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2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline

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ABSTRACT

Purpose

To update the 2000 American Society of Clinical Oncology guideline on the use of hematopoietic colony-stimulating factors (CSF).

Update Methodology

The Update Committee completed a review and analysis of pertinent data published from 1999 through September 2005. Guided by the 1996 ASCO clinical outcomes criteria, the Update Committee formulated recommendations based on improvements in survival, quality of life, toxicity reduction and cost-effectiveness.

Recommendations

The 2005 Update Committee agreed unanimously that reduction in febrile neutropenia (FN) is an important clinical outcome that justifies the use of CSFs, regardless of impact on other factors, when the risk of FN is approximately 20% and no other equally effective regimen that does not require CSFs is available. Primary prophylaxis is recommended for the prevention of FN in patients who are at high risk based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. CSF use allows a modest to moderate increase in dose-density and/or dose-intensity of chemotherapy regimens. Dose-dense regimens should only be used within an appropriately designed clinical trial or if supported by convincing efficacy data. Prophylactic CSF for patients with diffuse aggressive lymphoma aged 65 years and older treated with curative chemotherapy (CHOP or more aggressive regimens) should be given to reduce the incidence of FN and infections. Current recommendations for the management of patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of CSF or pegylated G-CSF.

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INTRODUCTION

The American Society of Clinical Oncology (ASCO) published its first evidence-based clinical practice guideline in 1994 on the use of hematopoietic colony-stimulating factors (CSF). An Update Committee of the original Expert Panel updated this guideline in 1996, 1997, and 2000. For the 2005 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 the 2000 Update. A series of computerized literature searches of MEDLINE and the Cochrane Library was performed. Details of the searches are reported in Appendix A.

The Update Committee had four face-to-face meetings to consider the evidence for each of the 2005 Recommendations. The guideline was circulated in draft form to the Update Committee for review and approval. ASCO's Health Services Committee and the ASCO Board of Directors also reviewed the final document.*

(*It is important to emphasize that guidelines and technology assessments cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result. Accordingly, ASCO considers adherence to

this technology assessment to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, this technology assessment describes the use of procedures and therapies in clinical practice; it cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment is needed. In that guideline and technology assessment development involve a review and synthesis of the latest literature, a practice guideline or technology assessment also serves to identify important questions and settings for further research.)

In this review, the Update Committee was guided by the 1996 ASCO outcomes criteria that justify the use of a drug or technology, and recommended therapy when compelling positive effects to those outcomes was demonstrated. *The 2005 Update Committee agreed unanimously that reduction in febrile neutropenia was an important clinical outcome that justified use of CSFs, regardless of impact on other factors, when the risk of febrile neutropenia (FN) was approximately 20% and no other equally effective regimen that did not require CSFs was available.*

SUMMARY OF RELEVANT BACKGROUND DATA

Myelotoxicity of Standard Chemotherapy Regimens

The use of any technology or drug requires a balance of the benefits and risks. In 1996, the American Society of Clinical Oncology published a list of important clinical outcomes that justify the use of a technology or drug in the guideline development process.[1] The clinical outcomes include the following: improvements in overall or disease-free survival; improvement in quality of life; reduced toxicity; and improved cost-effectiveness.

Table 1 lists many common chemotherapeutic regimens currently in use. Of note, unless these regimens meet or exceed the FN risk threshold suggested in the specific guideline recommendations that follow, the regimens are usually administered without growth factor support. Whenever possible, large clinical trials performed since the 2000 update are referenced. While this listing is not all-inclusive, it incorporates some new treatment trends such as dose-dense therapy. Studies dealing with older patients have been included to illustrate a growing interest in the treatment of older cancer patients and concern regarding their tolerance for chemotherapy, and a special recommendation has been added for those over 65 years of age.

Table 1 documents the febrile neutropenia rates for common regimens in everyday use. It is not intended to be a definitive guide to therapy, but as a guide to FN rates. Healthcare providers may wish to check the FN rate before prescribing CSFs.

SPECIFIC RECOMMENDATIONS

1. Recommendations for Primary Prophylactic CSF Administration (First and Subsequent-Cycle Use)

2005 recommendations

General circumstances. Primary prophylaxis is recommended for the prevention of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. For "dose dense" regimens, CSFs are required and recommended. New clinical trial data support the use of CSF when the risk of FN is in the range of approximately 20% or higher.[2,3] The use of regimens, if available, that do not require CSFs because of equal efficacy and lower risk of FN remains standard medical practice. In the absence of special circumstances, most commonly used regimens have risks of FN of less than 20% (Table 1). In making the decision to use prophylactic CSF or not, oncologists should consider not only the optimal chemotherapy regimen, but also the individual patient risk factors and the intention of treatment; that is, curative, prolongation of life, or symptom control and palliation. Examples of appropriate use in the curative setting include adjuvant treatment of early-stage breast cancer with more intensive regimens such as TAC or FEC100 or the use of CHOP or CHOP-like regimens in older patients with aggressive non-Hodgkin's lymphoma.

Special circumstances. Clinicians may occasionally be faced with patients who might benefit from relatively nonmyelosuppressive chemotherapy but who have potential risk factors for febrile neutropenia 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.

Certain clinical factors predispose to increased complications from prolonged neutropenia, including: patient age greater than 65 years; poor performance status; previous episodes of FN; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; cytopenias due to bone marrow involvement by tumor; poor nutritional status; the presence of open wounds or active infections; more advanced cancer, as well as other serious comorbidities. In such situations, primary prophylaxis with CSF is often appropriate even with regimens with FN rates less than 20%. This was the consensus opinion of the expert committee. Such high-risk patients are most often excluded from clinical trials, and this is not a situation likely to have additional clinical data.

The special circumstances have always been part of ASCO's CSF guidelines, in recognition that there are patient factors that predict for the rate and severity of febrile neutropenia. These special circumstances have been maintained from previous versions of the guideline. There are no additional new data on patients with special circumstances that predispose to high FN risk. The rate at which the use of CSFs should be considered has changed from 40% to 20%, consistent with the new evidence that demonstrates efficacy in reducing FN rates when the risk is approximately 20%, as noted above for usual risk patients.[2,3]

2005 update

Clinical efficacy data. In some situations, primary prophylaxis with CSFs is essential and recommended to alleviate the toxicity of certain "dose dense" chemotherapy regimens. Dose dense regimens have demonstrated efficacy in the adjuvant treatment of breast cancer and possible efficacy in the treatment of elderly patients with aggressive lymphoma, based on one large trial.[4]

Two large randomized clinical trials have documented that the risk of FN may be reduced substantially by primary prophylaxis with CSFs, when the risk of FN without CSFs is approximately 20%. Vogel et al randomized 928 patients with metastatic breast cancer (62%) or in the adjuvant setting (38%) to receive or not to receive pegfilgrastim

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

Cancer Histology	Stage and Prior Therapy	Regimen	No. of Patients	Leukopenia (grade 4; %)*	Neutropenia (grade 4; %)	Febrile Neutropenia (%)	Fever (grade ≥ 2; %)‡	Infection (grade ≥ 3; %)§	Infectious Death (%)
Adult AML[84]	Newly diagnosed	Ara-C/DNR	163	93	—	—	37 (no infection)	64	12
AIDS-related[85-87]	Advanced/1st and 2nd line	Lipo Dox [±G(M)-CSF]	133	36 (3 + 4)	6	—	1		0
Kaposi's Sarcoma		VP-16 (oral);	36;	—	19.4;	—	8	—	—
						—	—	—	—
		Paclitaxel	56	—	35				
AIDS-related†[88]	Intermediate	CHOP (modified)	40	—	25 (3 + 4)	2.5	—	—	10
NHL	High-grade, untreated	CHOP + G-CSF	25	—	13 (3 + 4)	0	—	—	
Bladder[89,90]	Advanced, no prior systemic therapy	GC	203	—	29.9	2	0	2.5	1
		MVAC	202	—	65.2	14	3.1	15.1	2.5
	Prior adjuvant allowed	CBDCA/Pac ± G-CSF	33	—	21	21	—	1 patient, sepsis	0
Breast[18,91-97]	Adjuvant	CA(60 mg/m^2)	1060	—	62	10 (hospitalized)	—	17	0
		CA→T(all dose levels)	1590	—	16	3	—	11	0
		CEF	351	49.9	89.7	8.5	—	—	0
		TAC	109	—	—	23.8	—	—	—
		A→T→C	484	1	24	3	—	3	0
	Adjuvant (dose dense)	A→T→C + G-CSF	493	—	3	2	—	4	0
		AC→T	501	11	43	6	—	5	0
		AC→T + G-CSF	495	6	9	2	—	3	0
	Metastatic (1st line)	A (75)	165	—	77.8	12.3	—	4.3	1 death
		Doc (100)	161	—	78.6	5.7	—	2.5	1 death
		AC	215	—	88 (3 + 4)	10	—	2	0.5
		AT	214	—	97 (3 + 4)	33	—	8	0
		TAC	54	—	100 (3 + 4)	34	—	2	0
	Metastatic (2nd line)	CapDoc	255	—	11	16	—	—	< 1
		Doc	256	—	12	21	—	—	0
Colorectal[98-103]	Adjuvant	5-FU/LV/L	449	2	—	—	—	—	< 1
		5-FU/LV	116	15 (high LV) 22 (low LV)	—	—	—	—	1.7
	Advanced	IFL	189	—	24	7.1	—	1.8	< 1
		FL	226	—	42.5	14.6	—	0	1.4
		I	226	—	12.1	5.8	—	2.2	< 1
		FOLFOX4	152	—	17	6	—	—	0
		FOLFIRI	145	20.4 (3 + 4)	28.8 (3 + 4)	9.3	—	1.9	< 1
	Advanced (one prior chemo allowed)	CPT-11 (350 mg/m^2 Q3wk)	213	36 (3 + 4)	48 (3 + 4)	14	—	< 1	3 deaths
Gastric[104]	Advanced	ECF (infusion)	289	13	32	—	1	6	< 1
Germ cell[105,106]	Advanced	BEP	141	—	34‖	—	—	—	2
		VIP	145	—	60‖	—	—	—	2.8
	Relapsed	VeIP	135	—	—	71	—	—	2.1 (all deaths)
Head/neck[107-109]	Recurrent; metastatic	5-FU/CBDCA	86	2.3	1.2	—	—	—	1.2
		CBDCA/Pac	41	4.9	9.8	—	—	—	2.4
		Cis/Doc	36	—	71	6	—	11	0
	Induction	Cis/Doc/5-FU	43	—	95 (3 + 4)	19	—	2	0
Lung[110-117]	Extensive SCLC	Cis/VP-16	159	14	38	—	—	8	≤ 6 (all toxic deaths)
	No prior treatment	CAV	156	28	52	—	—	16	≤ 4 (all toxic deaths)
		CBDCA/VP-16	74	5	—	—	—	—	2.6
		Cis/CPT-11	77	4	25.3	—	1.3	5.3	3.7
	Recurrent	Topo	107	31.7	70.2	28	—	4.7	
		CAV	104	43.6	71.7	26	—	4.8	1
	Advanced NSCLC	Cis/VNR	206	—	59	10	—	—	2
	No prior treatment								1
		Cis/Pac (24hr)	288	—	57	16	—	10	2
		Cis/Gem	288	—	39	4	—	7	1
		Cis/Doc	289	—	48	11	—	9	
		CBDCA/Pac	290	—	43	4	—	6	—
		CBDCA/Doc	406	49.5 (3 + 4)	74.4 (3 + 4)	3.7	—	11	—
	Recurrent (2nd line)	Doc (75 mg/m^2)	276	40.2 (3 + 4)	—	12.7	—	3.3	
		Pemetrexed	265	5.3 (3 + 4)		1.9	—	0	

(continued on following page)

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

Cancer Histology	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[63,118-122]	Relapsed HD; prior RT only	MOPP	123	—	22	—	3 (no infection)	13	1
		ABVD	115	—	3	—	5 (no infection)	2	0
	Intermediate to high grade						6		
	NHL; no prior treatment	CHOP	216	25	22	—		5 (≥ grade 4)	1
		CHOP-R	33	1.2	58	18	—	6	0
	Relapse NHL								
		VAPEC-B	39	—	72	44	—	5 pt	2 deaths
		ESHAP	122	—	500/μL median	30	—	—	4.1
		DHAP	90	—	53	48		31	11
Multiple myeloma[123,124]	Untreated	VAD ± Inf	169	—	—	—	—	—	1.2
	Recurrent/refractory	VAD ± Inf	52	65.4	—	—	—	32.7	7.7
Ovary[125,126]	Resected, minimal residual	Cis/Pac (24 hours)	400	12	78	Few instances	—	—	—
		CBDCA/Pac	392	6	72		—	—	—
	Salvage	Topo	139	30.1	82.4	18	—	—	0
Sarcoma[127,128]	Advanced, untreated	AD	186	32	38	—	—	—	0
		MAID	188	86	79	—	—	—	3.5
		A	263	13	—	—	5.3 (all study arms)	11 (all study arms)	—
		AI	258	32	—	—			
		CYVADIC	142	15	—	—			
Special populations[34,45] (elderly)	NHL, untreated	CHOP	197	—	—	—	5 (3 + 4)	20	16 patients (both arms)
		CHOP-R	202	—	—	—	2	12	
	Breast, adjuvant	CMF	76	4 (grade 3)	—	—	—	—	

NOTE. See cited publications for information regarding chemotherapy agents, doses, and schedules, and the use of CSFs and prophylactic antibiotics. "—" indicates no information.

Abbreviations: Ara-C, cytarabine; DNR, daunorubicin; Lipo Dox, liposomal doxorubicin; VP-16, etoposide; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; GC, gemcitabine, cisplatin; M-VAC, methotrexate, vinblastine, doxorubicin, cisplatin; CBDCA/Pac, carboplatin, paclitaxel; CA or AC, doxorubicin, cyclophosphamide; CEF, cyclophosphamide, epirubicin, fluorouracil; TAC, docetaxel, doxorubicin, cyclophosphamide; A, doxorubicin; T, paclitaxel; Doc, docetaxel; AT, doxorubicin, docetaxel; CapDoc, capecitabine, docetaxel; 5-FU/LV/L, fluorouracil, leucovorin, levamisole; IFL, irinotecan, fluorouracil, leucovorin; FOLFOX4, oxaliplatin, fluorouracil, leucovorin; FOLFIRI, irinotecan, fluorouracil (infusion), leucovorin; CPT-11, irinotecan; ECF, epirubicin, cisplatin, fluorouracil (infusion); BEP, bleomycin, etoposide, cisplatin; VIP, etoposide, ifosfamide, cisplatin; VeIP, vinblastine, ifosfamide, cisplatin; 5-FU/CBDCA, fluorouracil, carboplatin; 5-FU/Cis, fluorouracil, cisplatin; Cis/Doc, cisplatin, docetaxel; Cis/VP-16, cisplatin, etoposide; CAV, cyclophosphamide, doxorubicin, vincristine; CBDCA/VP-16, carboplatin, etoposide; Cis/CPT-11, cisplatin, irinotecan; Topo, topotecan; CDDP/VNR, cisplatin, vinorelbine; Cis/Pac, cisplatin, paclitaxel; Cis/Gem, cisplatin, gemcitabine; CBDCA/doc, carboplatin, docetaxel; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CHOP-R, cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab; VAPEC-B, vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin; ESHAP, etoposide, methylprednisolone, Ara-C, cisplatin; DHAP, dexamethasone, cisplatin, cytarabine; VAD, vincristine, doxorubicin, dexamethasone; inf, alpha interferon; AD, doxorubicin, dacarbazine; MAID, mesna, doxorubicin, ifosfamide, dacarbazine; A, doxorubicin; AI, doxorubicin, ifosfamide; CYVADIC, cyclophosphamide, vincristine, doxorubicin, dacarbazine; CMF, cyclophosphamide, methotrexate, fluorouracil.

*Grade 4 leukopenia: WBC count $< 1.0 \times 10^9$/L; grade 4 neutropenia: ANC $< 0.5 \times 10^9$/L.

†Most patients received antiretroviral therapy and data do not include opportunistic infections.

‡Common Toxicity Criteria Fever ≥ grade 2; ≥38.1°C (≥100.5°F).

§Infection ≥ grade 3: systemic infection requiring hospitalization.

‖Includes all grade 4 hematologic malignancies.

6 mg after 100 mg/m^2 docetaxol every 3 weeks for four cycles. The incidence of FN (1% versus 17%) and hospitalization for FN (1% *v* 14%) was reduced by more than 90% ($P < .001$).[3] A trial of intensified therapy in 171 patients with small-cell lung cancer, with companion randomizations to prophylactic CSF and/or antibiotics showed that the rate of FN in the first cycle was reduced from 23% with antibiotics alone to 10% with antibiotics and CSF; the rate of FN overall was similarly reduced from 32% to 18% ($P < .01$).[2] The use of CSF to reduce the risk of FN is justified to reduce the risk of FN when that risk is approximately 20%, as with both of these treatment regimens. However, if alternative but equal treatment that does not require CSF is available, it should be used. Results of efficacy from docetaxol 100 mg/m^2 in the first trial have not been reported yet. The efficacy of platinum-containing regimens for small-cell lung cancer, with equal efficacy and less risk of FN and need for prophylactic CSF, has made them a standard of care in the US.

The ASCO CSF Update Committee does not recommend for or against any specific chemotherapy regimen, but the evidence is clear that CSFs reduce the incidence of FN when the rate is approximately 20%. When available, alternative regimens offering equivalent efficacy, but not requiring CSF support, should be utilized. However, when regimens are used that have a FN incidence of greater than 20%, CSFs have been proven to be effective and are recommended. A new meta-analysis of prophylactic CSFs in patients with solid tumor or malignant lymphoma was presented at ASCO 2005 and reviewed by the Update Committee. The study reports significant reductions in the

risk of FN from 37% to 20% (14 studies, n = 3,091, relative risk reduction 46%, $P < .0001$) and the risk of infection-related mortality from 3.3% to 1.7% (10 studies, n = 2,468, relative risk reduction 48%, $P = .01$).[5] Impact on overall mortality has not been reported. If this result is confirmed in the final publication, it will provide more support for the use of prophylactic CSFs in regimens with sufficient risk.

There are new data for specific clinical situations. A meta-analysis of 12 randomized trials from 1992 to 2003 with 1,823 non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) patients found that, compared with no prophylaxis, prophylactic CSFs significantly reduced the relative risk (RR) of severe neutropenia (RR 0.67; 95% CI 0.60 to 0.73), febrile neutropenia (RR 0.74; 95% CI 0.62 to 0.89), and infection (RR 0.74; 95% CI 0.64 to 0.85). However, there was no evidence that CSFs reduced the number of patients requiring intravenous antibiotics (RR 0.82; 95% CI 0.57 to 1.18), lowered infection-related mortality (RR 1.37; 95% CI 0.66 to 2.82); or improved complete tumor response (RR 1.02; 95% CI 0.94 to 1.11), freedom from treatment failure (hazard ratio 1.11; 95% CI 0.91 to 1.35), or overall survival (hazard ratio 1.00, 95% CI 0.86 to 1.16).[6] One study evaluated quality of life and found no differences with CSFs.[7] Overall, the impact of CSFs on the disease has been small and does not routinely warrant use to improve survival. CSFs do reduce the risk of FN significantly, and were recommended by the update committee on that basis.

A valid model to predict who will develop FN, so that CSF use could be restricted to that group, would represent a major advance in patient management. A systematic review of previously reported models has identified a number of risk factors for either FN occurrence or for adverse outcome of established FN.[8,9] While current models are promising, they are based on retrospective data sets and need prospective validation. Future prospective models have the potential to improve the efficacy and cost-effectiveness of growth factor prophylaxis and therapy.

2. Recommendations for Secondary Prophylactic CSF Administration

2005 recommendation

Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.

2005 update

Since the 2000 update, no prospective studies of secondary CSF prophylaxis have been reported. Dose reduction or delay remains an appropriate strategy for the palliative treatment of cancer, as there is no evidence that dose maintenance or escalation improves clinically important outcomes in this setting.

For adjuvant therapy, conditional models have been developed based on the nadir neutrophil count during cycle 1. Rivera et al conducted a prospective clinical trial that assigned women receiving adjuvant breast cancer chemotherapy who experienced neutropenia of less than 500/mm^3 in cycle 1 to granulocyte colony stimulating factor (G-CSF) in subsequent cycles.[10] The G-CSF recipients experienced fewer episodes of hospitalization for FN and greater dose-intensity compared to historical controls without CSF support, but none of the other significant clinical outcomes (survival, quality of life, toxicity, or cost) were reported.

Based on the available data, no definitive conclusions can be drawn regarding the benefits of secondary prophylaxis on survival, quality of life, or cost. Randomized trials to properly test the hypothesis are required.

3. Recommendations for Therapeutic Use of CSF

A. Therapy of patients with afebrile neutropenia

2005 recommendation. CSFs should not be routinely used for patients with neutropenia who are afebrile.

2005 update. There are no new published data since the 2000 ASCO guideline that pertain to the use of CSF in patients who are afebrile and neutropenic.

B. Therapy of febrile patients with neutropenia

2005 recommendation. CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (> 10 days) and profound ($< 0.1 \times 10^9$/L) neutropenia, age greater than 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever. This was the consensus opinion of the update committee, as there are no new data. Prior Infectious Disease Society of America guidelines have supported the use of CSFs in similar circumstances, referring to the ASCO guidelines.

2005 update. Several relevant studies have been reported since 2000. In a multicenter trial conducted in Spain, adult patients with solid tumors or lymphoma who developed FN and had at least one high-risk factor, were treated with intravenous antibiotics and randomly assigned to receive G-CSF (5 μg/kg per day) until neutrophil recovery. CSF recipients had a shorter period of grade 4 neutropenia (median 2 versus 3 days, $P = .0004$), antibiotic therapy (median 5 versus 6 days, $P = .013$), and hospital stay (median 5 versus 7 days, $P = .015$).[11] Survival between groups was similar.

Two meta-analyses of trials of adjunctive CSF therapy for cancer patients with FN have now been reported. These analyses included different patient numbers as a consequence of different search strategies and the inclusion by one analysis of data that was not published in English. Berghmans' analysis, which incorporated 962 patients, detected no advantage for the use of CSF in terms of mortality from FN, with a relative risk of 0.71 (95% CI 0.44 to 1.15). No other analysis of clinical benefit was reported.[12] In a Cochrane systematic review and meta-analysis, which included 1518 patients from 13 trials, patients randomized to receive CSF experienced less prolonged neutropenia (25% versus 45%; OR = 0.32 [0.23-0.46]; $P < .00001$), less prolonged hospitalization (23% versus 32%; OR = 0.63 [0.49-0.82]; $P = .0006$), marginally less infection-related mortality (3.1% versus 5.7%; OR = 0.51 [0.26-1.00]; $P = .05$) and no significant difference in overall mortality (5.1% versus 7.1%; $r = 0.68$ [0.43-1.06]; $P = .10$).[13] Bone, joint pain, and arthralgias were more common in CSF treated patients ($P = .007$).

Clinical prediction models have been developed to help prospectively identify patients with cancer who are at higher risk of complications as a result of fever and neutropenia.[14,15] Reported risk factors for

serious medical complications, including death, in patients with established FN include the development of FN as an inpatient; hypotension; sepsis; various comorbidities, including cardiovascular and pulmonary disease; leukemia or lymphoma diagnosis; age greater than 65 years, prior fungal infection; visceral organ involvement; organ dysfunction; uncontrolled malignancy; and the severity and duration of neutropenia.

Two recent studies have reported that hypotension and bacteremia in the setting of neutropenia are significant risk factors for prolonged hospitalization ($>$ 7 days) and high mortality. Malik et al reported a mortality rate associated with FN in patients presenting with shock of 82%,[16] and a study from France reported that patients admitted to an ICU with FN experienced a 54% 30-day mortality.[17] While a number of clinical characteristics may provide prognostic information regarding the outcomes of hospitalized patients with FN, predictive models are needed to better identify high-risk patients who may benefit from the addition of adjunctive CSFs. A risk model for mortality in hospitalized cancer patients with FN has recently been reported. In a multivariate model, several independent risk factors for inpatient mortality among hospitalized patients with FN have been identified including: age $\geq$ 65, cancer type (leukemia, lung cancer), comorbidities (CHF, PE, lung, renal, liver, and cerebrovascular disease), and infectious complications (hypotension, pneumonia, bacteremia, and fungal infection).[5]

4. Recommendations for Use of CSFs to Increase Chemotherapy Dose-Intensity and Dose-Density

2005 recommendation

Use of CSFs allows a modest to moderate increase in dose-density and/or dose-intensity of chemotherapy regimens. Available data would suggest a survival benefit from the use of dose-dense (but not dose-intense) regimens with CSF support in a few specific settings (eg, node-positive breast cancer; and possibly NHL pending confirmation of results of individual trials). However, additional data in these settings are needed and these results cannot be generalized to other disease settings and regimens. Dose-dense regimens should only be used within an appropriately designed clinical trial or if supported by convincing efficacy data.

2005 update: Dose density

There has been increasing interest in the development of dose-dense chemotherapy schedules for a variety of tumor types. We have summarized the evidence from randomized studies of the most common tumor types treated in a dose-dense fashion.

Citron et al demonstrated a disease-free and overall survival benefit to dose-dense chemotherapy with CSF versus standard chemotherapy scheduling in node-positive breast cancer.[18]

The use of CSFs to intensify therapy for small-cell lung cancer has reduced the risk of FN but had mixed results in treatment of the disease. There are two recent trials of dose-dense therapy. Thatcher et al used every 2 week dose-dense therapy (doxorubicin, cyclophosphamide and etoposide) versus conventional every 3 week therapy in 403 patients with small-cell lung cancer; survival at 12 months was increased to 47% from 39% and to 13% from 8% at 24 months (HR = 0.80; 95% CI 0.65 to 0.99; $P = .04$). Quality of life and toxicities were similar in the two groups.[7] More recently, Lorrigan et al randomized 318 patients with good-prognosis small-cell lung cancer to standard chemotherapy or dose-dense chemotherapy with filgrastim and blood progenitor cell support. Treatment time was reduced, and the rate of FN was reduced by 4% in the dose-dense group (11% versus 15%), but there was no clinical advantage. Overall response rates, median survival, 1- and 2-year survival, and overall survival were unchanged.[19]

There are two recent trials of dose-intense therapy in small-cell lung cancer. A recent randomized trial of chemotherapy for small-cell lung cancer with cyclophosphamide, adriamycin, and etoposide attempted to increase relative dose-intensity and prevent infections by the use of G-CSF at standard doses, and/or prophylactic antibiotics. Increasing the dose-intensity by 70% was associated with more grade 4 leukopenia (79% versus 50%); grade 4 thrombocytopenia (44% versus 11%); anorexia, nausea, and mucositis; but not deaths. Response rates, median survival, and 2-year survival rates were not different between the experimental and control arms.[20] Timmer-Bonte et al intensified therapy for 171 patients with small cell lung cancer. As noted above, the rate of FN in the first cycle was reduced from 23% with antibiotics alone to 10% with antibiotics and CSF; the rate of FN overall was similarly reduced from 32% to 18%.[2] There was no major effect on the disease itself. As noted by the authors, this therapy is used in Europe but not the US where platinum-containing regimens are used with equal efficacy, and less need for routine CSF support. Berghmans et al performed a meta-analysis of 12 studies since 1991, including a total of 2,107 randomized patients.[21] The authors concluded that there was no significant impact of CSFs survival from dose-maintenance or dose-intensification.

A recent study[22] of young patients with diffuse aggressive NHL compared CHOP every 21 days (CHOP-21) to CHOP every 14 days with CSF support (CHOP-14), with or without etoposide (CHOEP-21, CHOEP-14) in 2 $\times$ 2 factorial design; the primary end point of the study was event-free survival (EFS). The addition of CSF to CHOP (CHOP-14 versus CHOP-21) displayed a statistically significant improvement to EFS (RR = 0.61; CI 0.38 to 0.99, $P = .048$), while the addition of CSF to the etoposide arm (CHOEP-14 versus CHOEP-21) showed no difference in EFS ($P = .842$) or overall survival ($P = .472$). In elderly diffuse aggressive lymphoma patients on another study of similar design, there appeared to be a greater benefit with the reduction in cycle length to two weeks, facilitated by the addition of CSF (CHOP-14), compared to standard CHOP (CHOP-21), with improvements in EFS (RR = 0.66, $P = .003$) and overall survival (RR = 0.58, $P < .001$).[4]

5. Recommendation for the Use of CSFs As Adjuncts to Progenitor-Cell Transplantation

2005 recommendation

Administration of CSFs to mobilize peripheral-blood progenitor cell (PBPC) often in conjunction with chemotherapy and their administration after autologous, but not allogeneic, PBPC transplantation is the current standard of care.

2005 update

The major complications of high-dose chemotherapy supported by autologous bone marrow transplantation (BMT) or PBPC transplantation are disease recurrence, infection, the need for RBC and platelet transfusions, delayed or incomplete engraftment, and organ damage from the ablative regimen. Prolonged hospitalization and the high cost of treatment are also associated

with autologous transplant. The same problems, plus graft-versus-host disease (GvHD) and graft rejection, are also present in patients undergoing allogeneic BMT or allogeneic PBPC transplantation. Among autologous PBPC patients, post-transplant G-CSF use has been associated with savings in the duration of hospitalization and overall medical costs.[23] In contrast, G-CSF use following allogeneic blood SCT has been shown to decrease the duration of absolute neutropenia, but did not lead to shorter hospitalizations, cost savings, or less frequent antibiotic use.[24]

However, CSFs used after allogeneic transplantation have been reported to increase the incidence of severe GvHD and to reduce survival. A 2004 European study of 1,789 patients with acute leukemia who received BMT[25] found a higher rate of GvHD of grades 2 to 4 among patients receiving G-CSF than among controls (50% versus 39%). The G-CSF group also had a higher risk of transplantation-related mortality (RR 1.73, $P = .00016$). Patients who received G-CSF also had a lower overall survival (RR 0.59, $P < .0001$) and lower leukemia-free survival (RR 0.645, $P = .0003$). An adverse effect on survival was not noted in recipients of peripheral blood stem cells.

The use of CSFs to mobilize peripheral blood progenitor cells (PBPC) and to shorten the period of neutropenia after cytoreduction and PBPC transplantation, is well established. Although rare, reports of splenic rupture and severe thrombocytopenia have been documented after use of filgrastim, lenograstim, and sargramostim for PBPC mobilization. Individuals receiving CSFs for mobilization should have their platelet counts monitored. Filgrastim is indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.[26,27] The efficacy and safety of newer CSFs in the setting of PBPC mobilization are currently being investigated in phase I/II studies.

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

Because considerations are different for acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS), evidence and recommendations for each are discussed separately.

AML

2005 recommendation for initial induction chemotherapy. Several studies have shown that CSF administration can produce modest decreases in the duration of neutropenia when begun shortly after completion of the initial induction chemotherapy. Beneficial effects on end points such as duration of hospitalization and incidence of severe infections have been variable and modest. CSF use following initial induction therapy is reasonable, although there has been no favorable impact on remission rate, remission duration or survival. Patients older than 55 years of age may be most likely to benefit from CSF use.

2005 update: Primary CSF administration after initial induction chemotherapy for AML

There have been no major studies published since the 2000 update.

CSF priming of leukemia cells in patients with AML

2005 recommendation for CSFs for priming effects. Use of CSFs for priming effects is not recommended.

2005 update: CSF priming of leukemia cells in patients with AML. A randomized trial published in 2003 evaluated priming with G-CSF in younger adults (aged 18 to 60 years) receiving initial induction therapy, and demonstrated a higher rate of disease-free survival in the G-CSF recipients, though there was no effect on CR rate or overall survival. The effect was most prominent in the subgroup of patients with "standard risk" cytogenetics, with no benefit for those in better or unfavorable risk groups. There is no standard definition of this biologically and clinically heterogeneous group of "standard risk" patients, and it is not clear how to apply this finding in clinical practice.[28] A large European trial randomized patients older than 60 years of age who had AML to receive either no growth factor or G-CSF given during, during and after, or after the completion of therapy. Although the complete remission rate was higher in the two groups of patients who received the G-CSF simultaneous with the chemotherapy (60% versus 50%, $P = .01$), there was no difference in event-free or overall survival, and the authors concluded that the "quality" of these remissions was poor.[29]

Consolidation therapy for patients with AML in complete remission

2005 recommendation for consolidation chemotherapy in AML. CSF use can be recommended after the completion of consolidation chemotherapy because of the potential to decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive postremission chemotherapy. There seems to be more profound shortening of the duration of neutropenia after consolidation chemotherapy for patients with AML in remission than for patients receiving initial induction therapy. There is no effect on the duration of complete response duration or overall survival.

There is, as yet, no information about the effect of longer acting, pegylated CSFs in patients with myeloid leukemias, and they should not be used in such patients outside of clinical trials.

2005 update: Consolidation therapy for patients with AML in complete remission. Postremission chemotherapy is routinely administered to patients with AML in an attempt to increase the probability 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 home. Two large randomized trials evaluated the role of G-CSF given after completion of relatively standard consolidation therapy to such patients.[30,31] Both demonstrated marked decreases in the duration of severe neutropenia, with elimination of severe neutropenia in a fraction 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.

MDS

2005 recommendation. No change from 2000 update. CSFs can increase the absolute neutrophil count in neutropenic patients with myelodysplastic syndromes (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.

2005 update. There have been no studies with results that change the recommendation.

ALL

2005 recommendation. CSFs are recommended after the completion of the initial 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. There are less consistent effects on the incidence and duration of hospitalization and the acquisition of serious infections. Although there was a trend for improved CR rates in one large study,[32] 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 unknown from the published data whether the CSFs significantly accelerate recovery to neutrophil counts 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 antibiotics or in-hospital days, although a small amount of additional costs was incurred, after taking into consideration the costs of the CSFs. Cost estimates of CSFs for adults with ALL have not been reported.

2005 update. Only one new study was published since the 2000 update. A large randomized study of children with high risk ALL receiving intensive induction and consolidation therapy failed to show any differences in the duration of hospitalization, incidence of FN, or incidence of severe infection in G-CSF recipients despite an improvement in time to neutrophil recovery of 2.5 days.[33]

Acute leukemia in relapse

2005 recommendation. CSFs should be used judiciously, or not at all, in patients with refractory or relapsed myeloid leukemia since the expected benefit is only a few days of shortened neutropenia. Because of the relatively low response rate in AML patients with relapsed or refractory disease, clinicians may be faced with the difficult dilemma of whether the persistence of leukemia after chemotherapy is a consequence of drug resistance or a stimulatory effect of the CSF. Although drug resistance is the most likely cause of treatment failure, it is sometimes necessary to stop the CSF and observe the patient for a few days to be certain. No significant change from 2000 recommendation.

2005 update. No additional studies have been published that would change the recommendation.

7. Recommendations for Use of CSFs in Patients Receiving Radiotherapy With or Without Concurrent Chemotherapy

2005 recommendation

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

2005 update

CSF use with chemoradiotherapy. No additional studies have been published that would change the recommendation.

CSFs with radiotherapy. No additional studies have been published that would change the recommendation.

8. Recommendations for Use of CSFs in Older Patients (Note: This Topic is New to the Guideline)

2005 recommendation

Prophylactic CSF for patients with diffuse aggressive lymphoma aged 65 and older treated with curative chemotherapy (CHOP or more aggressive regimens) should be given to reduce the incidence of FN and infections.

Definition of the problem

Age and risk of chemotherapy-induced neutropenia. Aging is one of the conditions for which prophylactic use of growth factors may be indicated irrespective of the threshold risk of neutropenia. Multiple studies, primarily in breast cancer patients, have found that the risk of neutropenia following chemotherapy increases with age.[34-37] The threshold for this effect varies with different studies, and has been associated with ages over 60, 65, and 70.[35-37] Mortality resulting from neutropenic infections is also increased for older patients with lymphoma.[38-40]

The most persuasive documentation of the association of aging and chemotherapy-induced myelosuppression (sometimes with infection) comes from the studies of older patients with NHL. In a retrospective study of community practice, the incidence of neutropenic fever was 34% in patients over 65 years and 21% for those younger,[41] and most of the episodes of FN occurred after the first course of treatment.[42] The average hospital duration for FN was also longer for older patients: 12.1 days for patients 65 years and older and 8.2 days for those younger.

Prospective studies of CHOP-like combinations of chemotherapy for individuals aged 60 and older have reported an incidence of neutropenic infections between 27% and 47%.[40,43-50] There is a single exception, a 2003 study reporting a cumulative incidence of infections (WHO grade 2-4) of 11% to 15%.[51] The incidence of infection was 32% during the first course of treatment and declined as the doses of chemotherapy were reduced and the treatment was administered at wider time intervals. In this study, FN (reported separately from infection) was observed in 36% to 45% of patients receiving CHOP chemotherapy, and patients older than 80 years completed significantly fewer treatments than younger patients (43% versus 80%, $P < .001$) as a result of toxicity, refusal of treatment, or death.[51]

Alternative strategies

Dose reduction. A strategy of dose reduction has been associated with reduced response rate and survival in several randomized controlled studies[46,48,49,52-54] of lymphoma patients undergoing curative therapy, and is therefore not recommended in this patient population. The data in other tumor types is lacking. Thus, dose reduction may be a reasonable approach in certain patient populations, but the available clinical data do not allow for a definitive conclusion.

Patient selection. Among patients aged 65 years and older, those with a poor performance status (2 or higher) are at increased risk of FN.[55] The use of performance status to select patients has significant drawbacks, however, including the subjectivity of assessment and its limited reliability as a predictor of FN. For patient selection to be a useful alternative to CSF use, additional risk factors must be considered to identify older patients at risk of FN. Aside from data available in patients with lymphoma, there is insufficient evidence to support the use of prophylactic CSFs in patients solely based on age. Further clinical trials are warranted to address this issue.

Review of relevant literature

The prophylactic use of CSFs in older patients was explored in several randomized studies of patients treated with CHOP or CHOP-like chemotherapy. In three cases, G-CSF reduced the risk of FN or infections by more than 50%.[44,50,52] Similar results were reported in two retrospective reviews of practice experiences.[42,56] Osby et al randomized patients receiving CHOP or CNOP to prophylactic G-CSF or not. CHOP patients randomized to receive G-CSF experienced significantly fewer episodes of severe (89% versus 55%) or febrile neutropenia (50% versus 34%; $P < .001$), and significantly fewer deaths (62% versus 45%) with projected five-year survivals of 45% and 60% in the control and G-CSF arms respectively ($P = .04$).[47]

In the study by Doorduijn et al, elderly NHL patients receiving CHOP and randomized to receive a fixed dose of G-CSF of 300 μg daily experienced significantly fewer episodes of severe neutropenia ($P < .001$), infection in cycle 1 ($P = .01$) with modest increase in relative dose-intensity ($P < .05$) and no difference in projected 5-year survival.[51] Therefore, the evidence related to the impact of CSF support on survival remains inconclusive.

9. Recommendations for Use of CSFs in the Pediatric Population

2005 recommendation

The use of CSFs in pediatric patients will almost always be guided by clinical protocols. As in adults, the use of CSFs is reasonable for the primary prophylaxis of pediatric patients with a likelihood of FN. Similarly, the use of CSFs for secondary prophylaxis or for therapy should be limited to high-risk patients.

However, the potential risk for secondary myeloid leukemia or myelodysplastic syndrome associated with CSFs represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the use of CSFs in children with ALL should be considered with caution.

2005 update

Since the 2000 review, several multicenter randomized clinical trials have evaluated prophylactic CSFs in children, particularly with acute leukemia. A meta-analysis has been presented of 16 RCTs of prophylactic CSFs in children receiving systemic chemotherapy reporting significant reductions in FN (RR = 0.80, 95% CI 0.67 to 0.95; $P = .01$), documented infection (RR = 0.78, 95% CI 0.62 to 0.97; $P = .02$), and a length of hospitalization (weighted mean difference = 1.9, 95% CI 1.1 to 2.7 days; $P < .00001$).[57] For pediatric ALL patients, however, G-CSF use is unlikely to lead to cost saving.[58] The recent observation[59] that the administration of G-CSF to children with ALL may increase the risk for developing a therapy-related myeloid leukemia or myelodysplastic syndrome adds a further note of caution to its usage, especially in patients receiving concurrent irradiation, topoisomerase II inhibitors, or alkylating agents.

For treatment of febrile neutropenia, Ozkaynak et al randomized pediatric patients with FN to receive antibiotics or antibiotics and CSF. The group that received CSF had fewer days of neutropenia, but only 1 less day with fever, and their hospital stay was decreased by 1 day.[60]

10. Recommendations for CSF Initiation, Duration, Dosing, and Administration

2005 recommendation for CSF dosing and administration

CSF. CSF should be given 24 to 72 hours after the administration of myelotoxic chemotherapy. In the setting of high-dose therapy and autologous stem-cell rescue, CSF can be given between 24 and 120 hours after administration of high-dose therapy. CSF should be continued until reaching an absolute neutrophil count (ANC) of at least 2 to 3×10^9/L. For PBPC mobilization, CSF should be started at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis.

In adults, the recommended CSF doses are 5 μg/kg/d for G-CSF and 250 μg/m^2/d for granulocyte macrophage colony stimulating factor (GM-CSF) for all clinical settings other than PBPC mobilization. In the setting of PBPC mobilization, if G-CSF is used, a dose of 10 μg/kg/d may be preferable. The preferred route of CSF administration is subcutaneous.

Pegylated G-CSF (pegfilgrastim). Pegfilgrastim 6 mg should be given once, 24 hours after completion of chemotherapy. Pegfilgrastim is not currently indicated for stem cell mobilization. The safety and efficacy of pegylated G-CSF has not yet been fully established in the setting of dose-dense chemotherapy. The 6 mg formulation should not be used in infants, children, or small adolescents weighing less than 45 kg.

2005 update

G-CSF and GM-CSF. A recent study by Papaldo et al[61] evaluated the role of alternative filgrastim dosing schedules for early stage breast cancer patients receiving epirubicin and cyclophosphamide chemotherapy. A total of 506 patients were assigned to five different treatment arms with or without CSF. The CSF schedules were as follows: (1) 480 mcg/d subcutaneously days 8 to 14; (2) 480 mcg/d days 8, 10, 12, and 14; (3) 300 mcg/d day 8 to 14; (4) 300 mcg/d day 8, 10, 12, and 14; and (5) 300 mcg/d days 8 and 12. The incidence of grade 4 neutropenia was reduced from 41.6% in controls to 5.4% in G-CSF arms. The more important parameter, febrile neutropenia, was observed in only 7% of non-CSF patients, so CSFs would not have been suggested under existing guidelines. Schedule 5 was equivalent to the daily or alternate day schedules of CSF with respect to grade 3 and 4 neutropenia ($P = .77$ and $P = .89$, respectively) and percentage of delayed cycles of chemotherapy ($P = .43$ and $P = .42$, respectively). Compared with daily CSF administration (schedules 1 and 3), schedule 5 demonstrated less grade 1 to 3 bone pain (53% versus 29%, respectively; $P = .01$) and less grade 1 to 2 fever (24% versus 8%, respectively; $P = .04$). However, the small number of patients in each arm (42 to 52) would have 80% power to detect only very large differences in FN incidence, eg, 20% to 30%. These findings from this underpowered trial, for patients in whom CSFs are not routinely indicated, are not definitive proof of the efficacy of less frequent CSF dosing, but suggest that alternative dose schedules warrant further study in larger randomized clinical trials to improve efficacy, reduce side effects, and reduce cost.

Pegylated G-CSF. The inconvenience associated with daily administration of CSFs prompted development of a longer-acting form by pegylation of G-CSF. Following initial phase II assessment of safety and efficacy, two phase II studies evaluated variable, weight-adjusted, and fixed doses of pegylated G-CSF, given 24

hours after chemotherapy. A recent combined, retrospective analysis[62] compared once-per-chemotherapy-cycle pegfilgrastim with daily G-CSF (filgrastim) in breast cancer patients undergoing myelosuppressive chemotherapy enrolled in two similarly designed, randomized, double-blind, pivotal trials. On day 2 of each chemotherapy cycle, patients received a single subcutaneous (SC) injection of pegfilgrastim (either 6 mg [n = 77] or 100 μg/kg [n = 149]) or daily G-CSF SC injections (5 μg/kg/d; n = 222). G-CSF injections were continued until either ANC $\geq 10 \times 10^9$/L after the expected nadir or for up to 14 days, whichever occurred first. Each of these trials demonstrated that a single pegfilgrastim injection per cycle is as effective at reducing the duration of severe neutropenia as daily injections of filgrastim. Clinical efficacy data from the two trials were combined for analysis (n = 448). The risk of FN (ANC $< 0.5 \times 10^9$/L with fever $\geq$ 38.2°C) was significantly lower (11% versus 19%, respectively [RR, 0.56; 95% CI 0.35 to 0.89]) in patients receiving pegfilgrastim than for those receiving filgrastim.

A smaller randomized phase-II study in patients with lymphoma treated with etoposide, methylprednisolone, cisplatin, and cytarabine showed equivalent effects of daily administration of G-CSF and one-time administration of pegylated G-CSF.[63] In a placebo-controlled phase III study of patients treated for breast cancer, pegylated G-CSF reduced the incidence of FN, hospitalization, and intravenous anti-infective use in patients receiving a docetaxel-based regimen, with an incidence of FN in the control arm of approximately 17% versus 1% in the treatment group ($P < .001$); the incidence of hospitalization was also reduced from 14% in the control group to 1% ($P < .001$).[3]

The long-term effects of long acting growth factors are unknown, and the Update Committee expressed concern about potential leukocytosis, late neutropenia after discontinuation of pegylated G-CSF, and the need for long-term safety data.

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

2005 recommendation

No change. No guideline recommendation can be made regarding the equivalency of the two colony-stimulating agents. As in 2000, further trials are recommended to study the comparative clinical activity, toxicity, and cost-effectiveness of G-CSF and GM-CSF.

2005 update

In a recent meta-analysis of effectiveness of the colony-stimulating factors, the issue of equivalency was not addressed.[12] A recent systematic review of the subject concluded that head-to-head trials of G-CSF and GM-CSF demonstrate higher incidence of fever in the GM-CSF arms but data on the comparative ability to reduce chemotherapy-induced complications are lacking.[64]

A variety of studies continue to investigate differences between the two agents as enhancers of progenitor cells following growth factor administration. Three of these studies compared G-CSF to GM-CSF as single agents in different settings. In a randomized study in 71 breast and ovarian cancer patients treated with carboplatin, etoposide, and melphalan, no difference in hematopoietic recovery was noted between G-CSF or GM-CSF patients, all treated at a dosed of 5 μg/kg of the designated agent until completion of stem cell harvest.[65] Patients treated with G-CSF had significantly higher T-cell levels in the early and late post-transplant periods and a longer time to progression (61 months for G-CSF-treated patients and 25 months for GM-CSF–treated patients). After a median follow-up of 40 months, the overall survival rate was 75% for patients who received G-CSF and 50% for patients who received GM-CSF. A phase III study in 156 patients with breast cancer, myeloma, or lymphoma concluded that G-CSF was superior to GM-CSF as demonstrated by a faster time to recovery of granulocyte counts (11 versus 14 days, $P = .0001$) and fewer patients with fever (18% versus 52%, $P = .001$).[66] The yield of CD 34^+ cells was also found to be higher for G-CSF. Earlier mobilization of CD 34^+ cells with G-CSF than with GM-CSF was also demonstrated in another study after high-dose nonmyeloablative therapy with cyclophosphamide, etoposide, and cisplatin.[67]

In addition to these studies comparing the single agents, three studies have examined a comparison of G-CSF with a combination of G- and GM-CSF. Utilizing a cross-over design, Koc et al found that G-CSF alone resulted in a mobilization of more CD 34^+ cells, and that the single agent was effective after failure of the combination to mobilize sufficient progenitors.[67] Two other studies using a standard comparative design failed to demonstrate significant differences between the two regimens with respect to granulocyte function,[68,69] though in the Recchia et al study,[69] patients on the G-CSF–alone arm had lower platelet counts one month after transplantation.

12. Special Comments on Growth Factors As a Treatment for Radiation Injury (Note: This Topic Is New to the Guideline)

2005 recommendation

Current recommendations for the management of patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of CSF or pegylated G-CSF.[70,71]

Accidental or intentional (eg, resulting from a terrorist attack or war) total body radiation leads to probable or certain death from bone marrow failure at doses of 3 to 10 Grays (Gy) without supportive care, CSFs, and/or a bone marrow transplant.[72-74] Doses below that level are almost always survivable with excellent nursing care, and higher doses are lethal because of injury to other organs such as the gastrointestinal tract. The chance for mortality from any radiation dose rises with combined injuries to the skin, lungs, and so on.[75]

Hematopoietic growth factors can increase the survival, proliferation, amplification, and differentiation of granulocyte progenitors to produce neutrophils. Although no prospective, randomized trials have been carried out to determine the benefit of hematopoietic growth factors in humans exposed to accidental or intentional radiation injury, they have been utilized in radiation accident victims, and neutrophil recovery appears to have been hastened in 25 of 28 cases (REACT/TS registry). In animal models, prompt administration of hematopoietic growth factors after otherwise lethal total body radiation exposure dramatically increases survival.[76-81]

13. Impact of CSFs on Quality of Life and Health Care Costs

The Update Committee had much discussion about the cost of CSFs, their impact on the health system and patients, and their impact on global quality of life. The Update Committee made the

recommendations for CSF use when the FN rate was approximately 20% based on clinical impact alone, due to the consensus that reduction in febrile neutropenia itself was an important clinical outcome. Evidence from meta-analysis that CSFs reduced infection-related mortality added to the clinical evidence that use of CSFs was important,[5] and further emphasized that the primary decisions were clinical and not economic.

In the original CSF guideline and subsequent updates, the use of CSFs could be justified on economic grounds if the rate of FN approached 40%, which was coincidentally the same as the clinical threshold for use of CSFs. With the new clinical threshold of benefit at a FN rate of 20%, and evidence of reduction in infection-related mortality, the Update Committee noted that CSFs should be used when indicated for clinical reasons, not economic ones. There was substantial discussion on the role of the Update Committee in limiting access to expensive but important drugs, the current threshold at which CSFs would be cost saving, and the impact of CSFs on health care costs. Doorduijn et al evaluated the efficacy and cost of prophylactic CSF in elderly patients with aggressive lymphoma treated with CHOP chemotherapy.[82] While response rates, overall survival, and event-free survival were no different between the CHOP and CHOP-CSF arms, total hospital costs were higher for patients treated with CHOP-CSF (€ 18,356; 95% CI € 15,807 to € 20,906) compared with CHOP alone (€ 12,178; 95% CI € 10,297 to €14,059). Even a low, fixed dose of CSF reduced febrile neutropenia rates. Given the low cost of a hospital day in the Netherlands (a few hundred dollars, not $2,500 as in the US, their conclusions hold for there alone. A better trial would have used enough CSF to allow dose-dense therapy and collected resource utilization to allow other countries to plug in their numbers. Further research into the cost implications of CSF use is warranted. The CSF Update Committee recognized that these are expensive agents. *As stated explicitly above, when available, alternative regimens offering equivalent efficacy, but not requiring CSF support, should be utilized.*

Recently published data by Papaldo et al suggest that, when compared with standard CSF dosing, less frequent CSF dosing schedules may equally prevent neutropenia and chemotherapy dose delay and cause less bone pain and fever.[61] This trial was a nonrandomized, observational study; its results should be considered hypothesis generating. As stated by Djulbegovic, because the uncertainty of benefits/harms of alternative treatment options is high and the benefit-harm ratio is unclear, a high level of evidentiary standards, such as a randomized clinical trial comparing standard versus alternative CSF dosing schedules, is needed.[83] If proven to be equally efficacious, less frequent CSF dosing could have a significant impact on the cost of treatment.

The quality-of-life impact of the CSFs has been less well studied, but the available data show no difference in formal quality of life between placebo and CSF. A recent study directly addressed quality of life in a subgroup of patients using a standardized instrument in patients receiving primary prophylactic CSF versus standard therapy alone. Although underpowered for this outcome, the authors found no difference in global quality of life between the study arms, even though fewer patients were hospitalized in the CSF group.[51] Thatcher et al noted that palliation of symptoms and quality of life was the same for small-cell lung cancer patients treated with a conventional every-3-week regimen, or a dose-intense every-2-week regimen with CSF.[7] Further research into this important area of patient experience is warranted before any conclusions can be drawn.

REFERENCES

1. American Society of Clinical Oncology: Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. J Clin Oncol 14:671-679, 1996

2. Timmer-Bonte JN, de Boo TM, Smith HL, et al: Cost-effectiveness of adding granulocyte colony-stimulatng factor to primary prophylaxis with antibodies in small-cell lung cancer. J Clin Oncol 24: 2991-2997, 2006

3. Vogel CL, Wojtukiewicz MZ, Carroll RR, et al: First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study. J Clin Oncol 23:1178-1184, 2005

4. Pfeundschuh M, Truemper L, Kloess M, et al: 2-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: Results of the NHL-B2 trial of the DSHNHL. Blood 104:634-641, 2004

5. Kuderer NM, Crawford J, Dale DC, et al: Complications and costs associated with febrile neutropenia in hospitalized adult cancer patients. J Clin Oncol 22, 2004 (abstr 6049)

6. Bohlius J, Reiser M, Schwarzer G, et al: Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma [Update of Cochrane Database Syst Rev. 2002]. Cochrane Database of Systematic Reviews CD003189, 2004

7. Thatcher N, Girling DJ, Hopwood P, et al: Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: Results of a British Medical Research Council Multicenter Randomized Trial—Medical Research Council Lung Cancer Working Party. J Clin Oncol 18:395-404, 2000

8. Lyman GH, Kuderer NM: Epidemilogy of febrile neurtopenia. Supportive Cancer Therapy 1:23-35, 2003

9. Lyman GH, Kuderer NM, Balducci L: Cost-benefit analysis of granulocyte colony-stimulating factor in the management of elderly cancer patients. Curr Opin Hematol 9:207-214, 2002

10. Rivera E, Erder MH, Moore TD, et al: Targeted filgrastim support in patients with early-stage breast carcinoma: Toward the implementation of a risk model. Cancer 98:222-228, 2003

11. Garcia-Carbonero R, Mayordomo JI, Tornamira MV, et al: Granulocyte colony-stimulating factor in the treatment of high-risk febrile neutropenia: A multicenter randomized trial. J Natl Cancer Inst 93:31-38, 2001

12. Berghmans T, Paesmans M, Lafitte JJ, et al: Therapeutic use of granulocyte and granulocyte-macrophage colony-stimulating factors in febrile neutropenic cancer patients: A systematic review of the literature with meta-analysis. Support Care Cancer 10:181-188, 2002

13. Clark OA, Lyman GH, Castro AA, et al: Colony-stimulating factors for chemotherapy-induced febrile neutropenia: A meta-analysis of randomized controlled trials. J Clin Oncol 23:4198-4214, 2005

14. Klastersky J, Paesmans M, Rubenstein EB, et al: The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 18:3038-3051, 2000

15. Talcott JA, Siegel RD, Finberg R, et al: Risk assessment in cancer patients with fever and neutropenia: A prospective, two-center validation of a prediction rule. J Clin Oncol 10:316-322, 1992

16. Malik I, Hussain M, Yousuf H: Clinical characteristics and therapeutic outcome of patients with febrile neutropenia who present in shock: Need for better strategies. J Infect 42:120-125, 2001

17. Darmon M, Azoulay E, Alberti C, et al: Impact of neutropenia duration on short-term mortality in neutropenic critically ill cancer patients. Intensive Care Med 28:1775-1780, 2002

18. Citron ML, Berry DA, Cirrincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 21:1431-1439, 2003

19. Lorigan P, Woll PJ, O'Brien ME, et al: Randomized phase III trial of dose-dense chemotherapy

supported by whole-blood hematopoietic progenitors in better-prognosis small-cell lung cancer. J Natl Cancer Inst 97:666-674, 2005

20. Ardizzoni A, Tjan-Heijnen VC, Postmus PE, et al: Standard versus intensified chemotherapy with granulocyte colony-stimulating factor support in small-cell lung cancer: A prospective European Organization for Research and Treatment of Cancer-Lung Cancer Group Phase III Trial-08923. J Clin Oncol 20:3947-3955, 2002

21. Berghmans T, Paesmans M, Lafitte JJ, et al: Role of granulocyte and granulocyte-macrophage colony-stimulating factors in the treatment of small-cell lung cancer: A systematic review of the literature with methodological assessment and meta-analysis. Lung Cancer 37:115-123, 2002

22. Pfreundschuh M, Truemper L, Schmits R, et al: 2-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good prognosis (normal LDH) aggressive lymphomas: Results of the NHL-B1 trial of the DSHNHL. Blood 104:626-633, 2004

23. McQuaker IG, Hunter AE, Pacey S, et al: Low-dose filgrastim significantly enhances neutrophil recovery following autologous peripheral-blood stem-cell transplantation in patients with lymphoproliferative disorders: Evidence for clinical and economic benefit. J Clin Oncol 15:451-457, 1997

24. Stinson TJ, Adams JR, Bishop MR, et al: Economic analysis of a phase III study of G-CSF versus placebo following allogeneic blood stem cell transplantation. Bone Marrow Transplant 26:633-666, 2000

25. Ringden O, Labopin M, Gorin NC, et al: Treatment with granulocyte colony-stimulating factor after allogeneic bone marrow transplantation for acute leukemia increases the risk of graft-versus-host disease and death: A study from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 22:416-423, 2004

26. Kloess M, Zeynalova S, Truemper L, et al: Effects of G-CSF schedule on leukocyte recovery and infection rate in the CHOP-14 regimen for elderly patients with aggressive lymphoma. Proc Am Soc Clin Oncol 22, 2003 (abstr 2403)

27. Kroger N, Zander AR: Dose and schedule effect of G-GSF for stem cell mobilization in healthy donors for allogeneic transplantation. Leuk Lymphoma 43:1391-1394, 2002

28. Lowenberg B, van Putten W, Theobald M, et al: Effect of priming with granulocyte colony-stimulating factor on the outcome of chemotherapy for acute myeloid leukemia. N Engl J Med 349:743-752, 2003

29. Amadori S, Suciu S, Jehn U, et al: Use of glycosylated recombinant human G-CSF during and/or after induction chemotherapy in elderly patients with acute myeloid leukemia: Final results of AML-13, a randomized phase III study of the EORTC and GIMEMA Leukemia Groups. Blood 106:27-34, 2005

30. Harousseau JL, Witz B, Lioure B, et al: Granulocyte colony-stimulating factor after intensive consolidation chemotherapy in acute myeloid leukemia: Results of a randomized trial of the Groupe Ouest-Est Leucemies Aigues Myeloblastiques. J Clin Oncol 18:780-787, 2000

31. Heil G, Hoelzer D, Sanz MA, et al: The International Acute Myeloid Leukemia Study Group: A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia—The International Acute Myeloid Leukemia Study Group. Blood 90:4710-4718, 1997

32. Larson RA, Dodge RK, Linker CA, et al: A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. Blood 92:1556-1564, 1998

33. Heath JA, Steinherz PG, Altman A, et al: Human granulocyte colony-stimulating factor in children with high-risk acute lymphoblastic leukemia: A Children's Cancer Group Study. J Clin Oncol 21: 1612-1617, 2003

34. Crivellari D, Bonetti M, Castiglione-Gertsch M, et al: Burdens and benefits of adjuvant cyclophosphamide, methotrexate, and fluorouracil and tamoxifen for elderly patients with breast cancer: The International Breast Cancer Study Group Trial VII. J Clin Oncol 18:1412-1422, 2000

35. Dees EC, O'Reilly S, Goodman SN, et al: A prospective pharmacologic evaluation of age-related toxicity of adjuvant chemotherapy in women with breast cancer. Cancer Invest 18:521-529, 2000

36. Gelman RS, Taylor SG: Cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in women more than 65 years old with advanced breast cancer: The elimination of age trends in toxicity by using doses based on creatinine clearance. J Clin Oncol 2:1404-1413, 1984

37. Kim YJ, Rubenstein EB, Rolston KV, et al: Colony-stimulating factors (CSFs) may reduce complications and death in solid tumor patients with fever and neutropenia. Proc Am Soc Clin Oncol 19:612a, 2000 (abstr 2411)

38. Armitage JO, Potter JF: Aggressive chemotherapy for diffuse histiocytic lymphoma in the elderly: Increased complications with advancing age. J Am Geriatr Soc 32:269-273, 1984

39. Doordujin J, Van Der Holt B, Van Der Kem F, et al: Randomized trial of colony-stimulating factor (G-CSF) added to CHOP in elderly patients with aggressive non-Hodgkin's lymphoma. Blood 96:133a, 2000

40. Gomez H, Mas L, Casanova L, et al: Elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy plus granulocyte-macrophage colony-stimulating factor: Identification of two age subgroups with differing hematologic toxicity. J Clin Oncol 16:2352-2358, 1998

41. Morrison VA, Picozzi V, Scott S, et al: The impact of age on delivered dose intensity and hospitalizations for febrile neutropenia in patients with intermediate-grade non-Hodgkin's lymphoma receiving initial CHOP chemotherapy: A risk factor analysis. Clinical Lymphoma 2:47-56, 2001

42. Chrischilles E, Delgado DJ, Stolshek BS, et al: Impact of age and colony-stimulating factor use on hospital length of stay for febrile neutropenia in CHOP-treated non-Hodgkin's lymphoma. Cancer Control 9:203-211, 2002

43. Aviles A, Nambo MJ, Talavera A, et al: Epirubicin (CEOP-Bleo) versus idaurubicin (CIOP-Bleo) in the treatment of elderly patients with aggressive non-Hodgkin's lymphoma: Dose escalation studies. Anticancer Drugs 8:937-942, 1997

44. Bertini M, Freilone R, Vitolo U, et al: The treatment of elderly patients with aggressive non-Hodgkin's lymphomas: Feasibility and efficacy of an intensive multidrug regimen. Leuk Lymphoma 22: 483-493, 1996

45. Coiffier B, Lepage E, Briere J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235-242, 2002

46. Gisselbrecht C, Haioun C, Lepage E, et al: Placebo-controlled phase III study of lenograstim (glycosylated recombinant human granulocyte colony-stimulating factor) in aggressive non-Hodgkin's lymphoma: Factors influencing chemotherapy administration: Groupe d'Etude des Lymphomes de l'Adulte. Leuk Lymphoma 25:289-300, 1997

47. Osby E, Hagberg H, Kvaloy S, et al: CHOP is superior to CNOP in elderly patients with aggressive lymphoma while outcome is unaffected by filgrastim treatment: Results of a Nordic Lymphoma Group randomized trial. Blood 101:3840-3848, 2003

48. Sonneveld P, de Ridder M, van der Lelie H, et al: Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. J Clin Oncol 13:2530-2539, 1995

49. Tirelli U, Errante D, Van Glabbeke M, et al: CHOP is the standard regimen in patients > or = 70 years of age with intermediate-grade and high-grade non-Hodgkin's lymphoma: Results of a randomized study of the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Study Group. J Clin Oncol 16:27-34, 1998

50. Zinzani PL, Storti S, Zaccaria A, et al: Elderly aggressive-histology non-Hodgkin's lymphoma: First-line VNCOP-B regimen experience on 350 patients. Blood 94:33-38, 1999

51. Doorduijn JK, van der Holt B, van Imhoff GW, et al: CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. J Clin Oncol 21:3041-3050, 2003

52. Bjorkholm M, Osby E, Hagberg H, et al: Randomized trial of R-methugranulocyte colony stimulating factors as adjunto to CHOP or CNOP treatment of elderly patients with aggressive non-Hodgkin's lymphoma. Blood 94:599a, 1999 (abstr 2665)

53. Dixon DO, Neilan B, Jones SE, et al: Effect of age on therapeutic outcome in advanced diffuse histiocytic lymphoma: The Southwest Oncology Group experience. J Clin Oncol 4:295-305, 1986

54. Meyer RM, Browman GP, Samosh ML, et al: Randomized phase II comparison of standard CHOP with weekly CHOP in elderly patients with non-Hodgkin's lymphoma. J Clin Oncol 13:2386-2393, 1995

55. Kouroukis CT, Browman GP, Esmail R, et al: Chemotherapy for older patients with newly diagnosed, advanced-stage, aggressive-histology non-Hodgkin lymphoma: A systematic review. Ann Intern Med 136:136-143, 2002

56. Zagonel V, Babare R, Merola MC, et al: Cost-benefit of granulocyte colony-stimulating factor administration in older patients with non-Hodgkin's lymphoma treated with combination chemotherapy. Ann Oncol 5:127-132, 1994 (suppl 2)

57. Sung L, Nathan PC, Lange B, et al: Prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor decrease febrile neutropenia after chemotherapy in children with cancer: A meta-analysis of randomized controlled trials. J Clin Oncol 22:3350-3356, 2004

58. Bennett CL, Stinson TJ, Laver JH, et al: Cost analyses of adjunct colony stimulating factors for acute leukemia: Can they improve clinical decision making. Leuk Lymphoma 37:65-70, 2000

59. Relling MV, Boyett JM, Blanco JG, et al: Granulocyte colony-stimulating factor and the risk of secondary myeloid malignancy after etoposide treatment. Blood 101:3862-3867, 2003

60. Ozkaynak MF, Krailo M, Chen Z, et al: Randomized comparison of antibiotics with and without granulocyte colony-stimulating factor in children with chemotherapy-induced febrile neutropenia: A report from the Children's Oncology Group. Pediatr Blood Cancer 45:274-280, 2005

61. Papaldo P, Lopez M, Marolla P, et al: Impact of five prophylactic filgrastim schedules on hematologic toxicity in early breast cancer patients treated with epirubicin and cyclophosphamide. J Clin Oncol 23:6908-6918, 2005

62. Siena S, Piccart MJ, Holmes FA, et al: A combined analysis of two pivotal randomized trials of a single dose of pegfilgrastim per chemotherapy cycle and daily filgrastim in paitents with stage II-IV breast cancer. Oncol Rep 10:715-724, 2003

63. Vose JM, Crump M, Lazarus H, et al: Randomized, multicenter, open-label study of pegfilgrastim compared with daily filgrastim after chemotherapy for lymphoma. J Clin Oncol 21:514-519, 2003

64. Dubois RW, Pinto LA, Bernal M, et al: Benefits of GM-CSF versus placebo or G-CSF in reducing chemotherapy-induced complications: A systematic review of the literature. Supportive Cancer Therapy 2:34-41, 2004

65. Pierelli L, Perillo A, Ferrandina G, et al: The role of growth factor administration and T-cell recovery after peripheral blood progenitor cell transplantation in the treatment of solid tumors: Results from a randomized comparison of G-CSF and GM-CSF. Transfusion 41:1577-1585, 2001

66. Weaver CH, Schulman KA, Wilson-Relyea B, et al: Randomized trial of filgrastim, sargramostim, or sequential sargramostim and filgrastim after myelosuppressive chemotherapy for the harvesting of peripheral-blood stem cells. J Clin Oncol 18:43-53, 2000

67. Ballestrero A, Ferrando F, Garuti A, et al: Effects of three cytokine regimens on hematologic recovery and progenitor cell mobilization after high-dose cyclophosphamide, etoposide, and cisplatin. Oncology 59:7-13, 2000

68. Comenzo RL, Sanchorawala V, Fisher C, et al: Intermediate-dose intravenous melphalan and blood stem cells mobilized with sequential GM+G-CSF or G-CSF alone to treat AL (amyloid light chain) amyloidosis. Br J Haematol 104:553-559, 1999

69. Recchia F, Accorsi P, Bonfini T, et al: Randomized trial of sequential administration of G-CSF and GM-CSF vs. G-CSF alone following peripheral blood progenitor cell autograft in solid tumors. J Interferon Cytokine Res 20:171-177, 2000

70. Dainiak N, Waselenko JK, Armitage JO, et al: The hematologist and radiation casualties, in Broudy VC, Prchal JT, Tricot GJ (eds): American Society of Hematology Education Program Book. San Diego, CA, 2003, pp 473-488

71. Waselenko JK, MacVittie TJ, Blakely WF, et al: Medical management of acute radiation syndrome (submitted). Ann Intern Med 140:1037-1051, 2004

72. US Department of Health and Human Services PHS, and Agency for Toxic Substances and Disease Registry: Toxicologyical Profile for Cesium (draft), p 13. http://www.atsdr.cdc.gov/toxprofiles/tp157.pdf

73. Hall EJ: Acute Effects of Total-Body Irradiation, Radiobiology for the Radiologist. Philadelphia, PA, Lippincott Williams & Wilkins, 2000, pp 124-135

74. Schull WJ: The somatic effects of exposure to atomic radiation: The Japanese experience, 1947-1997. Proc Natl Acad Sci U S A 95:5437-5441, 1998

75. Barabanova AV: Acute radiation syndrome with cutaneous syndrom, in Ricks RC, Berger MA, O'Hara FM (eds): The Medical Basis for Radiation-Accident Preparedness: The Clinical Care of Victims (ed 1). Boca Raton, FL, CRC Press, 2002, pp 217-224

76. Farese AM, Casey DB, Vigneulle RM, et al: A single dose of pegylated leridistim significantly improves neutrophil recovery in sublethally irradiated rhesus macaques. Stem Cells 19:514-521, 2001

77. Farese AM, Hunt P, Grab LB, et al: Combined administration of recombinant human megakaryocyte growth and development factor and granulocyte colony-stimulating factor enhances multilineage hematopoietic reconstitution in nonhuman primates after radiation-induced marrow aplasia. J Clin Invest 97:2145-2151, 1996

78. Farese AM, Williams DE, Seiler FR, et al: Combination protocols of cytokine therapy with interleukin-3 and granulocyte-macrophage colony-stimulating factor in a primate model of radiation-induced marrow aplasia. Blood 82:3012-3018, 1993

79. MacVittie TJ, Farese AM, Herodin F, et al: Combination therapy for radiation-induced bone marrow aplasia in nonhuman primates using synthokine SC-55494 and recombinant human granulocyte colony-stimulating factor. Blood 87:4129-4135, 1996

80. Nash RA, Schuening FG, Seidel K, et al: Effect of recombinant canine granulocyte-macrophage colony-stimulating factor on hematopoietic recovery after otherwise lethal total body irradiation. Blood 83:1963-1970, 1994

81. Neelis KJ, Dubbelman YD, Qingliang L, et al: Simultaneous administration of TPO and G-CSF after cytoreductive treatment of rhesus monkeys prevents thrombocytopenia, accelerates platelet and red cell reconstitution, alleviates neutropenia, and promotes the recovery of immature bone marrow cells. Exp Hematol 25:1084-1093, 1997

82. Doorduijn JK, Buijt I, van der Holt B, et al: Economic evaluation of prophylactic granulocyte colony stimulating factor during chemotherapy in elderly patients with aggressive non-Hodgkin's lymphoma. Haematologica 89:1109-1117, 2004

83. Djulbegovic B, Frohlich A, Bennett CL: Acting on imperfect evidence: How much regret are we ready to accept? J Clin Oncol 23:6822-6825, 2005

84. Dillman RO, Davis RB, Green MR, et al: A comparative study of two different doses of cytarabine for acute myeloid leukemia: A phase III trial of Cancer and Leukemia Group B. Blood 78:2520-2526, 1991

85. Evans SR, Krown SE, Testa MA, et al: Phase II evaluation of low-dose oral etoposide for the treatment of relapsed or progressive AIDS-related Kaposi's sarcoma: An AIDS Clinical Trials Group clinical study. J Clin Oncol 20:3236-3241, 2002

86. Gill PS, Tulpule A, Espina BM, et al: Paclitaxel is safe and effective in the treatment of advanced AIDS-related Kaposi's sarcoma. J Clin Oncol 17: 1876-1883, 1999

87. Northfelt DW, Dezube BJ, Thommes JA, et al: Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: Results of a randomized phase III clinical trial. J Clin Oncol 16:2445-2451, 1998

88. Ratner L, Lee J, Tang S, et al: Chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma in combination with highly active antiretroviral therapy. J Clin Oncol 19:2171-2178, 2001

89. Vaughn DJ, Malkowicz SB, Zoltick B, et al: Paclitaxel plus carboplatin in advanced carcinoma of the urothelium: An active and tolerable outpatient regimen. J Clin Oncol 16:255-260, 1998

90. von der Maase H, Hansen SW, Roberts JT, et al: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: Results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 18:3068-3077, 2000

91. Chan S, Friedrichs K, Noel D, et al: Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol 17:2341-2354, 1999

92. Henderson IC, Berry DA, Demetri GD, et al: Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 21:976-983, 2003

93. Levine MN, Bramwell VH, Pritchard KI, et al: Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer: National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 16:2651-2658, 1998

94. Martin M, Lluch A, Segui MA, et al: Prophylactic growth factor (CF) support with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) for node-negative breast cancer (BC): An interim safety analysis of the GEICAM 9805 study. J Clin Oncol 23:32, 2004 (abstr 620)

95. Nabholtz JM, Falkson C, Campos D, et al: Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: Results of a randomized, multicenter, phase III trial [erratum appears in J Clin Oncol 2003 May 15;21(10):2048]. J Clin Oncol 21:968-975, 2003

96. Nabholtz JM, Mackey JR, Smylie M, et al: Phase II study of docetaxel, doxorubicin, and cyclophosphamide as first-line chemotherapy for metastatic breast cancer. J Clin Oncol 19:314-321, 2001

97. O'Shaughnessy J, Miles D, Vukelja S, et al: Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results. J Clin Oncol 20:2812-2823, 2002

98. Douillard JY, Cunningham D, Roth AD, et al: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. Lancet 355:1041-1047, 2000

99. O'Connell MJ, Laurie JA, Kahn M, et al: Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. J Clin Oncol 16:295-300, 1998

100. Poon MA, O'Connell MJ, Wieand HS, et al: Biochemical modulation of fluorouracil with leucovorin: Confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer. J Clin Oncol 9:1967-1972, 1991

101. Rothenberg ML, Oza AM, Bigelow RH, et al: Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim results of a phase III trial. J Clin Oncol 21:2059-2069, 2003

102. Rougier P, Bugat R, Douillard JY, et al: Phase II study of irinotecan in the treatment of advanced colorectal cancer in chemotherapy-naive patients and patients pretreated with fluorouracil-based chemotherapy. J Clin Oncol 15:251-260, 1997

103. Saltz LB, Cox JV, Blanke C, et al: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 343:905-914, 2000

104. Ross P, Nicolson M, Cunningham D, et al: Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 20: 1996-2004, 2002

105. Nichols CR, Catalano PJ, Crawford ED, et al: Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: An Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. J Clin Oncol 16:1287-1293, 1998

106. Nichols CR, Catalano PJ, Crawford ED, et al: Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: An Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. J Clin Oncol 16:1287-1293, 1998

107. Forastiere AA, Metch B, Schuller DE, et al: Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: A Southwest Oncology Group study. J Clin Oncol 10:1245-1251, 1992

108. Glisson BS, Murphy BA, Frenette G, et al: Phase II Trial of docetaxel and cisplatin combination chemotherapy in patients with squamous cell carcinoma of the head and neck. J Clin Oncol 20:1593-1599, 2002

109. Posner MR, Glisson B, Frenette G, et al: Multicenter phase I-II trial of docetaxel, cisplatin, and fluorouracil induction chemotherapy for patients with locally advanced squamous cell cancer of the head and neck. J Clin Oncol 19:1096-1104, 2001

110. Fossella F, Pereira JR, von Pawel J, et al: Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: The TAX 326 study group. J Clin Oncol 21:3016-3024, 2003

111. Hanna N, Shepherd FA, Fossella FV, et al: Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22:1589-1597, 2004

112. Noda K, Nishiwaki Y, Kawahara M, et al: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346:85-91, 2002

113. Roth BJ, Johnson DH, Einhorn LH, et al: Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: A phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 10:282-291, 1992

114. Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92-98, 2002

115. Skarlos DV, Samantas E, Kosmidis P, et al: Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer: A Hellenic Co-operative Oncology Group study. Ann Oncol 5:601-607, 1994

116. von Pawel J, Schiller JH, Shepherd FA, et al: Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 17:658-667, 1999

117. Wozniak AJ, Crowley JJ, Balcerzak SP, et al: Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: A Southwest Oncology Group study. J Clin Oncol 16:2459-2465, 1998

118. Canellos GP, Anderson JR, Propert KJ, et al: Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 327:1478-1484, 1992

119. Fisher RI, Gaynor ER, Dahlberg S, et al: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328:1002-1006, 1993

120. Pettengell R, Gurney H, Radford JA, et al: Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: A randomized controlled trial. Blood 80:1430-1436, 1992

121. Velasquez WS, Cabanillas F, Salvador P, et al: Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 71:117-122, 1988

122. Velasquez WS, McLaughlin P, Tucker S, et al: ESHAP–an effective chemotherapy regimen in refractory and relapsing lymphoma: A 4-year follow-up study. J Clin Oncol 12:1169-1176, 1994

123. Gertz MA, Kalish LA, Kyle RA, et al: Phase III study comparing vincristine, doxorubicin (Adriamycin), and dexamethasone (VAD) chemotherapy with VAD plus recombinant interferon alfa-2 in refractory or relapsed multiple myeloma: An Eastern Cooperative Oncology Group study. Am J Clin Oncol 18: 475-480, 1995

124. Salmon SE, Crowley JJ, Grogan TM, et al: Combination chemotherapy, glucocorticoids, and interferon alfa in the treatment of multiple myeloma: A Southwest Oncology Group study. J Clin Oncol 12:2405-2414, 1994

125. Bookman MA, Malmstrom H, Bolis G, et al: Topotecan for the treatment of advanced epithelial ovarian cancer: An open-label phase II study in patients treated after prior chemotherapy that contained cisplatin or carboplatin and paclitaxel. J Clin Oncol 16:3345-3352, 1998

126. Ozols RF, Bundy BN, Greer BE, et al: Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group study. J Clin Oncol 21:3194-3200, 2003

127. Antman K, Crowley J, Balcerzak SP, et al: An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol 11:1276-1285, 1993

128. Santoro A, Tursz T, Mouridsen H, et al: Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: A randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol 13:1537-1545, 1995

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Appendix A

For the 2004 update, a methodology similar to that applied in the original ASCO practice guidelines for use of hematopoietic growth factors was used. Pertinent information published from 1999 through September 2005 was reviewed. The Medline database (National Library of Medicine, Bethesda, MD) was searched to identify relevant information from the published literature for this update. A series of searches was conducted using the medical subject headings or text words, "granulocyte colony-stimulating factors," "granulocyte-macrophage colony-stimulating factors," "filgrastim," "lenograstim," "sargramostim," and "pegfilgrastim." These terms were combined with the study design-related subject headings or text words (in truncated forms to allow for variations of the root word): "meta-analysis," "random," and "phase III;" with the subject heading "drug administration schedule" and the text word "dose dense;" and with the text word, "child." Search results were limited to human studies and English-language articles. The Cochrane Library was searched with the phrase, "colony-stimulating factors." Directed searches based on the bibliographies of primary articles were also performed. Finally, Update Committee members contributed articles from their personal collections. Update Committee members reviewed the resulting abstracts and titles that corresponded to their assigned section.

Appendix B.

Summary of Recommendations

Specific Recommendations			2005 Recommendations
Recommendations for the Use of Hematopoietic Colony-Stimulating Factors TREATMENT	Primary Prophylaxis	*General Circumstances*	Primary prophylaxis is recommended for the prevention of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. For "dose dense" regimens CSFs are required and recommended. Clinical trial data support the use of CSF when the risk of FN is in the range of 20% or higher. In the absence of special circumstances, most commonly used regimens have risks of FN of $< 20\%$ (see Table 1). In making the decision to use prophylactic CSF or not, oncologists should consider not only the optimal chemotherapy regimen but also the individual patient risk factors and the intention of treatment, that is, curative, prolongation of life, or symptom control and palliation. Examples of appropriate use in the curative setting include adjuvant treatment of early-stage breast cancer with more intensive regimens such as TAC or FEC100 or the use of CHOP or CHOP-like regimens in older patients with aggressive non-Hodgkin's lymphoma.
		Special Circumstances	Clinicians may occasionally be faced with patients who might benefit from relatively nonmyelosuppressive chemotherapy but who have potential risk factors for febrile neutropenia 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. Certain clinical factors predispose to increased complications from prolonged neutropenia, including: patient age greater than 65 yr; poor performance status; previous episodes of FN; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; bone marrow involvement by tumor producing cytopenias; poor nutritional status; the presence of open wounds or active infections; more advanced cancer, as well as other serious comorbidities. In such situations primary prophylaxis with CSF is often appropriate even with regimens with FN rates of $< 20\%$. The special circumstances have always been part of ASCO's CSF guidelines, in recognition that there patient factors that predict for the rate and severity of febrile neutropenia. These special circumstances have been maintained from previous versions of the guideline. The rate at which the use of CSFs should be considered has changed from 40% to 20%, consistent with the new evidence that demonstrates efficacy in reducing FN rates when the risk is approximately 20%.
	Secondary Prophylaxis		Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.
	Therapeutic Use of CSF's	*Patients With Neutropenia Who Are Afebrile*	CSFs should not be routinely used for patients with neutropenia who are afebrile.
		Patients With Neutropenia Who Are Febrile	CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (> 10 d) and profound ($< 0.1 \times 109$/L) neutropenia, age greater than 65 yr, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.

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Appendix B. (continued)

Summary of Recommendations			
Specific Recommendations			2005 Recommendations
	Use of CSFs to Increase Dose Intensity or Dose Density		Use of CSFs allows a modest to moderate increase in dose-density and/or dose-intensity of chemotherapy regimens. Available data would suggest a survival benefit from the use of dose-dense (but not dose-intense) regimens with CSF support in a few specific settings (eg, node-positive breast cancer, small cell lung cancer, and non-Hodgkin's lymphoma). However, additional data in these settings are needed and these results cannot be generalized to other disease settings and regimens absent specific trials. Dose-dense regimens should only be used within an appropriately designed clinical trial or if supported by convincing efficacy data.
	Use of CSFs As Adjuncts to Progenitor Cell Transplantation		Administration of CSFs to mobilize PBPC often in conjunction with chemotherapy and their administration after autologous, but not allogeneic, PBPC transplant is the current standard of care.
	Use of CSFs for Patients With Leukemia or Myelodysplastic Syndromes	*Initial or Repeat Induction Chemotherapy (AML)*	Several studies have shown that CSF administration can produce modest decreases in the duration of neutropenia when begun shortly after completion of the initial induction chemotherapy. Beneficial effects on end points such as duration of hospitalization and incidence of severe infections have been variable and modest. CSF use following initial induction therapy is reasonable, although there has been no favorable impact on remission rate, remission duration or survival. Patients $>$ 55 yr of age may be most likely to benefit from CSF use.
		CSF for Priming Effects (AML)	Use of CSFs for priming effects is not recommended.
		Consolidation Chemotherapy in AML	CSF use can be recommended after the completion of consolidation chemotherapy because of the potential to decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive post remission chemotherapy. There seems to be more profound shortening of the duration of neutropenia after consolidation chemotherapy for patients with AML in remission than for patients receiving initial induction therapy. There is no effect on the duration of complete response duration or overall survival. There is, as yet, no information about the effect of longer acting, pegylated CSFs in patients with myeloid leukemias and they should not be used in such patients outside of clinical trials.
		Myelodysplastic Syndrome (MDS)	No change from 2000 Update. CSFs can increase the absolute neutrophil count in neutropenic patients with myelodysplastic syndromes (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.
		Acute Lymphocytic Leukemia (ALL)	CSFs are recommended after the completion of the initial first few days of chemotherapy of the initial induction or first post remission course, thus shortening the duration of neutropenia of $<$ 1000/mm^3 by approximately one week. There are less consistent effects on the incidence and duration of hospitalization and the acquisition of serious infections. Although there was a trend for improved CR rates in one large study,[32] 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 unknown from the published data whether the CSFs significantly accelerate recovery to neutrophil counts of 100-200/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 antibiotics or in-hospital days, although a small amount of additional costs was incurred, after taking into consideration the costs of the CSFs. Cost estimates of CSFs for adults with ALL have not been reported.

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Appendix B. (continued)

Summary of Recommendations			
Specific Recommendations			2005 Recommendations
		Leukemia in Relapse	CSFs should be used judiciously, or not at all, in patients with refractory or relapsed myeloid leukemia since the expected benefit is only a few days of shortened neutropenia. Because of the relatively low response rate in AML patients with relapsed or refractory disease clinicians may be faced with the difficult dilemma of whether the persistence of leukemia after chemotherapy is a consequence of drug resistance or a stimulatory effect of the CSF. Although drug resistance is the most likely cause of treatment failure, it is sometimes necessary to stop the CSF and observe the patient for a few days to be certain. No significant change from 2000 recommendation.
	Use of CSFs in Patients Receiving Radiation Therapy		CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected.
	Use of CSFs in Older Patients		Prophylactic CSF for patients with lymphoma aged 65 and older treated with curative chemotherapy (CHOP or more aggressive regimens) should be given to reduce the incidence of FN and infections.
	Use of CSFs in the Pediatric Population		The use of G-CSF in pediatric patients will almost always be guided by clinical protocols. As in adults, the use of G-CSF is reasonable for the primary prophylaxis of pediatric patients with a likelihood of FN. Similarly, the use of G-CSF for secondary prophylaxis or for therapy should be limited to high-risk patients. However, the potential risk for secondary myeloid leukemia or myelodysplastic syndrome associated with G-CSF represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the specific use of G-CSF in children with ALL should be considered carefully.
	CSF Initiatiation, Dosing, Duration and Administration	*G-CSF (filgrastim)*	G-CSF should be given 24-72 h after the administration of myelotoxic chemotherapy. In the setting of high-dose therapy and autologous stem cell rescue G-CSF can be given between 24-120 h after administration of high-dose therapy. G-CSF should be continued until reaching an ANC of at least 2-3 $\times$ 10^9/L. For PBPC mobilization, G-CSF should be started at least 4 d before the first leukapheresis procedure and continued until the last leukapheresis.
		Pegylated G-CSF (pegfilgrastim)	Pegfilgrastim 6 mg should be given once, 24 h after completion of chemotherapy. Pegfilgrastim is not currently indicated for stem cell mobilization. The safety and efficacy of pegylated G-CSF has not yet been fully established in the setting of dose-dense chemotherapy.
		GM-CSF (sargramostim):	Because GM-CSF has been licensed specifically for use after autologous or allogeneic BMT and for AML, the manufacturer's instructions for administration are limited to those clinical settings. GM-CSF should be initiated on the day of bone marrow infusion and not less than 24 h from the last chemotherapy and 12 h from the most recent radiotherapy. GM-CSF should be continued until an ANC greater than 1.5 $\times$ 10^9/L for 3 consecutive days is obtained. The drug should be discontinued early or the dose be reduced by 50% if the ANC increases to greater than 20 $\times$ 10^9/L.
	Dosing	G-CSF (filgrastim) and GM-CSF (sargramostim): In adults, the recommended CSF doses are 5 μg/kg/d for G-CSF and 250 μg/m^2/d for GM-CSF for all clinical settings other than peripheral blood progenitor cell (PBPC) mobilization. In the setting of PBPC mobilization, if G-CSF is used, a dose of 10 μg/kg/d seems preferable. The preferred route of G-CSF administration is subcutaneous.	Pegylated G-CSF: Pegylated G-CSF (pegfilgrastim 6 mg) is given once in each chemotherapy cycle. The 6 mg formulation should not be used in infants, children, or small adolescents weighing $<$ 45 kg.

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Appendix B. (continued)

Summary of Recommendations		
Specific Recommendations		2005 Recommendations
	Special Comments on Comparative Clinical Activity of G-CSF and GM-CSF	No change. No guideline recommendation can be made regarding the equivalency of the two colony-stimulating agents. As in 2000, further trials are recommended to study the comparative clinical activity, toxicity, and cost-effectiveness of G-CSF and GM-CSF.
	Special Comments on Growth Factors As a Treatment for Radiation Injury	Current recommendations for the management of patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of CSF or pegylated G-CSF.[70,71] Accidental or intentional (eg, resulting from a terrorist attack or war) total body radiation leads to probable or certain death from bone marrow failure at doses of 3-10 Grays (Gy) without supportive care, CSFs, and/or a bone marrow transplant.[72-74] Doses below that level are almost always survivable with excellent nursing care and higher doses are lethal because of injury to other organs such as the gastrointestinal tract. The chance for mortality from any radiation dose rises with combined injuries to the skin, lungs, etc.[75] Hematopoietic growth factors can increase the survival, proliferation, amplification, and differentiation of granulocyte progenitors to produce neutrophils. Although no prospective, randomized trials have been carried out to determine the benefit of hematopoietic growth factors in humans exposed to accidental or intentional radiation injury, they have been utilized in radiation accident victims and neutrophil recovery appears to have been hastened in 25 of 28 cases (REACT/TS registry). In animal models, prompt administration of hematopoietic growth factors after otherwise lethal total body radiation exposure dramatically increases survival.[76-81]

Appendix C. ASCO Colony Stimulating Factors Update Committee

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