Chapter 9
Summary and Comparison of Myeloid Growth Factor Guidelines in Patients Receiving Cancer Chemotherapy

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Abstract Chemotherapy-induced neutropenia and its complications are major dose-limiting toxicities of cancer chemotherapy. The myeloid growth factors have been shown to reduce the risk of neutropenic events across malignancies, regimens, and associated risk categories often enabling the delivery of greater chemotherapy dose intensity. Three different practice guidelines for the myeloid growth factors have recently been published by major professional organizations. A comprehensive review and comparison of the guidelines using a priori structured content criteria and a previously validated quality appraisal tool are reported. Consistency in the final recommendations from these guidelines is observed for primary prophylaxis with the colony-stimulating factors (CSFs) when the risk of febrile neutropenia is in the range of 20% or greater. There is also consistency in the recommendation that patients receiving regimens associated with lower risk should have CSF use guided by individual risk assessment. Critical quality appraisal indicates that the scope and purpose, stakeholder involvement, and applicability of the guidelines differ little. There is more emphasis on comprehensive literature reviews in the ASCO and EORTC guidelines while the NCCN guidelines are more current based on systematic annual updates. The clarity of presentation also favors the NCCN guidelines with recommendations generally presented as both text and algorithmic diagram. All three new or updated guidelines recommend prophylactic use of the myeloid growth factors in patients at greater than a 20% risk of febrile neutropenia and in those with important factors increasing individual risk of neutropenic complications.

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Introduction

Chemotherapy-induced neutropenia, including febrile neutropenia (FN), is a major dose-limiting toxicity of many common systemic chemotherapy regimens. Although the reported risk of hematologic toxicity including FN has been consistently underreported in randomized controlled trials (RCTs), it clearly varies across treatment regimens and patient populations [1]. The risk of the initial FN event for many regimens appears to be greatest during the early cycles of chemotherapy [2]. However, when a prophylactic colony-stimulating factor (CSF) is not employed and dose intensity of the same regimen is maintained, the rates of severe or FN are nearly constant across cycles with approximately one-third experiencing two or more events [3]. Most patients with FN require hospitalization for prompt clinical evaluation and the administration of empiric, broad-spectrum antibiotics to reduce the mortality associated with delayed treatment of serious infections in the neutropenic patient. Whatever the risk of occurrence, FN and its consequences are associated with substantial morbidity, mortality, and cost [4].

Neutropenic complications are frequently associated with dose reductions and treatment delays resulting in reduced delivered chemotherapy dose intensity potentially compromising disease control and long-term survival in patients treated with curative intent [5, 6]. Both retrospective studies and prospective RCTs of adjuvant chemotherapy in early-stage breast cancer (ESBC) with patients randomized to different dose intensities have demonstrated a significant relationship between the chemotherapy dose intensity and both disease-free and overall survival [7–10]. In addition, dose-dense regimens based on shortened treatment intervals with CSF support permitting upward of 50% increase in relative dose intensity (RDI) have been shown to improve survival over standard regimens in ESBC and non-Hodgkin lymphoma (NHL) [11, 12]. Nevertheless, a large proportion of patients receiving chemotherapy for potentially curable malignancies are undertreated in the United States [5, 6]. In a study of nearly 20,000 women with ESBC treated in 1,200 oncology practices, more than half received less than 85% of standard dose intensity for their regimen often following an episode of severe or FN [5]. Undertreatment was more prevalent among elderly patients, those receiving certain regimens and overweight or obese patients [13]. Many authors have concluded that such reductions in dose intensity represent a major reason for subsequent treatment failure in patients with responsive malignancies [14].

The myeloid growth factors have been shown to reduce the incidence, duration, and severity of neutropenic events across a broad range of malignancies and regimens often enabling the delivery of full chemotherapy dose intensity [15, 16]. A number of additional RCTs confirming the impact of the myeloid growth factors on reducing the risk of FN have been published over the past few years [17–20]. An updated meta-analysis of RCTs of primary prophylactic G-CSF administered within 3 days of completing myelosuppressive chemotherapy in adult cancer patients has recently been presented [21]. Significant reductions in the risk of FN were observed in both NHL and solid tumor studies, in studies limited to elderly patients as well as all adult age groups and with all forms of G-CSF. In addition to confirming a

reduction in the relative risk of FN, this analysis has demonstrated a significant reduction in infection-related mortality.

The decision to use primary CSF prophylaxis in support of patients receiving cancer chemotherapy is generally based on clinical judgment including (1) the estimated risk of neutropenic complications expected based on the treatment regimen; (2) patient-specific characteristics, including age, functional status, and comorbidities; and (3) the treatment intention, balancing the anticipated *benefit* of chemotherapy with the *risk* of serious and life-threatening complications [22]. Treatment intention determines the relevance or potential harm associated with alternative options to the addition of CSF support, such as dose reduction, treatment delay, use of an alternative chemotherapy regimen, or withholding treatment altogether. When there are no compelling clinical indications for the use of myeloid growth factors based on reducing the risk of FN or infection-related mortality, the decision to use these agents may be based on economic considerations [23–25].

Older age is consistently identified as a predictor of neutropenic complications, including dose reductions and delays. Other predictors include poor performance status, the presence of comorbid conditions, and baseline laboratory abnormalities. A risk model for time to initial FN in aggressive non-Hodgkin's lymphoma patients receiving CHOP was derived from a retrospective series of 577 patients and included 6 independent risk factors: age, baseline hemoglobin, heart disease, renal disease, planned dose intensity, and no CSF prophylaxis [2]. A risk model for first-cycle severe or FN based on a prospective registry of nearly 4,500 patients treated with a new chemotherapy regimen at 117 randomly selected practices in the United States is under development [26]. Independent risk factors in multivariate analysis included the type of cancer, treatment regimen, age, certain comorbidities (liver disease, renal disease, diabetes) and concomitant medications, baseline blood counts, the intention to provide full-dose chemotherapy, and no prophylactic CSF support. Once fully validated, such a risk model may guide clinicians and patients on the most efficacious and cost-effective use of myeloid growth factors.

Clinical practice guidelines statements are generally based on a systematic review of a topic in order to guide practitioners and patients in making informed decisions about appropriate health care. This chapter summarizes and contrasts recently developed or updated guidelines for the use of the myeloid growth factors. The results of recently conducted RCTs and meta-analyses of these trials were reviewed by the respective guidelines panels. The similarities and differences between the guidelines content and process are summarized and contrasted.

Methods

Three sets of clinical practice guidelines for the use of the myeloid growth factors have recently been developed or updated by major professional oncology organizations. These include guidelines updates by The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) along with newly developed guidelines by the European Organization for Research

and Treatment of Cancer (EORTC). ASCO published their initial clinical practice guideline for the use of the hematopoietic CSFs in 1994 [27]. These guidelines were subsequently updated in 1996, 1997, and 2000, only recently completing the most recent update in 2006 with the most extensive revision provided since the original report [28, 29]. In 2005, the NCCN presented and published their initial guidelines on the use of the myeloid growth factors which were updated in 2006 as a part of a systematic annual update [30, 31]. In 2006, the EORTC published guidelines for the use of the CSFs in adults with lymphoma and solid tumors [32]. The EORTC guidelines were intended to complement previously published guidelines on the use of the CSFs in the elderly [33].

The authors undertook a comprehensive review and comparison of the three guidelines using a priori structured content criteria and previously validated quality appraisal tools. Content areas extracted for each guideline included recommendations related to: primary prophylaxis; secondary prophylaxis; therapeutic use; afebrile neutropenia; sustaining dose intensity; progenitor cell transplant; acute leukemia and myelodysplasia; older patients; pediatric patients; schedule and dose; G-CSF versus GM-CSF; and radiation injury. In addition, risk factors associated with disease, treatment, and patient-specific factors such as age, gender, ethnicity, performance status, the presence of comorbidities, and laboratory abnormalities. Guideline content was also contrasted for the major chemotherapy regimens and assumed rates of FN associated with each regimen.

The quality of the recently updated or developed guidelines was then critically appraised using the Appraisal of Guidelines Research and Evaluation (AGREE) Instrument which provides a framework for assessing the quality of clinical practice guidelines based on the potential for bias in guideline development as well as the internal and external validity and feasibility for practice [34]. The AGREE instrument was developed using a sequential process including item generation, selection, scaling, field evaluation, and finalization. An initial list of 82 items was extracted from existing tools and relevant literature addressing these domains [35]. A draft was field tested on the 100 guidelines by 194 appraisers and after further refinement, a final instrument underwent further validation The internal consistency of the final instrument was acceptable with Cronbach's alpha ranging from 0.64 to 0.88 and intraclass correlation coefficients ranging from 0.57 to 0.91 with different appraisers [36]. The use of the AGREE instrument involves taking into account the benefits, harms, and costs of the recommendations, as well as their practical use. Therefore, the assessment includes judgments about the methods used for developing the guidelines, the content of the final recommendations, and the factors linked to their application. The AGREE Instrument assesses both the quality of the recommendations as well as reporting. The tool consists of 23 key items organized in 6 domains, each intended to capture a separate dimension of quality. Items 1–3 assess the scope and purpose of guideline, the clinical questions being asked, and the target population. Items 4–7 reflect the stakeholder involvement or the extent to which the guideline represents the views of its users. Items 8–14 assess the rigor of guideline development or the process used to gather and synthesize the evidence, the methods of developing the recommendations as well as to update them. Items

15–18 evaluate the clarity and presentation of the guidelines in terms of language and format. Items 19–21 assess the applicability of the guidelines including the impact on behavior and costs. Items 22–23 evaluate the editorial independence of the recommendations and any conflicts of interest. As recommended by the developers, the guidelines were assessed by two independent appraisers (GHL, JMK). Each scale item was rated from 4 "Strongly Agree" to 1 "Strongly Disagree", with 3 "Agree" and 2 "Disagree." Domain scores were calculated by summing up all the scores of the individual scale items in a domain. The total score was standardized by presenting the score as a percentage of the maximum possible score for each domain. The developers recommend that the domain scores not be aggregated into a single score and that they be presented and compared independently.

Results

Myeloid growth factor guidelines from the NCCN were initially put forward in 2005 and then updated in 2006. As summarized in Fig. 9.1, these guidelines recommend a stepwise process of starting with an initial evaluation based on the type of cancer, chemotherapy regimen, patient-specific risk factors, and treatment intention. This is to be followed by a formal risk assessment, then a recommendation on the use of

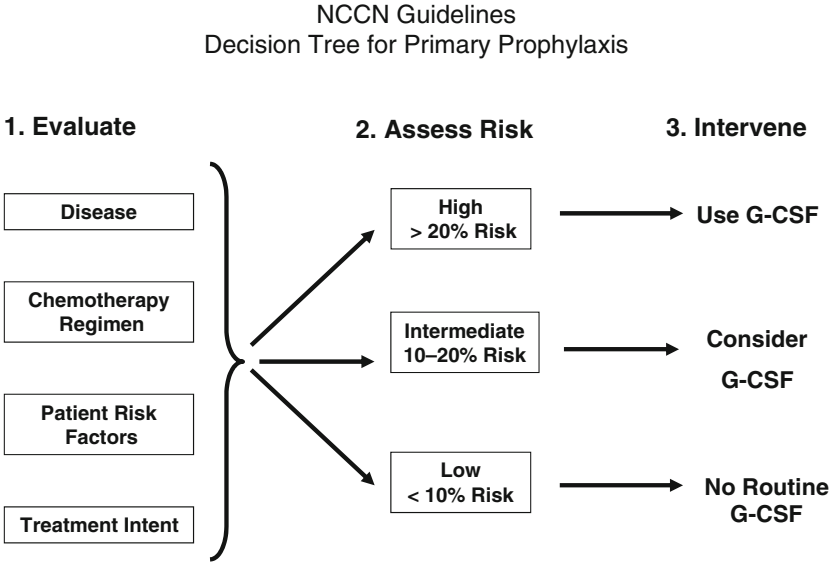

Fig. 9.1 Schematic diagram of the decision process for the use of the myeloid growth factors based on the NCCN Guidelines [3]. After an initial evaluation based on disease, regimen, patient risk factors, and the intention of treatment, the risk of febrile neutropenia should be formally assessed with each patient classified as high (>20%), intermediate (10–20%), or low (<10%) risk. The use of prophylactic CSFs can then be based on the individual patient's assessed risk

the myeloid growth factors based on the level of risk. Unlike the ASCO guidelines in effect at the time, the NCCN guidelines recommended use of G-CSF prophylaxis when patients are thought to be at 20% or greater risk. Patients at intermediate risk, 10–20%, may be considered for prophylactic G-CSF if there are additional considerations that either may place the patient at greater risk for FN or for serious consequences of FN such as prolonged hospitalization or death. Routine prophylaxis with G-CSF should not be employed in patients thought to have a low risk of FN (under 10%). The 2006 ASCO White Blood Cell Growth Factor Guidelines Update Committee agreed unanimously that reduction in FN was an important clinical outcome that justified use of the CSFs when the risk of FN was about 20% and no other equally effective regimen that did not require CSF was available. This was a distinct change from the threshold recommended in previous ASCO guidelines for some 12 years. An additional change with the 2006 guidelines was the introduction of several derivative products including executive and patient summaries, a PowerPoint slide set, and a work sheet or flow sheet to assist practitioners in the application of the guidelines as well as monitoring for guidelines compliance when appropriate. As shown in Fig. 9.2, along with other information, this flow sheet assessed the justification for use of the CSFs and the treatment plan including dose, schedule, route, and duration of use of the white blood cell growth factors. The EORTC also issued guidelines for the use of G-CSF in 2006. As shown in Fig. 9.3, the overall recommendation for prophylactic use of G-CSF is remarkably similar to that of the NCCN and revised ASCO guidelines with routine use in those receiving a regimen with a 20% or greater risk, none when the risk is less than 10%, and then an individual risk assessment in those receiving a regimen associated with a risk of 10–20%. If the individual patient risk for FN after such assessment is deemed to be 20% or greater, primary prophylaxis with G-CSF is recommended.

Table 9.1 summarizes and compares recommendations of the three myeloid growth factor guidelines for the major topics considered as discussed in the methods section. Clearly, not every topic was discussed or equally considered across all guidelines. However, remarkable similarity in the final recommendations is observed for the three guidelines for primary prophylaxis, secondary prophylaxis, sustaining dose intensity, and management of the elderly. There is consistency across the guidelines in the recommendation to consider prophylactic use of the CSFs when the risk of FN is in the range of 20% or greater (Table 9.2). Likewise, there is consistency in the recommendations that patients at lower levels of risk should have their individual risk assessed by the clinician and CSF use considered if there are sufficient risk factors such as advanced age to indicate a greater level of individual patient risk than the RCTs for a given regimen might otherwise indicate.

Table 9.3 summarizes and contrasts the disease-related, treatment-related, and patient-related factors considered to increase the risk of FN and its complications in each of the guidelines. While some differences in emphasis exist, there is consistency across guidelines in recognizing the importance of assessing patient-specific risk factors such as advanced disease, previous episodes of FN, prior extensive chemotherapy, age $\geq$ 65, poor performance or nutritional status, serious

White Blood Cell Growth Factors (CSF) Orders and Flow Sheet

Patient Name: _____ Date: _____ Weight: _____

Diagnosis: _____ Most recent chemotherapy date: _____ Regimen: _____

Insurance: _____ Approved by: _____ Date Approved: _____

JUSTIFICATION FOR USE:

Primary Administration (Preventive)

- ☐Chemotherapy regimen with the risk of febrile neutropenia (FN) at 20% or higher
- ☐ "Dose dense" chemotherapy regimen
- ☐Patient is ≥ 65 years old, has diffuse aggressive lymphoma and receives curative chemotherapy
- ☐Pediatric patient with likelihood of developing FN
- ☐Patient is at higher risk for chemotherapy-induced infectious complications including, but not limited to:
  - ○>65 years old
  - ○Poor performance status
  - ○Poor nutritional status
  - ○Other serious comorbidities: _____
  - ○Previous episodes of FN
  - ○Administration of combined chemoradiotherapy
  - ○Presence of open wounds/active infections
  - ○Extensive prior tx (large radiation ports, prior chemotherapy)
  - ○Cytopenias due to bone marrow involvement by tumor
  - ○Advanced cancer

Secondary Administration (Preventive)

- ☐Patient had a neutropenic complication from prior chemotherapy (primary prophylaxis not received) and dose reduction or delay may compromise survival or treatment outcome
- ☐Pediatric patient is high-risk

Therapeutic Use

- ☐Patient has FN and is at high-risk for infection-associated complications
- ☐Pediatric patient is high-risk
- ☐Patient has prognostic factors that predict a poor clinical outcome:
  - ○Expected prolonged (>10days) and profound (<0.1 x 109/L) neutropenia
  - ○Patient age >65 years (esp. with poor performance status, consider additional risk factors)
  - ○Hypotension and multi-organ dysfunction (sepsis syndrome)
  - ○Patient gets radiotherapy-only (if prolonged delays secondary to neutropenia are expected)
  - ○Uncontrolled primary disease
  - ○Pneumonia
  - ○Invasive fungal infection
  - ○Hospitalization at time of fever development

Other Clinical Circumstance

- ☐Patient has AML and tx follows completion of consolidation chemotherapy or patient is >55 years old and tx follows initial induction therapy
- ☐Patient has ALL and tx follows the completion of the initial days of chemotherapy of the initial induction or first post-remission course
- ☐Patient has MDS and severe neutropenia with recurrent infection(s)
- ☐To mobilize PBPC (esp. in conjunction with chemotherapy and their administration after autologous, but not allogeneic, PBPC transplant)
- ☐Patient exposed to lethal doses of total body radiotherapy (prompt administration of CSF or pegylated G-CSF)
- ☐Other: _____

PLAN:

Growth Factor	Setting	Dose/basis	Dose	Route	Schedule
G-CSF (filgrastim)	Myelotoxic chemotherapy	Adults: 5 ug/kg/d		Sub Q	Continue until ANC at least 2-3 x 10^9/L— 24-72 hours after administration of myelotoxic chemotherapy
	High-dose therapy and autologous stem cell rescue	Adults: 5 ug/kg/d		Sub Q	Continue until ANC at least 2-3 x 10^9/L — 24-120 hours after administration of high-dose therapy
	PBPC mobilization	Adults: 10 ug/kh/d		Sub Q	Continue until last leukapheresis — Start at least 4 days before first leukapheresis
Pegylated G-CSF (pegfilgrastim)	Myelotoxic chemotherapy	6mg (6mg=0.6mL)		Sub Q	Once in each chemotherapy cycle — 24 hours after completion of chemotherapy
GM-CSF (sargramostim)	Bone marrow transplant or AML	Adults: 250 ug/m^2/d		Sub Q IV Infusion	Continue until ANC >1.5 x 10^9/L for 3 consecutive days — Day of bone marrow infusion and not less than 24 hours from the last chemotherapy and 12 hours from most recent radiotherapy

Write dose to be given in appropriate box. After it is administered, write in site and your initials.

Cycle #	Day of cycle	Date to be given	Dose to be given	MD Initials	Dose given	Site	RN Initials

Reviewed by_____on _____

Insurance: _____ Approved by: _____ Date: _____

Fig. 9.2 Flow sheet developed by ASCO to accompany the updated 2006 White Blood Cell Growth Factor Guidelines [29]. The flow sheet assesses the justification for use of a white blood cell growth factor for primary or secondary prevention, therapeutic use, or other reasons and then provides a framework for documenting the dose, schedule, and actual administration of such support. The flow sheet is available on the website of the *Journal of Oncology Practice*. http://www.jopasco.org/jopasco/Main/

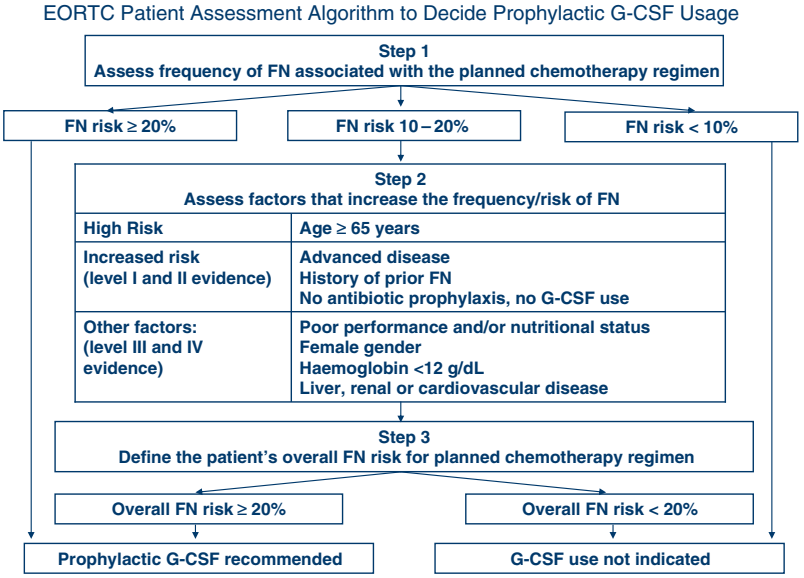

Fig. 9.3 Schematic of the clinical decision pathway for the use of prophylactic G-CSF from the recently published EORTC CSF Guidelines [32]. Primary prophylaxis is recommended routinely for a risk of FN $\geq$ 20% and not for patients at a <10% risk. Patients with a risk of FN of 10–20% should be further assessed for their individual risk based on age and other disease-specific, treatment-specific, and patient-specific risk factors. Patients should be considered for primary G-CSF prophylaxis if their individual risk is thought to be $\geq$20%

comorbidities, and low baseline blood counts or bone marrow involvement. The issues related to the use of the CSFs for treating FN, afebrile neutropenia, progenitor cell transplantation, acute leukemia and myelodysplastic syndrome (MDS), pediatric patients, and the recommended dose and schedule are not addressed by all of the guidelines (Table 9.1).

Each of the guidelines lists common regimens associated with varying levels of risk for FN. Table 9.4 summarizes and compares the regimens that were considered representative of those used in the treatment of common cancers and the assumed level of risk for FN associated with these regimens. Given the differences in process and the inherent variation in oncology practice between Europe and the United States, differences in the regimens mentioned are not a surprise. The EORTC guidelines present considerably more regimens including many that are not mentioned in the ASCO and NCCN guidelines probably reflecting differences in oncology practice in Europe. Although the presumed risk of FN associated with regimens presented across guidelines is relatively comparable, there are some differences evident in the interpretation of clinical trial data on the risk of FN with common regimens presented in these guidelines including doxorubicin and cyclophosphamide (AC) and AC–Docetaxel in breast cancer and cisplatin and paclitaxel (DP) in lung cancer.

Table 9.1 Comparison of guidelines recommendations

Topic	ASCO	EORTC	NCCN
Primary prophylaxis			
CSFs indicated	Risk of FN associated with chemotherapy is approximately 20% or greater[a] Prior FN[b]	Risk of FN > 20% when individual patient risk factors for FN are considered[a] Prior FN[b]	Risk of FN > 20% when individual patient risk factors for FN are considered Prior FN[b]
Consider use of CSFs	If risk of FN < 20%, consider individual risk factors that may increase risk of neutropenic complications[a]	If risk of FN = 10–20%, consider individual risk factors that may increase risk of FN	If risk of FN = 10–20%[c]
No indication for CSFs	Risk of FN < 20% and patient low risk for neutropenic complications	Risk of FN associated with chemotherapy is <10%	Risk of FN <10% and patient low risk for neutropenic complications
Secondary prophylaxis	Patients with previous FN in which dose reduction/delay would compromise outcome	Consider with previous FN when dose reduction/delay would compromise care	Patients with previous FN in which dose reduction/delay would compromise outcome
Therapeutic use for febrile neutropenia	Should not use routinely but consider in patients at high risk for infectious complications	Should not use routinely; consider when unresponsive to antibiotics or with life-threatening complications	Not addressed
Afebrile neutropenia	Not indicated	Not addressed	Not addressed
Sustain dose intensity	Indicated when there is a survival benefit for dose-dense schedules or dose reduction/delay would compromise care	Indicated when there is a survival benefit for dose-dense schedules or dose reduction/delay would compromise care	Indicated when there is a survival benefit for dose-dense schedules or dose reduction/delay would compromise care
Progenitor cell transplant	*Autologous*: indicated for stem cell mobilization and after transplantation *Allogeneic*: indicated for stem cell mobilization only	Not addressed	Not addressed

Table 9.1 (continued)

Topic	ASCO	EORTC	NCCN
Acute leukemia and MDS	*AML*: indicated after induction and consolidation *MDS*: indicated with severe neutropenia and recurrent infection *ALL*: indicated after initial induction and first post-remission chemotherapy	Not addressed	GM-CSF indicated in older adults with AML following induction chemotherapy
Older patients	Indicated in patients ≥ 65 years with aggressive lymphoma receiving curative chemotherapy	Indicated in elderly patients to sustain doses and schedule and reduce risk of neutropenic complications[d]	Use in all patients ≥ 65 years receive chemotherapy equivalent to CHOP[d]
Pediatric patients	*See adult guidelines*: use in ALL with caution	Not addressed	Not addressed
Schedule	Initiate 24–72 h after chemotherapy or 24–120 h after high-dose chemotherapy. Continue until ANC 2–3 $\times 10^9$/L	Not addressed	Initiated 1–3 days after completion of chemotherapy and continued until post-nadir ANC recovery

Table 9.1 (continued)

Topic	ASCO	EORTC	NCCN
Dose	G-CSF 5 μg/kg/d GM-CSF 250 μg/m^2/d; pegylated G-CSF 6 mg 24 h after completion of chemotherapy	Not addressed	G-CSF 5 μg/kg/d[e] GM-CSF 250 μg/m^2/d; pegylated G-CSF 6 mg 24 h after completion of chemotherapy[e]
G-CSF vs GM-CSF	No recommendations can be made regarding the equivalency of G-CSF and GM-CSF. Further trials are needed to compare activity, toxicity, and cost-effectiveness	Filgrastim, lenograstim, and pegfilgrastim are all recommended to prevent FN or FN-related complications	Level 1 evidence to support filgrastim or pegfilgrastim for the prevention of FN. Insufficient evidence to recommend GM-CSF for the prevention of FN. GM-CSF is indicated in older adults with AML
Radiation injury	Prompt administration indicated immediately following lethal doses of total body irradiation	Not addressed	Not addressed

FN, febrile neutropenia; CSF, colony-stimulating factor.
[a]When no equally efficacious regimen available with less risk of FN.
[b]Patients who have had a neutropenic complication during previous cycle and in which dose reduction/delay would compromise cure/care.
[c]Physician–patient discussion indicated. If indication for treatment is palliation, consider an alternative CTR.
[d]Separate Guidelines for CSF use in the elderly:
EORTC, Repetto et al. [33]
NCCN Senior Adult Oncology Guidelines, NCCN, v.1.2005.
[e]Insufficient data available to support pegylated G-CSF in chemotherapy schedules less than 2 weeks.

Table 9.2 Summary of primary prophylaxis recommendations

Neutropenic event risk	ASCO 2006	EORTC 2006	NCCN 2006
Moderate to high	Use CSF ≥ 20%	Use CSF > 20%	Use CSF > 20%
Intermediate	Recommend <20% (with risk factors)	Consider CSF (10–20% with risk factors)	Consider CSF (10–20% with risk factors)
Low	Not further specified	CSF is not recommended <10%	CSF is not recommended for most patients <10%

Table 9.3 Risk factors for febrile neutropenia and its complications

Category	ASCO	EORTC	NCCN
Disease-related	Advanced stage disease	Advanced disease/metastasis	Advanced stage disease; bone marrow involvement; elevated LDH (lymphoma); leukemia; lung cancer
Treatment-related	Previous episode of FN; extensive prior chemotherapy Concurrent XRT or large prior radiation ports	Previous episode of FN; no antibiotic prophylaxis[a]; no G-CSF use; planned dose intensity > 80%	Prior history of severe neutropenia; planned dose intensity > 80% Extensive prior chemotherapy Concurrent/prior radiation
Patient-related			
–Age	Age ≥ 65	Age ≥ 65	Age ≥ 65
–Gender		Female	Female
–Ethnicity		Asian origin	
–Performance status	Poor performance status	Poor performance status	Poor performance status (ECOG ≥ 2)
–Comorbidities	Poor nutritional status; open or infected wounds; serious comorbidities	Poor nutritional status; cardiovascular, renal disease; ≥1 comorbidity Body surface area <2.0 m^2	Poor nutritional, immune status; open or infected wounds; COPD; cardiovascular disease; diabetes mellitus
–Laboratory	Cytopenia secondary to bone marrow involvement	Abnormal liver transaminases Hb < 12 g/dL; serum albumin ≤ 3.5 g/dL; pre-treatment ANC < 1,500	Elevated bilirubin or alkaline phosphatase Low hg; pre-existing ANC <1,000 or lymphocytopenia

[a]Indiscriminant use of antibiotic prophylaxis is not recommended.

Table 9.4 Incidence of febrile neutropenia for selected chemotherapy regimens: reported rates across guidelines

		Myeloid growth factor guideline (%FN)		
Cancer type	Regimen	ASCO	EORTC	NCCN
Breast	AC	10	10–20	10–20
	AC–Doc	3–6	5–25	>20
	A–T–C	3	3	
	CEF	8–9	14	
	TAC	24–34	21–24	>20
	APac		21–32	>20
	ADoc	33	33–48	
	FEC120		9–14	
	FEC100		0–2	
	FAC		5	
	CMFiv		0–3	
	CMFpo		1	
	Doc	21	16–17	10–20
	DocCapec		13	10–20
SCLC	Carbo/VP-16			10–20
	TopC			10–20
	CAE		24–57	>20
	Topotecan		28	>20
	TopT		>20	>20
	ICE		24	
	VICE		70	
NSCLC	VIG		25	>20
	DP	3.7	26	>20
	Cis/Pac	16	16	10–20
	Cis/Gem	4	1–7	
	Cis/Doc	11	5–11	
	Carbo/Pac	4	0–9	
	VP-16/Cis		54	
	Vinor/Cis		1–10	
NHL	ESHAP	30	30–64	>20
	ACOD		11	10–20
	FM		11	10–20
	CHOP		17–50	
	RCHOP	18	19	10–20
	DHAP	48	48	
Colorectal	5-FU/LV		1–15	
	FOLFIRI		3–14	
	FOLFOX		0–8	
	IFL		3–7	
	Irinotecan		2–7	
Germ cell	VIP			>20
	EC		10	10–20
	BEP → EP		13	
	BOP → VIP-B		46	
Ovary	Top	18	10–18	>20, 10–20
	Pac		22	>20

Table 9.4 (continued)

Cancer type	Regimen	Myeloid growth factor guideline (%FN)		
		ASCO	EORTC	NCCN
	Doc		33	>20
	Cis/Pac	Rare		
	Carbo/Pac		3–8	
	Gem/Cis		9	
Sarcoma	MAID		58	>20
	Doxorubicin			>20
	Dox/Ifos			>20

AC, doxorubicin/cyclophosphamide; AC–Doc, doxorubicin/cyclophosphamide/docetaxel; A–T–C, doxorubicin/paclitaxel/cyclophosphamide; CEF, cyclophosphamide/epirubicin/fluorouracil; TAC, docetaxel/doxorubicin/cyclophosphamide; APac, doxorubicin/paclitaxel; ADoc, doxorubicin/docetaxel; FEC120, cyclophosphamide/epirubicin/fluorouracil; FEC100, cyclophosphamide/epirubicin/fluorouracil; FAC, fluorouracil/doxorubicin/cyclophosphamide; CMFiv, cyclophosphamide/methotrexate/fluorouracil-intravenous; CMFpo, cyclophosphamide/methotrexate/fluorouracil-oral; Doc, docetaxel; DocCapec, docetaxel/capecitabine; Carbo/VP-16, carboplatin/etoposide; TopC, topotecan/cisplatin; CAE, cyclophosphamide/doxorubicin/etoposide; TopT, topotecan/paclitaxel; ICE, ifosfamide/carboplatin/etoposide; VICE, vincristine/ifosfamide/carboplatin/etoposide; VIG, gemcitabine/ifosfamide/dacarbazine; DP, docetaxel/carboplatin; Cis/Pac, cisplatin/paclitaxel; Cis/Gem, cisplatin/gemcitabine; Cis/Doc, cisplatin/docetaxel; Carbo/Pac, carboplatin/paclitaxel; VP-16/Cis, etoposide/cisplatin; Vinor/Cis, vinorelbine/cisplatin; ESHAP, etoposide/methylprednisolone/cisplatin/cytarabine; ACOD, doxorubicin/cyclophosphamide/vincristine/prednisone; FM, fludarabine/mitoxantrone; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; RCHOP, cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab; DHAP, cisplatin/cytarabine/dexamethasone; 5-FU/LV, 5-FU/leucovorin; FOLFIRI, 5-FU/leucovorin/irinotecan; FOLFOX, 5-FU/leucovorin/oxaliplatin; IFL, irinotecan/fluorouracil/leucovorin; VIP, vinblastine/ifosfamide/cisplatin; EC, etoposide/cisplatin; BEP → EP, bleomycin/etoposide/cisplatin → etoposide/cisplatin; BOP → VIP-B, bleomycin/vincristine/cisplatin → cisplatin/ifosfamide/etoposide/bleomycin; Top, topotecan; Pac, paclitaxel; MAID, mesna/adriamycin/ifosfamide/dacarbazine; Dox/Ifos, doxorubicin/ifosfamide.

Finally, each guideline was critically appraised by the authors independently using the previously validated AGREE measurement tool and discrepancies resolved as discussed in the methods section. Table 9.5 summarizes and contrasts the results of this critical appraisal by domain of focus of the scale. For issues related to the scope and purpose, stakeholder involvement, and applicability of the guidelines, little or no differences in appraisal were found. The NCCN guideline was appraised as less rigorous in its development largely related to the recognized consensus process employed compared to a more rigorous evidence-based approach used by ASCO and EORTC. While a literature review was undertaken by each of the Panels, the review process was found to be more systematic and comprehensive in the ASCO and EORTC guidelines than in the NCCN guidelines in which no criteria for the search and selection of relevant literature are presented. Differences are also noted in the review process with an explicit process for independent and external review of the ASCO and EORTC guidelines. Similarly, there appears to

Table 9.5 Critical appraisal of myeloid growth factor guidelines

	ASCO 2006	EORTC	NCCN
Scope and purpose			
1. The overall objectives of the guideline are specifically described	4 To update the 2000 ASCO guideline on the use of CSFs	4 To develop European focused guidelines to assist in the use of CSF in patients at risk for FN	4 To develop guidelines to assist clinicians in the appropriate prophylactic use of CSFs
2. Clinical questions covered by the guideline are specifically described	4 Clinical questions are clearly described	4 Clinical questions are clearly described	4 Clinical questions are clearly described
3. Patients to whom the guideline is meant to apply are specifically described	4 Population is clear within each specific clinical area. Much broader populations than other guidelines	4 Adult cancer patients at risk for chemotherapy-induced FN	4 Adult patients with solid tumors and non-myeloid malignancies
Domain score	100%	100%	100%
Stakeholder involvement			
4. Guideline development group includes individuals from all the relevant professional groups	3 A full list of committee members are provided, but their areas of specialty/interest are not indicated	4 The development group members are representative of relevant professional groups	3 The development group members are representative of NCCN member institutions with some external consultation
5. Patients' views and preferences have been sought	2 Literature review addressing QOL completed. Direct patient interviews were not conducted. No patient representative	2 Literature review addressing QOL completed. No indication that direct patient interviews were conducted	2 Literature review addressing QOL completed. No indication that direct patient interviews were conducted
6. Target users of the guidelines are clearly defined	3 Specific user of the guideline is never stated directly, although it is strongly implied	3 Specific user of the guideline is never stated directly, although it is strongly implied	3 Specific user of the guideline is never stated directly, although it is strongly implied
7. Guideline has been piloted among target users	1 No indication that the guideline had been tested prior to its publication	1 No indication that the guideline had been tested prior to its publication	1 No indication that the guideline had been tested prior to its publication
Domain score	42%	50%	42%

Table 9.5 (continued)

	ASCO 2006	EORTC	NCCN
Rigor of development			
8. Systematic methods were used to search for evidence	4 Systematic method used for searching the literature was clearly delineated	4 Systematic method used for searching the literature was clearly delineated	2 No systematic literature search. Updated literature is reviewed, guidelines consensus based
9. Criteria for selecting the evidence clearly described	4 Criteria for evidence selection was clearly delineated	4 Criteria for evidence selection was clearly delineated	1 No indication of the criteria used for selecting relevant evidence
10. Methods used for formulating the recommendations are clearly described	4 Clear description of the methods used to formulate the guideline recommendations provided	4 Clear description of the methods used to formulate the guideline recommendations provided	2 Guidelines are consensus based. Specifics of how the consensus was obtained are not provided
11. Health benefits, side effects and risks considered in formulating the recommendations	3 Benefits of CSFs are clearly stated. Some side effects and risks of growth factors are not addressed at all	2 Benefits of CSFs are clearly stated. Side effects and risks of growth factors are not addressed at all	2 Benefits of CSFs are clearly stated. Side effects and risks of growth factors are not addressed at all
12. Explicit link between recommendations and supporting evidence	4 Each point in the guideline is backed with a reference	4 Each point in the guideline is backed with a reference	4 Each point in the guideline is backed with a reference
13. Guideline has been externally reviewed by experts prior to publication	3 Reviewed by ASCO Health Service Committee and Board of Directors. No description of the reviewers' areas of expertise. No indication of review outside of ASCO	4 External review by experts in several fields was performed	1 Guideline drafts are reviewed by experts at each center. No indication that external review occurred

Table 9.5 (continued)

	ASCO 2006	EORTC	NCCN
14. Procedure for updating the guideline is provided	1 No clear statement of when the next ASCO update will occur available in the guidelines	1 No clear procedure for updating the guideline is indicated	4 Guidelines updated annually and based on evaluation of scientific data integrated with expert judgment by multidisciplinary panels of experts from NCCN institutions
Domain score	76%	76%	48%
Clarity and presentation			
15. Recommendations are specific and unambiguous	4 Recommendations are specific and unambiguous	4 Recommendations are specific and unambiguous	4 Recommendations are specific and unambiguous
16. Different options for management are clearly presented	4 Patient management options are discussed	4 Patient management options are discussed	4 Patient management options are discussed
17. Key recommendations are easily identifiable	3 Key recommendations are easy to identify in guideline manuscript and guideline summary, but are wordy	4 Key recommendations are italicized in the manuscript	4 Key recommendations are available in manuscript text and as user-friendly diagrams and tables
18. The guideline is supported with tools for application	4 Guideline summary available as an appendix to the manuscript. Derivative slide set and flow sheet available	2 User-friendly diagram provided in the manuscript directing CSF use. No other application tools are provided	4 User-friendly tables and diagrams are provided online with convenient links between relevant treatment decision points
Domain score	92%	83%	100%

Table 9.5 (continued)

	ASCO 2006	EORTC	NCCN
Applicability			
19. Potential organizational barriers in applying recommendations discussed	1 Guideline did not contain discussion of potential organizational barriers to applying the guidelines	1 Guideline did not contain discussion of potential organizational barriers to applying the guidelines	1 Guideline did not contain discussion of potential organizational barriers to applying the guidelines
20. Cost implications of applying recommendations considered	4 Clear discussion of cost benefit analysis was provided	4 Clear discussion of cost benefit analysis was provided	4 Clear discussion of cost benefit analysis was provided
21. Guideline presents key review criteria for monitoring or audit purposes	4 Separate worksheet developed for review and audits	4 Flow chart presented that outlines details criteria to meet recommendations	4 Flow chart presented that outlines criteria to meet recommendations
Domain score	67%	67%	67%
Editorial independence			
22. Guideline is editorially independent from the funding body	2 Guideline approved by ASCO Panel, Health Services Committee and Board of Directors. Process has industry input but is editorially independent	2 Guideline approved by EORTC Panel, Infectious Disease Group and Governing Board. Process has industry input but is editorially independent	2 Guideline approved by NCCN Panel and Institutions. Process has industry input and receives industry support for distribution of the guideline library on CD-ROM but is editorially independent
23. Conflicts of interest of guideline development members have been recorded	4 Conflicts of interest of guideline committee members are clearly stated	4 Conflicts of interest of guideline committee members are clearly stated	2 Conflicts of interest statement made for entire panel is available
Domain score	67%	67%	33%

CSFs, colony-stimulating factors; QOL, quality of life.

be no indication of individual conflicts of interest for Panel members of the NCCN Panel as there are for the ASCO and EORTC guidelines. In contrast, the NCCN guidelines are updated on an annual basis while no explicit process for update of the ASCO and EORTC guidelines are stated. In addition, the clarity of presentation favors the NCCN guidelines with the recommendations generally presented in both text and algorithmic diagrams for ease of access and use. While no meaningful overall summary measure can be derived from the critical appraisal, the differences observed are largely accountable by the differences in process employed by the different professional groups involved. All guidelines in the end recommend further clinical investigation of a number of areas that remain unclear.

Discussion

Chemotherapy-induced neutropenia and its complications are major dose-limiting toxicities of cancer chemotherapy. The myeloid growth factors have been shown to reduce the risk of FN and its related complications. Three different practice guidelines for the myeloid growth factors have recently been published by major professional organizations. A comprehensive review and comparison of the guidelines demonstrates remarkable consistency in the final recommendations from these guidelines for the use of CSF primary prophylaxis in patients at approximately a 20% risk of FN or greater. All guidelines also recommend CSF use be considered when individual risk assessment by the clinician concludes a patient is at increased risk.

The quality of clinical practice guidelines has recently been brought into question [37]. Overall, the quality of the myeloid growth factor guidelines was rated as good with little or no difference between guidelines in the stated scope and purpose, stakeholder involvement, and applicability of the guidelines. There is clearly more emphasis on systematic and comprehensive literature reviews in the ASCO and EORTC guidelines, while the NCCN guidelines are updated on an annual basis and appear to offer better clarity of presentation.

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