival compared with irradiation alone.^{148,149} Although mucositis and pneumonitis have been the primary dose-limiting toxicities with radiation, the addition of chemotherapy has provoked sufficient hematologic toxicity to spur interest in administration of CSFs.

Clinical Outcomes

CSF support of chemoradiotherapy might be expected to decrease the incidence and severity of neutropenic complications. In addition, based on preliminary observations,¹⁵⁰ there has been the prospect that mucositis associated with combined-modality cytotoxic treatment might also be reduced by CSF use.

Alternative Approaches

The principal alternative to intervention with a CSF has been chemotherapy dose modification or interruption in administration of radiotherapy. Antibiotics, pain relief, nutritional support, corticosteroids, and other similar measures have been provided to blunt the toxicities of combined-modality therapy.

1996 Recommendation. CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy.

2000 Update. CSFs have been shown in several studies to reverse the effect of radiation therapy, with or without chemotherapy, on neutrophil counts. The clinical benefit of this effect may facilitate the administration of radiation according to schedule, but an impact on outcomes has not been demonstrated. The major concern about the use of CSFs as supportive therapy for combined chemoradiation lies with findings that suggest a possible deleterious effect on platelet count. The principal study demonstrating this finding is the Southwestern Oncology Group study of the role of CSFs in patients treated with concurrent chemoradiation.¹⁵¹ This randomized trial treated 215 assessable small-cell lung cancer patients with a regimen of cisplatin, etoposide, and thoracic irradiation; 108 received GM-CSF and 107 did not. Although grade 4 neutropenia occurred, the study also found a significant increase in thrombocytopenia in the GM-CSF arm: the incidences of grade 3 and grade 4 platelet toxicity were 54% and 35%, respectively, in the treated group and only 12% and 6% in the control population. Most of the toxicity occurred in the second course of treatment, although the effect persisted in subsequent courses. In addition, there were more toxic deaths (nine v one, $P < .01$) in the GM-CSF arm, with the majority being related to pulmonary toxicity. Studies of lesser strength demonstrating the deleterious effect on platelets include a nonrandomized comparison of non-small-cell lung cancer patients treated with cisplatin, etoposide, mitomycin, and chest irradiation, in which the mean nadir platelet count was 131×10^3 in seven patients who received the growth factor.

Several small studies of CSFs in patients undergoing large-field irradiation have demonstrated that CSFs may help ameliorate the effect of radiation on neutropenia. These possible benefits have been seen in studies using CSFs after WBC count depression in craniospinal radiotherapy and a variety of large-field applications, and prophylactically in Hodgkin's disease and multiple myeloma. A possible mechanism for the impact on platelets may be the demonstration that blood colony-forming units-megakaryocytes induced by CSFs may be more radiosensitive to radiation than nonrecruited marrow progenitors. There is evidence indicating the potential for an adverse interaction between mediastinal radiotherapy and CSF administration. However, it should be noted that the thrombocytopenia observed might be unique to this site of irradiation and only in the setting of combined chemoradiation. At present, the routine use of CSF in this setting should be avoided unless studied as part of a clinical trial with appropriate monitoring of thrombocytopenia and pulmonary toxicity. CSF use to support large-field irradiation may have benefits, but further studies are required to recommend this usage. CSF use in conjunction with radiation has not been studied extensively, and

further studies are required to ascertain the optimal sequencing.

2000 Recommendation. CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, in patients receiving radiation therapy involving large fields, therapeutic use of CSFs may be considered if prolonged delays secondary to neutropenia are expected.

8. Guidelines for Use of CSFs in the Pediatric Population

Definition of Problem

In contrast to adults with cancer, the majority of pediatric patients are treated on clinical research protocols. Chemotherapy for pediatric cancers is generally more intensive, and myelosuppression is thus more frequent and severe. Infants receiving chemotherapy are at a particular risk for neutropenic morbidity because of the immaturity of the hematopoietic and immune systems. These factors can increase the incidence of FN and the potential for life-threatening infections. However, there is an acceptable risk-to-benefit ratio because of the greater curability of most pediatric cancers.

Clinical Outcomes

The same end points used in the previous guidelines should be considered in determining CSF benefit in pediatric patients, eg, incidence of FN, length of hospital stay, antibiotic use, therapeutic costs, and quality of life.

Alternative Approaches

Alternative approaches for pediatric patients receiving chemotherapy would be to treat without CSFs, modifying chemotherapy doses and providing antibiotic support as necessary.

1996 Recommendation. In the absence of conclusive pediatric data, the guidelines recommended for adults are generally applicable to the pediatric age group. However, optimal CSF doses have yet to be determined. Further clinical research into the use of these factors in support of chemotherapy and PBPC transplantation in the pediatric age group should be given high priority.

2000 Update. Although the pediatric community is well aware of the ASCO guidelines on growth factor use, a number of important differences in the care of children with cancer impact the application of the ASCO guidelines. Perhaps most important is the fact that the vast majority of children with cancer are enrolled in clinical protocols directed by National Cancer Institute-sponsored national cooperative group efforts. Accordingly, the use of growth

factors is largely determined by the requirements delineated in these protocols. A recent review of the practices within the Pediatric Oncology Group¹⁵² indicates that primary prophylaxis with growth factors occurs more commonly in children than in adults and is guided by the anticipated duration of neutropenia (> 7 days) in the pediatric population. At the same time, use of growth factors in primary prophylaxis is not uniform across all protocols and diseases and is influenced by physician preference as well as by available data. The use of growth factors for secondary prophylaxis seems more similar in children and adults, although a reduction in chemotherapy dosage is rarely selected by pediatric oncologists as an alternative to use of a growth factor. Although a near majority of pediatric oncologists surveyed reported using growth factors in children presenting with fever and neutropenia, this was less commonly done in uncomplicated fever and neutropenia but was more frequently used in patients who had perceived complicated illness with fever and neutropenia. Overall, pediatric oncologists seem to use growth factors more commonly than their adult colleagues for primary and secondary prophylaxis than the current ASCO guidelines would indicate but less often for uncomplicated fever and neutropenia. It seems that differences in utilization are guided by treatment strategies in adult and pediatric patients and, in particular, by the perceived toxicity of high-dose-intensity regimens in children.

2000 Recommendation. No change.

9. Guidelines for CSF Dosing and Route of Administration

Definition of Problem

A variety of CSF doses have been tested. Phase I studies have examined escalating doses; however, toxicity, not efficacy, has been the major end point, and small cohort sizes have hindered dose-response assessments. Phase II and III trials often used a single, arbitrarily chosen dose of CSFs. Only a few trials have evaluated a dose range of CSFs in a randomized fashion. Additionally, differences in the biologic activities and toxicities of G-CSF and the two types of GM-CSF, sargramostim and molgramostim, have potential implications for dosing.

Clinical Outcomes

The primary end points of benefit assessed by the panel included rates of FN, hospitalization, and antibiotic use, convenience, and cost. A review of CSF dose and route effects on ANC was also necessary because many studies have been inadequately sized to detect differences in other clinical outcomes. Relative toxicity was also evaluated

across CSF dose levels (see Impact of CSFs on Economics of Febrile Neutropenia, under Summary of Relevant Background Data).

1996 Recommendation

In adults, the recommended CSF doses are 5 $\mu\text{g}/\text{kg}/\text{d}$ for G-CSF (filgrastim) and 250 $\mu\text{g}/\text{m}^2/\text{d}$ for GM-CSF (sargramostim). These agents can be administered subcutaneously or intravenously as clinically indicated. CSF dose escalation is not advised. The available data suggest that rounding the dose to the nearest vial size may enhance patient convenience and reduce costs without clinical detriment.

2000 Update

Higher doses of either G-CSF or GM-CSF have not been associated with improved clinical benefits.^{153,154} One exception may be in the setting of PBPC mobilization, where a dose of 10 $\mu\text{g}/\text{kg}/\text{d}$ resulted in an improved leukapheresis product compared with lower doses.¹⁵⁵⁻¹⁵⁸ The schedule of administration of G-CSF (5 $\mu\text{g}/\text{kg}$ bid v 10 $\mu\text{g}/\text{kg}$ as single injection) may also result in improved mobilization.¹⁵⁹ No randomized trials of doses below those recommended for G-CSF and GM-CSF have been reported. Clinical and clinical trial experience continue to support rounding of dose to the nearest vial size. Pharmacokinetic analysis favors subcutaneous administration compared with IV use for both agents.¹⁶⁰⁻¹⁶²

2000 Recommendation.

In adults, the recommended CSF doses are 5 $\mu\text{g}/\text{kg}/\text{d}$ for G-CSF (filgrastim) and 250 $\mu\text{g}/\text{m}^2/\text{d}$ for GM-CSF (sargramostim) for all clinical settings other than PBPC mobilization. In the setting of PBPC mobilization, if G-CSF is used, a dose of 10 $\mu\text{g}/\text{kg}/\text{d}$ seems preferable. Outside of this indication, CSF dose escalation is not advised. Rounding the dose to the nearest vial size is an appropriate strategy to maximize cost benefit. The preferred route of CSF administration is subcutaneous.

10. Guidelines for Initiation and Duration of CSF Administration

Definition of Problem

Appropriate timing of CSF administration relative to chemotherapy and the duration of CSF use are important concerns in trying to achieve the greatest degree of clinical benefit with the least possible cost.³⁵ The package insert recommends that G-CSF be initiated no earlier than 24 hours after the administration of chemotherapy and that daily dosing with the drug be continued until the ANC has

reached at least 10,000/ μ L after the neutrophil nadir. It has also been advised that G-CSF not be given in the period 24 hours before treatment with the next cycle of chemotherapy. In patients undergoing BMT, the manufacturer recommends tapering the G-CSF dose from 10 μ g/kg/d to 5 μ g/kg/d once the ANC has recovered to 1,000/ μ L for at least 3 days and then discontinuing the G-CSF once the ANC has been greater than 1,000/ μ L for 3 additional days. Because GM-CSF (sargramostim) has been licensed specifically for use after autologous or allogeneic BMT and for AML, the manufacturer's instructions for administration have been limited to those clinical settings. Current recommendations for BMT are to initiate GM-CSF beginning on the day of bone marrow infusion and not less than 24 hours from the last chemotherapy and 12 hours from the most recent radiotherapy. GM-CSF should be continued until an ANC greater than 1,500 cells/mm³ for 3 consecutive days is obtained. It is also advised that the drug be discontinued early or the dose be reduced by 50% should the ANC increase to greater than 20,000/ μ L. However, based on recent publications, the optimal timing of CSF administration is still under investigation: CSFs, when administered within 1 to 5 days after PBPC reinfusion, shorten the duration of neutropenia.^{96,97} In the setting of graft failure or engraftment delay, the recommended dose of GM-CSF is 250 μ g/m²/d for 14 days followed by a 7-day break. Up to three such courses, with dose escalation to 500 μ g/m²/d in the third course, are advised.

Clinical Outcomes

In assessing the impact of schedule on the benefits of CSF administration, the duration of neutropenia has most often been used as a surrogate marker of benefit. Correlations also need to be made with clinical measures of benefit, eg, incidence of hospitalization, reduced cost, increased convenience, or enhanced maintenance of chemotherapy delivery.

1996 Recommendation. Existing clinical data suggest that starting G-CSF or GM-CSF between 24 and 72 hours subsequent to chemotherapy may provide optimal neutrophil recovery. Continuing the CSF until the occurrence of an ANC of 10,000/ μ L after the neutrophil nadir, as specified in the G-CSF package insert, is known to be safe and effective. However, a shorter duration of administration that is sufficient to achieve clinically adequate neutrophil recovery is a reasonable alternative, considering issues of patient convenience and cost.

2000 Recommendation. The optimal timing and duration of CSF administration are still under investigation. Starting CSFs up to 5 days after PBPC reinfusion is reasonable based on available clinical data.

11. Special Commentary on Comparative Clinical Activity of G-CSF and GM-CSF

1996 Recommendation. Guidelines about equivalency of the available recombinant preparations of G-CSF and GM-CSF cannot be proposed because there have been no large-scale, prospective, comparative trials evaluating relative CSF efficacy. The strength of evidence to support the use of G-CSF or GM-CSF varies based on the specific indication for CSF administration, eg, support after BMT or use with nontransplantation chemotherapy regimens. The panel strongly encourages additional clinical investigation that will guide clinical application of these biologically distinct molecules by addressing issues of comparative clinical activity, toxicity, and cost-effectiveness.

2000 Update. Guidelines about the equivalency of the available recombinant preparations of G-CSF and GM-CSF cannot be proposed because there have been no large-scale, comparative trials evaluating relative CSF efficacy in primary or secondary prophylaxis. Since the last update of the ASCO CSF guidelines was published in 1996,¹⁶³ a comparison study was published in 1998.¹⁶⁴ This randomized, double-blind study was performed in patients who had received chemotherapy and were neutropenic at the time of study entry, with a mean ANC of 277/ μ L for the GM-CSF group and 282/ μ L for the G-CSF group. Entry criteria required chemotherapy within 4 weeks of registration, age over 17, ANC less than 500/ μ L, and absence of fever. Patients were excluded if they met any of the following exclusion criteria: use of long-acting chemotherapeutic agents within 6 weeks of study entry; concurrent thoracic radiation or history of pelvic radiation; use of growth factors within 6 weeks of study entry; concurrent use of oral or IV antibiotics or systemic antifungal agents; pregnancy or lactation; allergy to either growth factor; and infection with the human immunodeficiency virus. End points of the study were time to ANC recovery, incidence of fever, infection, and hospitalization, and duration of hospitalization. One hundred eighty-one patients were assessable for safety and 170 patients were assessable for efficacy of the two study arms. There was no significant difference in the time needed for patients to reach an ANC of 500/ μ L, but there was a statistically significant, but not clinically important, measurably shorter time to an ANC of 1,000/ μ L and an ANC of 1,500/ μ L for G-CSF over GM-CSF. There was no difference in the reported incidence of fever or hospitalization. This study has many design flaws that make comparative analysis of the relative efficacy of G-CSF versus GM-CSF impossible. It does provide an opportunity to compare the relative toxicity of these two agents. There were no significant differences in adverse events between the two groups.

The G-CSF group did have a 10.7% incidence of grade 2 fever 4 hours after injection, compared with a 3.8% incidence for the GM-CSF group, but no conclusions can be drawn from this difference because of the study design. From this study, one can probably conclude that the two agents probably have fairly similar toxicities; otherwise, a greater disparity would have been observed in adverse events.

In the setting of progenitor-cell transplantation, a second, more recently published randomized trial compared G-CSF with GM-CSF or the sequential combination of both cytokines in mobilization of CD34⁺ progenitor cells in patients with myeloma, lymphoma, or breast cancer.¹⁶⁵ All patients in this trial then received G-CSF after CD34⁺-cell infusion and chemotherapy. During the mobilization period after chemotherapy (median duration, 12 to 13.5 days), patients demonstrated faster recovery of neutrophils and an increased incidence of sargramostim-related fever. In addition, there was an unexpected and unexplained increase in the incidence of anemia and RBC transfusions in the sargramostin group. There were no differences in platelet

nadirs and only nonsignificant differences in platelet transfusions. Compared with those who received GM-CSF mobilization, patients who received either G-CSF alone or the combination demonstrated significant improvement in days to ANC of 500/mm³, as well as in incidence of fever, hospitalization, antibiotic therapy, and RBC and platelet transfusions. Improved outcomes after peripheral stem-cell infusions were a direct result of the improvement in CD34⁺-cell yield with each apheresis in those patients receiving either the G-CSF or combination G-CSF plus GM-CSF mobilization regimens in comparison to GM-CSF alone.

2000 Recommendation. No change.

ACKNOWLEDGMENT

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Summary of Guideline Updates

1. Guidelines for Primary Prophylactic CSF Administration

1996 Recommendation: Primary administration of CSFs was shown to reduce the incidence of febrile neutropenia (FN) by approximately 50% in the three major randomized trials in adults in which the incidence of FN was greater than 40% in the control group. The value of primary CSF administration has not been clearly established in less myelosuppressive regimens, and the cost benefit of primary versus secondary administration for the majority of initial chemotherapy regimens is unproven. It is recommended that primary administration of CSFs be reserved for patients expected to experience levels of FN that are at least comparable to or greater than those seen in control patients in these randomized trials, ie, an expected incidence \geq 40%. Thus, for previously untreated patients receiving most chemotherapy regimens, primary administration of CSFs cannot be recommended.

2000 Recommendation: No change.

Special Circumstances

1996 Recommendation: Clinicians may occasionally be faced with patients who might benefit from relatively nonmyelosuppressive chemotherapy but who have potential risk factors for FN or infection because of bone marrow compromise or comorbidity. It is possible that primary CSF administration may be exceptionally warranted in patients at higher risk for chemotherapy-induced infectious complications, even though the data supporting such use are not conclusive. Such risk factors might include the following: pre-existing neutropenia due to disease, extensive prior chemotherapy, or previous irradiation to the pelvis or other areas containing large amounts of bone marrow; a history of recurrent FN while receiving earlier chemotherapy of similar or lesser dose-intensity; or conditions potentially enhancing the risk of serious infection, eg, poor performance status and more advanced cancer, decreased immune function, open wounds, or already-active tissue infections. This is not meant to be an all-inclusive list; it is anticipated that, depending on the unique features of the clinical situation, there will be instances when the administration of a CSF will be appropriate outside of uses recommended in other guidelines.

2000 Recommendation: No change.

2. Guidelines for Secondary Prophylactic CSF Administration

1996 Recommendation: There is evidence that CSF administration can decrease the probability of FN in subsequent cycles of chemotherapy after a documented occurrence in an earlier cycle. Even if FN has not occurred, the use of CSFs may be considered if prolonged neutropenia is causing excessive dose reduction or a delay in chemotherapy. However, in the absence of clinical data supporting maintenance of chemotherapy dose-intensity, physicians should consider chemotherapy dose reduction as an alternative to the use of CSFs.

2000 Recommendation: In the setting of many tumors exclusive of curable tumors (eg, germ cell tumors), dose reduction after an episode of severe neutropenia should be considered as a primary therapeutic option. No published regimens have demonstrated disease-free or overall survival benefits when the dose of chemotherapy was maintained and secondary prophylaxis was instituted. In the absence of clinical data or other compelling reasons to maintain chemotherapy dose-intensity, physicians should consider chemotherapy dose reduction after neutropenic fever or severe or prolonged neutropenia after the previous cycle of treatment.

3. Guidelines for CSF Therapy

A. Afebrile Patients

1996 Recommendation: Data are inadequate in regard to whether patients with neutropenia but no fever will benefit clinically from the initiation of a CSF at the time neutropenia is diagnosed; intervention with a CSF in afebrile neutropenic patients is not recommended.

2000 Recommendation: Current evidence supports the recommendation that CSFs should not be routinely used for patients with neutropenia who are afebrile. The strength of this recommendation has increased with the trial reported in 1997.⁶⁶

B. Febrile Patients

1996 Recommendation: For the majority of patients with FN, the available data do not clearly support the routine initiation of CSFs as adjuncts to antibiotic therapy. However, certain FN patients may have prognostic factors that are predictive of clinical deterioration, such as pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), or fungal infection. The use of CSFs together with antibiotics may be reasonable in such high-risk patients, even though the benefits of administration under these circumstances have not been definitively proven.

2000 Recommendation: The collective results of the eight trials⁶⁷⁻⁷⁴ provide strong and consistent support for the recommendation that CSFs should not be routinely used as adjunct therapy for the treatment of uncomplicated fever and neutropenia. Uncomplicated fever and neutropenia are defined as follows: fever of ≤ 10 days in duration; no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan dysfunction, or invasive fungal infection; and no uncontrolled malignancies. The eight trials have consistently shown a decrease in the duration of neutropenia of less than 500/ μ L, but clinical benefit has not consistently accompanied the decreased duration of neutropenia.

Certain patients with fever and neutropenia are at higher risk for infection-associated complications and have prognostic factors that are predictive of poor clinical outcome. The use of a CSF for such high-risk patients may be considered, but the benefits of a CSF in these circumstances have not been proven. These factors include profound (absolute neutrophil count [ANC] $< 100/\mu$ L) neutropenia, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), and invasive fungal infection. Age greater than 65 years and posttreatment lymphopenia may also be high-risk factors but have not been consistently confirmed by multicenter trials.

4. Guidelines for Use of CSFs to Increase Chemotherapy Dose-Intensity

1996 Recommendation: Outside of clinical research trials, there is little justification for the use of CSFs to increase chemotherapy dose-intensity. In settings in which clinical research demonstrates that dose-intensity therapy not requiring progenitor-cell support produces improvement in disease control, CSFs should be used when these therapies are expected to produce significant rates of FN (eg, in $\geq 40\%$ of patients).

2000 Recommendation: In the absence of more trials demonstrating a favorable effect on overall survival, disease-free survival, quality of life, or toxicity, there is no justification for the use of CSFs to increase chemotherapy dose-intensity or schedule or both outside of a clinical trial. This application of CSF use remains the domain of appropriately designed clinical investigation.

5. Guidelines for Use of CSFs as Adjuncts to Progenitor-Cell Transplantation

1996 Recommendation: CSFs can successfully shorten the period of neutropenia and reduce infectious complications in patients undergoing high-dose cytotoxic therapy with autologous bone marrow transplantation (BMT). CSFs are effective in mobilizing autologous peripheral-blood progenitor cells (PBPCs) for transplantation, and autologous PBPC transplantation has been shown to lead to earlier hematopoietic recovery than autologous BMT.^{86,87} Trials have demonstrated the value of CSF administration after high-dose chemotherapy and PBPC transplantation.⁸⁸⁻⁹⁰ Available data suggest clinical benefits after allogeneic BMT, and routine primary CSF administration in this setting seems warranted.⁹¹ CSFs can also be used to mobilize donor PBPC for allogeneic transplantation.⁹²⁻⁹⁵ There also may be a role for the CSFs in assisting in the recovery of patients who experience delayed or inadequate neutrophil engraftment after PBPC transplantation. CSFs can be routinely recommended as adjuncts to allogeneic and autologous PBPC transplantation, both for mobilization of PBPCs and as a means to speed hematopoietic reconstitution after BMT or PBPC transplantation. Administration of a CSF in cases of engraftment failure is warranted.

2000 Recommendation: CSFs are recommended to help mobilize PBPCs and after PBPC infusion. Mobilized PBPCs have largely replaced bone marrow-derived cells for use in autologous transplantation. Side effects associated with mobilization and subsequent apheresis are usually limited and include constitutional symptoms and a decrease in platelets and other hematopoietic elements, especially after mobilization with combinations of chemotherapeutic agents and a CSF. The optimal dose of CSFs and chemotherapeutic agents is the subject of ongoing investigations, but a higher (10 $\mu\text{g}/\text{kg}/\text{d}$) dose of granulocyte CSF (G-CSF) in the setting of mobilization may yield greater content of CD34⁺ progenitor cells in the PBPC product, as documented in patients with hematologic malignancies and in patients with rheumatoid arthritis.^{88,108} Although the optimal method of mobilization needs further investigation, especially in heavily pretreated patients, administration of G-CSF, either alone or in combination with granulocyte-macrophage CSF (GM-CSF), or after the use of chemotherapeutic agents, generates PBPCs, leading to rapid hematopoietic recovery, shorter hospitalization, and possibly reduced costs.^{87,109-111} Further investigations are necessary to assess the potential risks, especially that of secondary hematologic malignancies associated with the use of combining chemotherapeutic agents and CSFs.¹¹² The role of CSF-mobilized donor bone marrow in the autologous transplant setting is also under assessment.¹¹³

6. Guidelines for Use of CSFs in Patients With Acute Leukemia and Myelodysplastic Syndromes

A. Acute Myeloid Leukemia (AML)

1996 Recommendation: Primary administration of a CSF can be used after completion of induction chemotherapy in patients 55 years of age or older. Although there are fewer data, it is likely that the results showing shortening of the duration of neutropenia may apply to younger patients as well. CSFs given either before and/or concurrently with chemotherapy for priming effects still cannot be recommended outside of a clinical trial.

2000 Recommendation: CSF use can be considered in this setting if benefits in terms of possible shortening of hospitalization outweigh the costs of CSF use. Several studies have shown that CSF administration can produce modest decreases in the duration of neutropenia when begun shortly after completion of the initial days of chemotherapy of the initial or repeat induction. Beneficial effects on end points such as duration of hospitalization and incidence of severe infections have been variable and modest, although patients 55 years of age or older are most likely to benefit from CSF use. No study has yet demonstrated significant improvement in complete response rates or long-term outcome. Thus, while there seems to be minimal risk associated with the use of CSFs in this situation, the choice of whether or not to use the CSF is likely to be determined by cost considerations. In a nutshell, the cost of the cytokine must be balanced against any possible shortening of hospitalization associated with the slightly more rapid marrow recovery, as, for example, in patients 55 years of age or older. It is not known from the published data whether the CSFs significantly accelerate recovery to ANC of 100 to 200/ mm^3 . In most patients, regenerating counts of this level are sufficient to protect against infection so as to permit safe discharge of patients from hospital.

There is no evidence that CSFs given either before or concurrently with chemotherapy for *priming effects* are of benefit, and their use in this fashion cannot be recommended outside the setting of the clinical trial.

There seems to be more profound shortening of the duration of neutropenia after *consolidation chemotherapy* for patients with AML in remission. Although the randomized studies did not address this issue, it is likely that this will be associated with decreased rates of hospitalization and possibly shorter durations of hospitalization in such patients. No benefit has been demonstrated in terms of prolongation of complete response duration or overall survival; however, the available evidence indicates that the CSFs can be recommended after the completion of consolidation chemotherapy.

B. Myelodysplastic Syndromes

1996 Recommendation: CSFs can increase the ANC in neutropenic patients with myelodysplastic syndromes. Data supporting the routine, long-term, continuous use of CSFs in these patients are lacking. Intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infection.

2000 Recommendation: No change.

C. Acute Lymphoblastic Leukemia (ALL) (Note. This topic is new to the guideline.)

2000 Recommendation: The data are sufficient to recommend G-CSF administration begun after completion of the first few days of chemotherapy of the initial induction or first postremission course, thus shortening the duration of neutropenia of less than 1,000/ mm^3 by approximately 1 week. Effects on the incidence and duration of hospitalization and the acquisition of serious infections are less consistent. Although there was a trend for improved complete response rates in one large study,¹³⁴ particularly in older adults, there was no prolongation of disease-free or overall survival in any of the trials. G-CSF can be given together with the continued corticosteroid/antimetabolite therapy, which is a feature of many ALL regimens, without evidence that such concurrent therapy prolongs the myelosuppressive effects of the chemotherapy. As in AML, it is not known from the published data whether the CSFs significantly accelerate recovery to ANC of 100 to 200/ mm^3 . In most patients, regenerating counts of this level are sufficient to protect against infection so as to permit safe discharge of patients from the hospital. The use of G-CSF for children with ALL was associated with small benefits in days of antibiotic use or in-hospital days, although a small amount of additional costs was incurred, after the costs of the CSFs were taken into consideration. Cost estimates of CSFs for adults with ALL have not been reported.

D. Leukemia in Relapse (Note. This topic is new to the guideline.)

2000 Recommendation: The available data are not sufficient to recommend either for or against the use of CSFs in patients with refractory or relapsed ALL. Few controlled studies have evaluated CSFs in patients with relapsed or refractory acute leukemia. The available data suggest shortening of the duration of neutropenia but are inadequate to comment on any effects on infectious complications and, in particular, on whether there may be an adverse effect on response rates in some patients with myeloid malignancies because of a stimulatory effect on leukemia growth in a situation in which there is less of a guarantee that chemotherapy will produce sufficient cytoreduction. Therefore, there is no evidence that CSFs are of important benefit in patients with refractory or relapsed myeloid leukemia, and they should be used judiciously or not at all in such patients.

7. Guidelines for Use of CSFs in Patients Receiving Concurrent Chemotherapy and Irradiation

1996 Recommendation: CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy.

2000 Recommendation: CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, in patients receiving radiation therapy involving large fields, therapeutic use of CSFs may be considered if prolonged delays secondary to neutropenia are expected.

8. Guidelines for Use of CSFs in the Pediatric Population

1996 Recommendation: In the absence of conclusive pediatric data, the guidelines recommended for adults are generally applicable to the pediatric age group. However, optimal CSF doses have yet to be determined. Further clinical research into the use of these factors in support of chemotherapy and PBPC transplantation in the pediatric age group should be given high priority.

2000 Recommendation: No change.

9. Guidelines for CSF Dosing and Route of Administration

1996 Recommendation: In adults, the recommended CSF doses are 5 $\mu\text{g}/\text{kg}/\text{d}$ for G-CSF (filgrastim) and 250 $\mu\text{g}/\text{m}^2/\text{d}$ for GM-CSF (sargramostim). These agents can be administered subcutaneously or intravenously as clinically indicated. CSF dose escalation is not advised. The available data suggest that rounding the dose to the nearest vial size may enhance patient convenience and reduce costs without clinical detriment.

2000 Recommendation: In adults, the recommended CSF doses are 5 $\mu\text{g}/\text{kg}/\text{d}$ for G-CSF (filgrastim) and 250 $\mu\text{g}/\text{m}^2/\text{d}$ for GM-CSF (sargramostim) for all clinical settings other than PBPC mobilization. In the setting of PBPC mobilization, if G-CSF is used, a dose of 10 $\mu\text{g}/\text{kg}/\text{d}$ seems preferable. Outside of this indication, CSF dose escalation is not advised. Rounding the dose to the nearest vial size is an appropriate strategy to maximize cost benefit. The preferred route of CSF administration is subcutaneous.

10. Guidelines for Initiation and Duration of CSF Administration

1996 Recommendation: Existing clinical data suggest that starting G-CSF or GM-CSF between 24 and 72 hours subsequent to chemotherapy may provide optimal neutrophil recovery. Continuing the CSF until the occurrence of an ANC of 10,000/ μL after the neutrophil nadir, as specified in the G-CSF package insert, is known to be safe and effective. However, a shorter duration of administration that is sufficient to achieve clinically adequate neutrophil recovery is a reasonable alternative, considering issues of patient convenience and cost.

2000 Recommendation: The optimal timing and duration of CSF administration are still under investigation. Starting CSFs up to 5 days after PBPC reinfusion is reasonable based on available clinical data.

11. Special Commentary on Comparative Clinical Activity of G-CSF and GM-CSF

1996 Recommendation: Guidelines about equivalency of the available recombinant preparations of G-CSF and GM-CSF cannot be proposed because there have been no large-scale, prospective, comparative trials evaluating relative CSF efficacy. The strength of evidence to support the use of G-CSF or GM-CSF varies based on the specific indication for CSF administration, eg, support after BMT or use with nontransplantation chemotherapy regimens. The panel strongly encourages additional clinical investigation that will guide clinical application of these biologically distinct molecules by addressing issues of comparative clinical activity, toxicity, and cost-effectiveness.

2000 Recommendation: No change.

NOTE. Superior numbers refer to reference numbers in the main text.

APPENDIX
Hematopoietic Growth Factors Update Subcommittee

Investigator	Institution
Howard Ozer, MD, PhD, Chair	University of Oklahoma Cancer Center, Oklahoma City, OK Hematology/Oncology
James O. Armitage, MD	University of Nebraska Medical Center, Omaha, NE Medical Oncology/Hematology
Charles L. Bennett, MD, PhD	Veterans Affairs Chicago Health Care System and Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL Hematology/Oncology
Jeffrey Crawford, MD	Duke Medical Center, Durham, NC Medical Oncology/Hematology
George Demetri, MD	Dana-Farber Cancer Institute, Boston, MA Medical Oncology/Hematology
Philip A. Pizzo, MD	Harvard Medical School, Boston, MA Children's Hospital, Boston
Charles A. Schiffer, MD	Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI Medical Oncology/Hematology
Thomas J. Smith, MD	Division of Hematology/Oncology, Massey Cancer Center, Richmond, VA Medical Oncology/Hematology
George Somlo, MD	City of Hope National Medical Center, Duarte, CA
James C. Wade, MD	Fred Hutchinson Cancer Research Center, Seattle, WA
James L. Wade III, MD	Cancer Care Specialists, Decatur, IL Medical Oncology/Hematology
Rodger J. Winn, MD	M. D. Anderson Cancer Center, Houston, TX Medical Oncology
Antoinette J. Wozniak, MD	Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Harper Hospital, Detroit, MI Medical Oncology/Hematology

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