



American Society of Clinical Oncology

*Making a world of difference in cancer care*

**White Blood Cell Growth**

**Factors:**

**2006 Update**

**Clinical Practice Guideline**

# Introduction

- ASCO convened an Update Committee to review recommendations regarding the use of hematopoietic colony-stimulating factors (CSF).
- These guidelines were originally published in 1994 and previously updated in 1996, 1997 and 2000.
- This review was guided by the 1996 outcomes criteria that justify the use of a drug or technology, and recommended therapy when compelling positive effects to those outcomes were demonstrated.
- The 2006 update lowers the risk percentage for administering CSF and includes new recommendations on CSF use in older patients and as treatment of radiation injury.

# Guideline Methodology

- An ASCO Expert Panel completed a review of the pertinent literature through September 2005:
  - ✓ MEDLINE
  - ✓ Cochrane Collaboration Library

# Guideline Methodology (cont'd): Panel Members

- Thomas J. Smith, M.D., *Chair* Massey Cancer Center, Virginia Commonwealth University
- Howard Ozer, M.D., Ph.D., *Co-Chair* University of Oklahoma
- Julie L. Ross, Pharm D Cancer Centers of the Carolinas
- James O. Armitage, MD University of Nebraska Medical Center
- Lodovico Balducci, MD H. Lee Moffitt Cancer Center & Research Institute
- Charles L. Bennett, MD, PhD VA Chicago Health Care System Lakeside Division
- Scott B. Cantor, PhD UT MD Anderson Cancer Center
- Jeffrey Crawford, MD Duke Medical Center
- Scott J. Cross, MD Duke Medical Center
- George Demetri, MD Dana-Farber Cancer Institute
- James Khatcheressian, MD Massey Cancer Center, Virginia Commonwealth University
- Gary H. Lyman, MD University of Rochester
- Cheryl L. Perkins, MD Susan G. Komen Breast Cancer Foundation
- Philip A. Pizzo, MD Stanford University School of Medicine
- Charles A. Schiffer, MD Wayne State University School of Medicine
- Lee Schwartzberg, MD, FACP The West Clinic
- George Somlo, MD City of Hope National Medical Center
- William Thames, RPh US Oncology
- James C. Wade, MD, MPH Medical College of Wisconsin
- James L. Wade, III, MD Cancer Care Specialists of Central Illinois
- Rodger J. Winn, MD National Quality Forum
- Antonio C. Wolff, MD, FACP Sidney Kimmel Cancer Center at Johns Hopkins
- Antoinette J. Wozniak, MD Karmanos Cancer Institute, Wayne State University

# 2006 Recommendation Categories (12) for the Use of CSF

- Primary Prophylactic CSF Administration
- Secondary Prophylactic CSF Administration
- Therapeutic Use of CSF
- CSF to Increase Chemotherapy Dose-Intensity and Dose-Density
- CSF as Adjuncts to Progenitor-Cell Transplantation
- CSF in Patients With Acute Leukemia and Myelodysplastic Syndromes
- CSF in Patients Receiving Radiotherapy with or without Concurrent Chemotherapy
- CSF in Older Patients *NEW!*
- CSF in the Pediatric Population
- CSF Initiation, Duration, Dosing, and Administration
- Special Comment: Comparative Clinical Activity of G-CSF and GM-CSF
- Special Comment: Growth Factors as Treatment for Radiation Injury *NEW!*

# 2006 Updated Recommendation

*The 2006 Update Committee agreed unanimously that reduction in febrile neutropenia was an important clinical outcome that justified use of CSF, regardless of impact on other factors, when the risk of FN was about 20% and no other equally effective regimen that did not require CSF was available.*

**Please Note: The rate of FN risk has changed from 40% to 20%.**

# Incidence of Hematologic and Infectious Toxicities With Selected Chemotherapy Regimens

Cancer Histology	Stage and Prior Therapy	Regimen	No. of Pts.	Leukopenia (Grade 4) (%) *	Neutropenia (Grade 4) (%)	Febrile Neutropenia (%)	Fever (Grade <sup>3</sup> 2) (%) †	Infection (Grade <sup>3</sup> 3) (%) ‡	Infectious Death (%)
Adult AML	Newly diagnosed	Ara-C/DNR	163	93	—	—	37 (No Infection)	64	12
AIDS-related Kaposi's Sarcoma	Advanced/1 <sup>st</sup> & 2 <sup>nd</sup> line	Lipo Dox [±G(M)-CSF]	133	36(3+4)	6	—	1	—	0
		VP-16 (oral)	36	—	19.4	—	8	—	—
		Paclitaxel	56	—	35	—	—	—	—
AIDS-related** NHL	Intermediate-High-grade, untreated	CHOP(Modified)	40	—	25(3+4)	2.5	—	—	10
		CHOP + G-CSF	25	—	13(3+4)	0	—	—	—
Bladder	Advanced, no prior systemic therapy Prior adjuvant allowed	GC	203	—	29.9	2	0	2.5	1
		MVAC	202	—	65.2	14	3.1	15.1	2.5
		CBDCA/Pac ± G-CSF	33	—	21	21	—	1pt sepsis	0
Breast	Adjuvant	CA(60mg/m <sup>2</sup> )	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	—	—	—
	Adjuvant (dose dense)	A→T→C	484	1	24	3	—	3	0
		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

\* Grade 4 leukopenia: WBC count < 1.0x10<sup>9</sup>/L; grade 4 neutropenia: ANC < 0.5x10<sup>9</sup>/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.

# Incidence of Hematologic and Infectious Toxicities With Selected Chemotherapy Regimens (cont'd)

Cancer Histology	Stage and Prior Therapy	Regimen	No. of Pts.	Leukopenia (Grade 4) (%) *	Neutropenia (Grade 4) (%)	Febrile Neutropenia (%)	Fever (Grade 3 2) (%) †	Infection (Grade 3 3) (%) ‡	Infectious Death (%)
Breast (cont'd)	Metastatic(1 <sup>st</sup> 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 (2 <sup>nd</sup> line)	CapDoc	255	—	11	16	—	—	<1
	Doc	256	—	12	21	—	—	0	
Colorectal	Adjuvant	5-FU/LV/L	449	2	—	—	—	—	<1
		5-FU/LV	116	15 (highLV) 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 (350mg/m <sup>2</sup> Q3wk)	213	36 (3+4)	48(3+4)	14	—	<1	3 deaths	
Gastric	Advanced	ECF (infusion)	289	13	32	—	1	6	<1
Germ Cell	Advanced	BEP	141	—	34 (all heme	—	—	—	2
		VIP	145	—	60 toxicities)	—	—	—	2.8
	Relapsed	VeIP	135	—	—	71	—	—	2.1 (all deaths)

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Head/Neck	Recurrent; Metastatic	5-FU/CBDCA	86	2.3	1.2	—	—	—	1.2
		CBDCA/Pac	41	4.9	9.8	—	—	—	2.4
	Induction	Cis/Doc	36	—	71	6	—	11	0
		Cis/Doc/5-FU	43	—	95(3+4)	19	—	2	0
Lung	Extensive SCLC No Prior Treatment	Cis/VP-16	159	14	38	—	—	8	≤6
		CAV	156	28	52	—	—	16	≤4
		CBDCA/VP-16	74	5	—	—	—	—	0
		Cis/CPT-11	77	4	25.3	—	1.3	5.3	2.6
	Recurrent	Topo	107	31.7	70.2	28	—	4.7	3.7
		CAV	104	43.6	71.7	26	—	4.8	2.9
	Advanced NSCLC No Prior Treatment	Cis/VNR	206	—	59	10	—	—	1
		Cis/Pac(24hr)	288	—	57	16	—	10	2
		Cis/Gem	288	—	39	4	—	7	1
		Cis/Doc	289	—	48	11	—	9	2
		CBDCA/Pac	290	—	43	4	—	6	1
		CBDCA/Doc	406	49.5(3+4)	74.4(3+4)	3.7	—	11	—
	Recurrent (2 <sup>nd</sup> line)	Doc(75mg/m <sup>2</sup> )	276	40.2(3+4)	—	12.7	—	3.3	—
		Pemetrexed	265	5.3(3+4)	—	1.9	—	0	—

\* Grade 4 leukopenia: WBC count < 1.0x10<sup>9</sup>/L; grade 4 neutropenia: ANC < 0.5x10<sup>9</sup>/L

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Lymphoma	Relapsed HD; prior RT only	MOPP	123	—	22	—	3	13	1
		ABVD	115	—	3	—	5	2	0
	Intermediate - High grade	CHOP	216	25	22	—	—	5(≥ grade 4)	1
		CHOP-R	33	1.2	58	18	6	6	0
	NHL; No prior Treatment	VAPEC-B	39	—	72	44	—	5 pt	2 deaths
	Relapse NHL	ESHAP	122	—	500/μl median	30	—	—	4.1
		DHAP	90	—	53	48	—	31	11
	Multiple Myeloma	Untreated Recurrent/Refractory	VAD ± Inf	169	—	—	—	—	—
VAD + Inf			52	65.4	—	—	—	32.7	7.7
Ovary	Resected, minimal residual Salvage	Cis/Pac(24hr)	400	12	78	Few instances	—	—	—
		CBDCa/Pac	392	6	72	—	—	—	—
		Topo	139	30.1	82.4	18	—	—	0
Sarcoma	Advanced, Untreated	AD	186	32	38	—	—	—	0
		MAID	188	86	79	—	—	—	3.5
		A	263	13	—	—	5.3	11	—
		AI	258	32	—	—	(all arms)	(all arms)	—
		CYVADIC	142	15	—	—	—	—	—
Special Populations (Elderly)	NHL, untreated	CHOP	197	—	—	—	5(3+4)	20	16 pts
		CHOP-R	202	—	—	—	2	12	—
	Breast, adjuvant	CMF	76	4 (grade 3)	—	—	—	—	0

# Primary Prophylactic CSF Administration (First and Subsequent-Cycle Use)

- Recommended for the prevention of FN in patients who have a high risk of FN based on:
  - Age
  - Medical history
  - Disease characteristics
  - Myelotoxicity of the chemotherapy regimen
- Required and recommended for “dose dense” regimens
- Clinical trial data support the use of CSF when the risk of FN is in the range of 20% or higher

## Primary Prophylactic CSF Administration (First and Subsequent-Cycle Use) (cont'd): Special Circumstances

- When the following clinical factors are present, primary prophylaxis with CSF is often appropriate even with regimens with FN rates of <20% :
  - Age >65 years
  - Poor performance status
  - Previous FN
  - Poor nutritional status
  - Open wounds or active infections
  - More advanced cancer
  - Extensive prior treatment, including large XRT ports
  - Administration of combined chemoradiotherapy
  - Cytopenias due to bone marrow involvement by tumor
  - Other serious comorbidities

# Secondary Prophylactic CSF Administration

- Recommended for patients who:



Experienced a neutropenic complication from a prior cycle of chemotherapy;



For which primary prophylaxis was not received; and,



In which a reduced dose may compromise disease-free or overall survival or treatment outcome.

# Therapeutic Use of CSF

- CSF should not be routinely used for patients with neutropenia who are afebrile
- CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia . . .

HOWEVER 

# Therapeutic Use of CSF (cont'd)

- CSF should be considered for the following patients:
  - Patients with FN who are at high risk for infection-associated complications

**OR**

- Patients who have prognostic factors that are predictive of poor clinical outcome

# Therapeutic Use of CSF (cont'd)

- High risk features in patients with fever and neutropenia include:
  - Prolonged (>10 days) and profound (<0.1 x 10<sup>9</sup>/L) neutropenia
  - Age >65 years
  - Uncontrolled primary disease
  - Pneumonia
  - Hypotension and multi-organ dysfunction (sepsis syndrome)
  - Invasive fungal infection
  - Being hospitalized at the time of fever development

# Therapeutic Use of CSF (cont'd)

Clinical Prediction Model & Risk Model for Mortality in Hospitalized Patients	
Clinical Prediction Model for Prospectively Identifying Cancer Patients at Higher Risk of Complications due to Fever and Neutropenia: Reported Risk Factors for Serious Medical Complications in Patients with Established FN	Risk Model for Mortality in Hospitalized Patients: Independent Risk Factors for Inpatient Mortality in Hospitalized Patients with FN
Development of FN as inpatient	Comorbidities: CHF, PE, lung, renal, liver, and cerebrovascular disease
Hypotension	Infectious complications: hypotension, pneumonia, bacteremia, fungal infection
Sepsis	Cancer type (leukemia, lung cancer)
Cardiovascular disease	Age $\geq 65$
Pulmonary disease	
Leukemia or lymphoma diagnosis	
Age >65 years	
Prior fungal infection	
Visceral organ involvement	
Organ dysfunction	
Uncontrolled malignancy	
Severity & duration of neutropenia	

# CSF to Increase Chemotherapy Dose-Intensity and Dose-Density

- Dose-dense regimens should only be used within an appropriately designed clinical trial, or if supported by convincing efficacy data

## CSF as Adjuncts to Progenitor-Cell Transplantation

- Administration of CSF to mobilize PBPC often in conjunction with chemotherapy and their administration after autologous, but **NOT** allogeneic, PBPC transplant is the current standard of care.

# CSF in Patients with Acute Leukemia and Myelodysplastic Syndromes

## Acute Myeloid Leukemia (AML)

- CSF use following initial induction therapy is reasonable. Patients >55 years of age may be most likely to benefit
- CSF use can be recommended after the completion of consolidation chemotherapy
- CSF use for priming effects is not recommended

## Myelodysplastic Syndrome (MDS)

- Intermittent administration of CSF may be considered in a subset of patients with severe neutropenia and recurrent infection

## Acute Lymphocytic Leukemia (ALL)

- CSF is recommended after the completion of the initial first few days of chemotherapy of the initial induction or first post-remission course

## Acute 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

# CSF in Patients Receiving Radiotherapy with/without Concurrent Chemotherapy

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

# CSF in Older Patients

- **Tumor Type:** Diffuse Aggressive Lymphoma
- **Patient Age:**  $\geq 65$  years
- **Treatment:** Curative chemotherapy (CHOP or more aggressive regimens):
  - ✓ Prophylactic CSF should be given to reduce the incidence of FN and infections
  - ✓ Dose reduction is associated with reduced response rate and survival in lymphoma and is not recommended
  - ✓ Please Note: Aside from data available in patients with lymphoma, there is insufficient evidence to support the use of prophylactic CSF in patients solely based on age.

# CSF in the Pediatric Population

- The use of CSF in pediatric patients will almost always be guided by clinical protocols
- Primary prophylaxis is reasonable in pediatric patients with a likelihood of FN
- Secondary prophylaxis or therapeutic CSF administration should be limited to high-risk pediatric patients
- The potential risk for secondary myeloid leukemia or MDS associated with CSF represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the use of CSF in children with ALL should be considered with caution

# CSF Initiation, Duration, Dosing, and Administration

Growth Factor	Setting	Initiation	Duration	Dose
G-CSF (filgrastim)	Myelotoxic chemotherapy	24-72 hours after administration of myelotoxic chemotherapy	Continue until ANC at least $2-3 \times 10^9/L$	Adults: 5 ug/kg/d Subcutaneous
	High-dose therapy and autologous stem cell rescue	24-120 hours after administration of high-dose therapy		
	PBPC mobilization	Start at least 4 days before first leukapheresis	Continue until last leukapheresis	
Pegylated G-CSF (pegfilgrastim)[1]	Myelotoxic chemotherapy	24 hours after completion of chemotherapy	Once in each chemotherapy cycle	6mg[2]
GM-CSF (sargramostim) [3]	Bone marrow transplant or AML	Day of bone marrow infusion & not less than 24 hours from the last chemotherapy & 12 hours from most recent radiotherapy	Continue until ANC $>1.5 \times 10^9/L$ for 3 consecutive days[4]	Adults: 250 ug/m <sup>2</sup> /d for all clinical settings other than PBPC mobilization

Note: 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

[1] Pegfilgrastim is not currently indicated for stem cell mobilization. The safety and efficacy of pegylated G-CSF has not yet been established in the setting of dose-dense chemotherapy.

[2] The 6 mg formulation should not be used in infants, children, or small adolescents weighing  $<45$  kg.

[3] 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.

[4] The drug should be discontinued early or the dose be reduced by 50% if the ANC increases to greater than  $20 \times 10^9/L$ .

# Special Comment: Comparative Clinical Activity of G-CSF and GM-CSF

- No recommendation can be made regarding the equivalency of G-CSF and GM-CSF
- Further trials are recommended to study the comparative clinical activity, toxicity, and cost-effectiveness of these agents

## Special Comment: Growth Factors as Treatment for Radiation Injury

- 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, should receive prompt administration of CSF or pegylated G-CSF

# Impact of CSF on Quality of Life and Health Care Costs

- CSF should be used when indicated for clinical reasons, not economic ones. When available, alternative regimens offering equivalent efficacy but not requiring CSF support should be utilized.
- Further research into CSF cost implications and impact on quality of life is warranted.

# Summary

Setting/Indication	✓ Recommended	✗ Not Recommended
General Circumstances	FN risk in the range of 20% or higher	
Special Circumstances	Clinical factors dictate use	
Secondary Prophylaxis	Based on chemotherapy reaction among other factors	
Therapy of Afebrile Neutropenia		Not to be used routinely
Therapy of Febrile Neutropenia	If high-risk for complications or poor clinical outcomes	Not to be used routinely as adjunctive treatment with antibiotic therapy
Acute Myeloid Leukemia	Following induction therapy, patients >55 years old most likely to benefit	Not to be used for priming effects
	After the completion of consolidation chemotherapy	
Myelodysplastic Syndrome		Intermittent administration for a subset of patients with severe neutropenia and recurrent infection
Acute Lymphocytic Leukemia	After the completion of initial chemotherapy or first post remission course	
Radiotherapy	Consider if receiving radiation therapy alone and prolonged delays are expected.	Avoid in patients receiving concomitant chemotherapy and radiation therapy
Older Patients	If ≥ 65 years old with diffuse aggressive lymphoma and treated with curative chemotherapy	
Pediatric Population	For the primary prophylaxis of pediatric patients with a likelihood of FN and the secondary prophylaxis or therapy for high-risk pts.	G-CSF use in children with ALL should be considered carefully
Radiation Injury	Prompt administration of CSF or pegylated G-CSF if exposed to lethal doses of total body radiotherapy	

☞ Please note that proper use of CSF happens in conjunction with consideration of varied factors and circumstances. This summary table is provided to assist in summarizing the guideline slide set. There are additional recommendations not presented in this table. For a complete review of CSF guideline specifications, please refer to previous slides in this show or the CSF guidelines directly.

# ASCO Resources

- This slide set, the full text guideline, and additional ASCO resources on CSF can be found at:  
<http://www.asco.org/guidelines/wbcgf>
- A patient guide can be found at <http://www.cancer.net>



# ASCO Guidelines

It is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. A guideline is 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 results. Accordingly, ASCO considers adherence to this guideline 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, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.