



CED-CCO Special Advice Report 14-2 EDUCATION AND INFORMATION 2013

The Prophylactic Use of Filgrastim in Patients with Breast Cancer

Y. Madarnas, A. Eisen, R. Myers, and A.E. Haynes

Report Date: October 1, 2009

The CED-CCO Special Advice Report 14-2 was put in the Education and Information section in 2013. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#)).

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SUMMARY

QUESTIONS

- 1) Does the use of filgrastim as primary prophylaxis in patients with early stage (I, II, or III) breast cancer receiving myelosuppressive chemotherapy with curative intent improve clinical outcomes?
- 2) Does the use of filgrastim as secondary prophylaxis in patients with early stage (I, II, or III) breast cancer receiving myelosuppressive chemotherapy with curative intent improve clinical outcomes?
- 3) Does the use of filgrastim as secondary prophylaxis in patients with advanced stage (IV) breast cancer receiving palliative myelosuppressive chemotherapy after previous dose reduction for neutropenia improve clinical outcomes?

Outcomes of interest include the incidence of febrile neutropenia (FN), death from infection, and maintenance of dose intensity.

TARGET POPULATION

This report applies to adult patients receiving myelosuppressive chemotherapy for breast cancer.

RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report. We endorse the recommendations published by the European Organization for the Research and Treatment of Cancer (EORTC) and the American Society of Clinical Oncology (ASCO) regarding the use of prophylactic colony-stimulating factors (CSFs). Specific recommendations include the following:

- **Primary prophylaxis with CSFs is justified for patients with early stage breast cancer treated with curative intent who receive:**
 - Any adjuvant dose dense chemotherapy regimen
 - Any adjuvant chemotherapy regimen with expected rates of FN $\geq 20\%$ (e.g., FEC-D, TC, CEF/FEC100)
 - Any adjuvant chemotherapy regimen with expected rates of FN $< 20\%$ in the presence of patient related risk factors:
 - age > 65 yrs
 - comorbidity that in the opinion of the treating physician may increase the risk of FN, or that may be complicated by the development of FN
 - poor performance status
 - poor nutritional status
- **Secondary prophylaxis with CSFs is justified for patients with early-stage breast cancer treated with curative intent who did not receive primary CSF prophylaxis and have experienced a neutropenic event, or a dose delay, with a prior cycle of chemotherapy and who require continued treatment where a reduced dose may compromise treatment outcome**
- **For patients with advanced breast cancer receiving palliative myelosuppressive therapy who have suffered FN despite an initial schedule or dose adjustment, and for whom continued treatment is required and the treating physician feels that a further reduction in dose or schedule delay may compromise treatment outcome, secondary prophylaxis with CSF is appropriate.**
- **For patients with advanced breast cancer receiving palliative myelosuppressive chemotherapy, a schedule or dose adjustment, with or without prophylactic antibiotics, is the preferred initial strategy to minimize the risk of FN. However, in exceptional circumstances where even with such an intervention, the treating physician feels that there is a persistent and substantial risk of FN, primary prophylaxis with CSF can be considered on a case by case basis via the Expanded Access Program.**

KEY EVIDENCE

- Guidelines published by both ASCO (1) and the EORTC (2,3) have made several recommendations regarding the use of CSF in patients with solid tumours, including breast cancer. Those guidelines were both high quality and formed the strongest evidence regarding the use of CSFs in patients with breast cancer.

QUALIFYING STATEMENTS

- Filgrastim, GCSF, is one of several growth factors and the most widely used. Other formulations exist; specifically, pegfilgrastim and lenograstim, with few clinically

important differences between them, and any one of these agents is considered effective in the prevention of FN (2).

FUTURE RESEARCH

The efficacy and safety of CSFs is well established, and their use is widespread in routine clinical practice. In this context, randomized trials examining their use versus placebo or control for a given regimen are unlikely to be conducted. Furthermore, patient populations at particular risk for toxicity of myelosuppressive chemotherapy, such as the elderly, those with comorbidity, or those with prior exposure to cytotoxic chemotherapy are often excluded from clinical trials, and, thus, data that are generalizable to these populations are unlikely to be forthcoming.

IMPLICATIONS FOR POLICY

The recommendations in this document will align clinical practice in Ontario with the European and American (US) clinical oncology community. There is likely to be a resultant increased use of CSFs but, in exchange, a decrease in morbidity from myelosuppressive therapy for breast cancer.

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REFERENCES—SUMMARY

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3. Repetto L, Biganzoli L, Koehne CH, Luebke AS, Soubeyran P, Tjan-Heijnen VCG, et al. EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. *Eur J Cancer*. 2003 Nov;39(16):2264-72.

FULL REPORT

QUESTIONS

- 1) Does the use of filgrastim as primary prophylaxis in patients with early stage (I, II, or III) breast cancer receiving myelosuppressive chemotherapy with curative intent improve clinical outcomes?
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Outcomes of interest include incidence of febrile neutropenia (FN), death from infection, and maintenance of dose intensity.

Throughout this document, the terms growth factors (GF) and colony stimulating factors (CSFs) are used interchangeably. Filgrastim, GCSF, is one of several GFs and the most widely used. Other formulations exist, specifically pegfilgrastim and lenograstim, with few clinically important differences between them, and any one of these agents is considered effective in the prevention of FN (1).

INTRODUCTION

This Special Advice Report was initiated at the request of the Committee to Evaluate Drugs - Cancer Care Ontario Subcommittee (CED-CCO). The CED-CCO asked the PEBC to provide advice on the prophylactic use of CSFs in breast cancer.

METHODS

This advice report, produced by the CCO Program in Evidence-based Care (PEBC), is a convenient and up-to-date source of the best available evidence on the prophylactic use of filgrastim in the treatment of adult patients receiving myelosuppressive chemotherapy for breast cancer, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

MEDLINE (Ovid) (1990 through August Week 2 [August 22] 2009), EMBASE (Ovid) (1990 through Week 34 [August 22] 2009), and the Cochrane Library (2009, Issue 3) databases were searched. The search strategy for MEDLINE is shown in Appendix 1. Search strategies in other databases were similar.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO) 2005 to 2009, the American Society of Hematology (ASH) (2004 to 2008), and the San Antonio Breast Cancer Symposium (SABCS) (2004 to 2008) were searched for abstracts of relevant trials.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published full-report articles or published meeting abstracts involving:

1. Randomized trials that compared the primary or secondary prophylactic use of filgrastim to either placebo, no filgrastim, or best supportive care, including prophylactic antibiotics
2. Patients receiving myelosuppressive chemotherapy for breast cancer.
3. Systematic reviews, meta-analyses, or clinical practice guidelines of the use of filgrastim in patients with breast cancer.
4. Publications of randomized trials, systematic reviews, or meta-analyses reporting data on one or more of the following outcomes: FN, death from infection, or maintenance of dose intensity.

Exclusion Criteria

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publications.
2. Articles published in a language other than English, due to financial considerations for translation.

Synthesizing the Evidence

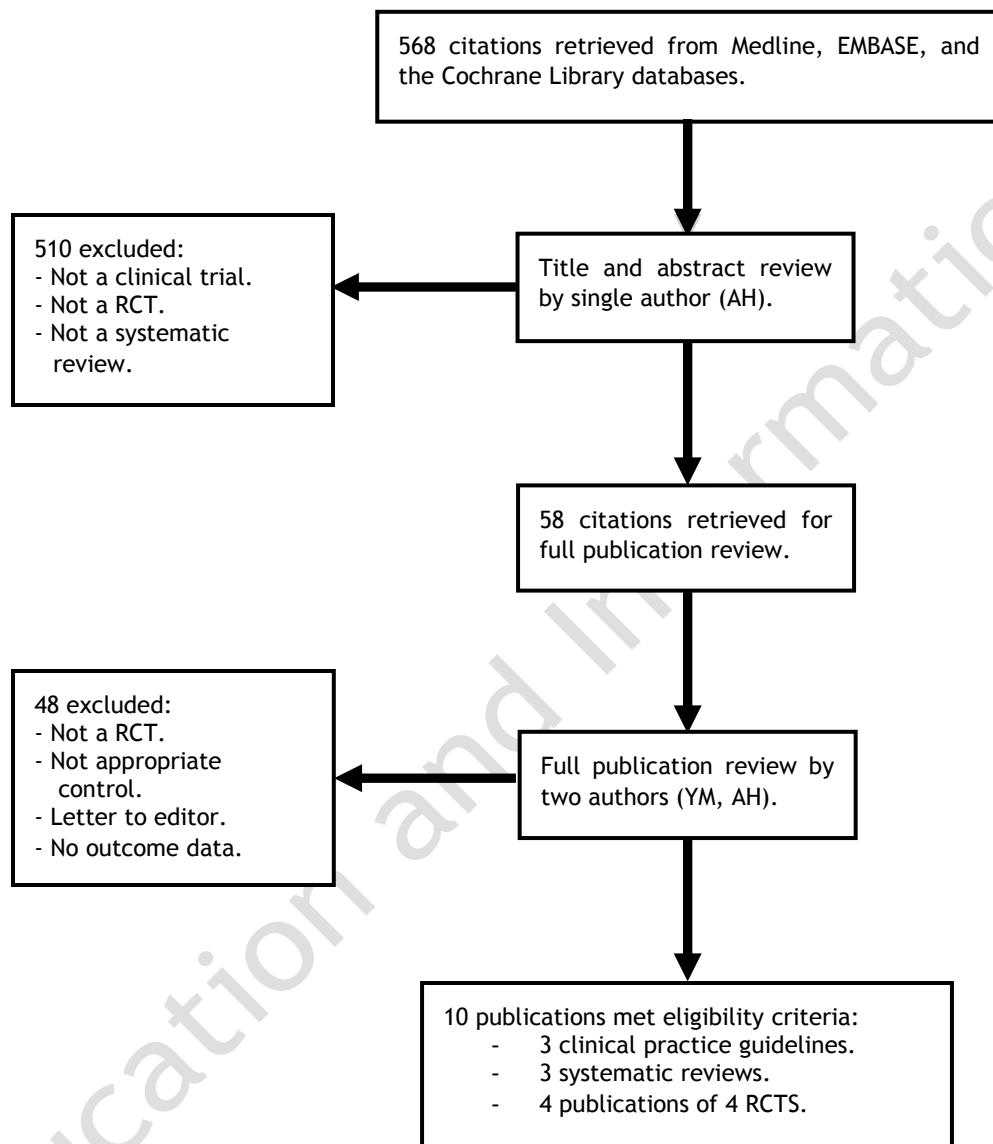
A meta-analysis of trial results will be conducted if sufficient data are available. Outcomes to be considered for meta-analysis include incidence of FN and death from infection.

RESULTS

Literature Search Results

A total of 568 citations of studies were identified from the MEDLINE, EMBASE, and Cochrane Library databases. From those citations, a total of 48 full publications were retrieved for full review. Ten publications met our eligibility criteria (Figure 1). Three clinical practice guidelines (1-3), three systematic reviews (4-6), and four publications of four randomized controlled trials (RCTs) (7-12) were identified. In addition, 18 abstracts were identified. Of those, 14 abstracts were of subsequently fully published trials or did not report data on outcomes of interest. In total, three abstracts of three trials were included (13-15). The results section has been divided into the following sections: clinical practice guidelines, systematic reviews, and clinical trials.

Figure 1. Selection of studies investigating the prophylactic use of filgrastim in patients with breast cancer receiving myelosuppressive chemotherapy, from the search results of MEDLINE, EMBASE, and the Cochrane Library databases.



Clinical Practice Guidelines

Three clinical practice guidelines were identified that provided advice on the prophylactic use of filgrastim (G-CSF) growth factor support in patients with solid tumours. The European Organization for the Research and Treatment of Cancer (EORTC) has developed two guidelines: The first is on the use of G-CSF to reduce the incidence of chemotherapy-induced FN in adult patients with lymphomas and solid tumours (1). The evidentiary base of the guideline was a systematic review, and the methods used to identify relevant studies were thorough. The authors searched multiple databases up to September 2005. The second guideline was on the use of CSFs in elderly patients (3). The authors performed a systematic review to form the evidentiary base of the guideline and searched MEDLINE up to March 2002. The third guideline was the 2006 update of the ASCO white blood cell growth factors guideline (2). The date that the literature search went up to was not reported.

Summary of Existing Guidelines/Recommendations:

EORTC 2003/2006 Guideline

The EORTC guidelines (1,3) authors first approach the issue by accepting that intervention with GF support (G-CSF and other products) is effective at reducing the rates of FN as a primary or secondary prophylaxis and is indicated in situations where the risk of FN is high. They then approach the issue with a risk-adapted strategy, defining patient-related factors that increase the risk of FN, regimens that are associated with an increased risk of FN, and special situations where GF support is intended to support chemotherapy dose intensity or dose density. They make the following recommendations:

- Recommendation 1: *“Patient-related risk factors should be evaluated in the overall assessment of FN risk prior to administering each cycle of chemotherapy. Particular consideration should be given to the elevated risk of FN for elderly patients (aged 65 and over). Other adverse risk factors that may influence FN risk included: advanced stage of disease; experience of a previous episode(s) of FN; lack of G-CSF use and lack of antibiotic prophylaxis. However, please note that the indiscriminate use of antibiotics prophylaxis is not recommended by either the working party or the EORTC Infectious Disease Group.”* This recommendation is supported by grade B evidence.
- Recommendation 2: *“Consideration should be given to the elevated risk of FN when using certain chemotherapy regimens... It should be noted that this list is not comprehensive and there may be other drugs or regimens associated with an increased risk of FN”.* This recommendation is supported by grade A/B evidence.
- Recommendation 3: *“In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF should be used as supportive treatment. If reductions in chemotherapy dose intensity or density are known to be associated with a poor prognosis, primary G-CSF prophylaxis should be used to maintain chemotherapy. Examples of this could be when the patient is receiving adjuvant or potentially curative treatment, or when the treatment intent is to prolong survival. Where it is not crucial, use of less myelosuppressive chemotherapy or dose/schedule modification should be considered.”* This recommendation is supported by grade A evidence.
- Recommendation 4: *“The risk of complications related to FN should be assessed individually for each patient. When assessing FN risk, the clinician should take into account patient-related risk factors (recommendation 1), the chemotherapy regimen and associated complications (recommendations 2 and 3) and treatment intent (recommendation 3). If the patient is at $\geq 20\%$ overall risk of FN, prophylactic G-CSF is recommended. When using chemotherapy regimens associated with an FN risk of 10-20%, particular attention should be given to the assessment of patient characteristics*

that may increase the overall risk of FN.” This recommendation is supported by grade A evidence.

- Recommendation 5: “Treatment with G-CSF for patients with solid tumours and ongoing FN is indicated in only special situations. These are limited to those patients who are not responding to appropriate antibiotic management and who are developing life threatening infections (such as severe sepsis or septic shock).” This recommendation is supported by grade B evidence.
- Recommendation 6: “Filgrastim, lenograstim and pegfilgrastim have clinical efficacy and we recommend the use of any of these agents to prevent FN and FN-related complications, where indicated.” This recommendation is supported by grade A evidence.
- Recommendation from the elderly position paper (3) page 2270: “the Working Party recommends the use of prophylactic G-CSF to support the administration of planned doses of chemotherapy on schedule and reduce the incidence of chemotherapy-induced neutropenia, febrile neutropenia and infections in elderly patients receiving myelotoxic chemotherapy.” This recommendation is supported by grade A/B evidence.

ASCO 2006 Guideline

The authors of the ASCO clinical practice guideline (2) approach the subject by defining indications for the use of GFs as a primary or a secondary prophylaxis, the therapeutic use of colony-stimulating factors (CSFs), and to increase chemotherapy dose intensity and dose density, as well as other indications pertaining to hematological malignancies, pediatric populations, and other special settings.

1) Recommendations for primary prophylactic CSF administration (first and subsequent cycle use):

“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 (16,17).

.....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.....

Special circumstances.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 tumour; 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 data.”

2) Recommendation for secondary prophylactic CSF administration:

“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.”

The authors of the current report used the list of trials in the guidelines to identify trials published prior to the date of their latest search—September 2005. Therefore, our literature search was changed to focus on the time period from September 2005 to the present.

Systematic Reviews

Three publications of systematic reviews were identified. Two systematic reviews investigated the prophylactic use of filgrastim in patients with cancer (5,6). Neither provided subgroup data for the trials of patients with breast cancer. The remaining report, by von Minckwitz et al (4), investigated the use of primary prophylactic pegfilgrastim compared to current practice neutropenia management in patients with breast cancer. The authors aimed to conduct an individual patient data meta-analysis.

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool (18) was used to assess the methodological quality of the systematic review, because the tool has been demonstrated to be both reliable and valid (19,20). The AMSTAR tool consists of 11 items assessing the quality of systematic reviews. The systematic review by the authors scored four out of 11 on the AMSTAR instrument (Table 1). The authors only searched MEDLINE and did not provide a list of excluded studies, although a list of included studies was provided. Other than the study design, the quality of the identified studies was not reported. The authors did not assess publication bias.

The authors reported that the odds for FN occurring in the primary prophylaxis group were significantly lower compared to current practice management of neutropenia (0.12, $p < 0.0001$). The odds for requiring a dose reduction $\geq 15\%$ were significantly lower for primary prophylaxis compared to current practice management (0.58, $p = \text{not reported}$).

Table 1. AMSTAR ratings of included systematic reviews of GCSF in breast cancer.

Item	von Minckwitz, 2009 (4)
A priori design provided?	Y
Duplicate study selection and data extraction?	CA
Comprehensive literature search performed?	N
Status of publication used as an inclusion criteria?	CA
List of included/excluded studies provided?	N
Characteristics of included studies provided?	Y
Scientific quality of included studies assessed and reported?	N
Scientific quality of included studies used appropriately to form conclusions?	CA
Study findings combined appropriately?	Y
Assessment of publication bias?	N
Declaration of conflict of interest?	Y

Notes: CA=cannot answer; N=no; Y=yes.

Randomized Trials

Trial and Patient Characteristics

Only two randomized trials comparing the use of GCSF combined with myelosuppressive chemotherapy to the same therapy without GCSF in patients with breast cancer were identified (10,15). Six additional trials were identified that compared chemotherapy with GCSF to similar chemotherapy without GCSF, or with a different dose of GCSF (7,11-14). Although these did not strictly meet the eligibility criteria, given their potential relevance to the research question, they were included for review. Four trials were

fully published (7-12), and three were reported in abstract form only (13-15). Table 2 contains the trial and patient characteristics.

Trial Quality

Quality characteristics of the seven trials are shown in Table 3. For the two RCTs that compared GCSF plus chemotherapy to the same chemotherapy without GCSF, neither reported many details regarding study quality (Table 3). Papaldo et al (10) reported that the sample-size requirement was met and that the report was a final analysis, with 1.8% of 506 enrolled patients lost to follow-up. Brugger et al (15) did not report any information regarding study quality.

The remaining two trials reported in abstract form only did not have any information regarding study quality available (13,14). The remaining three fully published trials all reported a sample size calculation, and all met that requirement. All the reports were final analyses; however, only two were reported to be intent-to-treat (11,12). Only Holmes et al reported further details on study quality: patients were randomized using a stratified permuted block strategy, and the trial was double-blind. No information was given on who was blinded.

Outcomes

Data on the outcomes of interest can be found in Table 4. Papaldo et al (10) reported a significant difference in the rates of grade 3/4 neutropenia for patients receiving epirubicin and cyclophosphamide in combination with primary prophylaxis with GCSF (28.6% of 257 patients) compared to no GCSF (81.6% of 249 patients; $p=0.00001$). Brugger et al (15) reported that the mean absolute neutrophil count was greater than or equal to $1.0 \times 10^9/L$ (grade 3 neutropenia) from day nine in patients who received primary prophylaxis with GCSF in combination with fluorouracil/epirubicin/cyclophosphamide (FEC) chemotherapy, and from day 18 in those who received FEC chemotherapy without GCSF. No p-value was reported.

Other Studies

Given the lack of RCT data addressing the use of G-CSF in patients with breast cancer, the authors agreed that the rates of FN as well as grade 3/4 neutropenia and infection should be established for the common adjuvant chemotherapy regimens in use for breast cancer. The seminal publications for the major trials supporting the use of those regimens were identified, and the above outcomes were extracted from the publications. Data on those outcomes can be found in Table 5. The studies included in Table 5 were not identified through a systematic review of the literature.

The authors were aware through their own clinical experience that the rates of FN at regional cancer centres in Ontario appeared to be higher than those published in the identified RCTs. The authors contacted physicians at each centre to establish their local clinical experience with FN rates associated with common breast cancer regimens in use Ontario. In addition, data from the Cancer Care Ontario CSQI were sought on febrile neutropenic events in Ontario. These data can be found in Figure 2.

Table 2. Patient and intervention details for RCTs of GCSF in breast cancer.

Author, year (ref)	Patient characteristics	Treatment	Differences between treatment groups at baseline
Fully Published			
Liu, 2008 (7)	Operable BC with ≥ 1 involved axillary lymph node, ECOG PS 0-2.	A 37.5 mg/m ² iv d1,2 + C 2000 mg/m ² iv d1 + FGM 5 mcg/kg/d + cipro 750 mg 2x/d; q21d x 5 → T 175 mg/m ² iv q21d x 4 A 37.5 mg/m ² iv d1,2 + C 2000 mg/m ² iv d1 + FGM 10 mcg/kg/d + cipro 750 mg 2x/d; q21d x 5 → T 175 mg/m ² iv q21d x 4	NR
Papaldo, 2006 (8)	Stage I/II BC, age 18-65 years.	E 120 mg/m ² iv d1 + C 600 mg/m ² iv d1; q21d	Arms balanced
Papaldo, 2005 (9)		E 120 mg/m ² iv d1 + C 600 mg/m ² iv d1 + LND 225-450 mg/d; q21d	
Papaldo, 2003 (10)		E 120 mg/m ² iv d1 + C 600 mg/m ² iv d1 + FGM various schedules ^A ; q21d E 120 mg/m ² iv d1 + C 600 mg/m ² iv d1 + LND 225-450 mg/d + FGM various schedules ^A ; q21d	
Citron, 2003 (11)	Primary operable BC.	A 60 mg/m ² q21d x 4 → T 175 mg/m ² q21d x 4 → C 600 mg/m ² q21d x 4	Arms balanced
		A 60 mg/m ² q14d x 4 → T 175 mg/m ² q14d x 4 → C 600 mg/m ² q14d x 4; FGM 5 mcg/kg d3-10 of each cycle	
		A 60 mg/m ² + C 600 mg/m ² q21d x 4 → T 175 mg/m ² q21d x 4	
		A 60 mg/m ² + C 600 mg/m ² q14d x 4 → T 175 mg/m ² q14d x 4; FGM 5 mcg/kg d3-10 of each cycle	
Holmes, 2002 (12)	High-risk stage II or stage III/IV BC, ECOG PS ≤ 2 .	A 60 mg/m ² d1 + D 75 mg/m ² d1 + PEG 100 mcg/kg d2, q21d A 60 mg/m ² d1 + D 75 mg/m ² d1 + FGM 5 mcg/kg/d, q21d	Arms balanced
Abstracts			
Satheesh, 2009 (13)	BC, age <65 years, ECOG PS 0-1.	A 60 mg/m ² + C 600 mg/m ² + D 75 mg/m ² q21d + FGM 5 mg/kg/d A 60 mg/m ² + C 600 mg/m ² + D 75 mg/m ² q21d + PEG 6 mg	NR
Brugger, 2007 (15)	Stage II or III BC, age ≥ 65 years.	F 500 mg/m ² + E 100 mg/m ² + C 500 mg/m ² + PEG 6 mg sc d2, x 6 F 500 mg/m ² + E 100 mg/m ² + C 500 mg/m ² , x 6	NR
Moebus, 2006 (14)	High-risk BC.	E 150 mg/m ² + T 225 mg/m ² + C 2500 mg/m ² + FGM 5 mcg/kg d3-10 sc, q14d x 3 E 90 mg/m ² + C 600 mg/m ² , q21d x 4 → T 175 mg/m ² q21d x 4	Risk factors in each arm balanced

Notes: A=doxorubicin (Adriamycin®); abs=abstract; BC=breast cancer; C=cyclophosphamide; d=day(s); D=docetaxel; E=epirubicin; ECOG=Eastern Cooperative Oncology Group; F=fluorouracil; FGM=filgrastim; iv=intravenous; LND=lonidamine; NR=not reported; PEG=pegfilgrastim; PS=performance status; q=every; ref=reference; sc=subcutaneously; T=paclitaxel (Taxol®); w=week(s); →=followed by.

^ASchedules: 480 mcg/d d8-14; 480 mcg/d d8,10,12,14; 300 mcg/d d8-14; 300 mcg/d d8,10,12,14; 300 mcg/d d8,12.

Table 3. Quality characteristics of identified RCTs.

Author, year (ref)	Primary outcome	Required sample size	Secondary outcomes	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Losses to follow-up	Ethical Approval
Fully published											
Liu, 2008 (7)	Duration of hospitalizations for toxicity	100 pts based on a SD of length of hospital stay of 4 days. No power or α -value was reported.	Toxicity	NR	NR	No	NR	Yes	No	NR	NR
Papaldo, 2003 (10)	DFS for GF vs. control and LND vs. control	480 pts req'd to detect an improvement in 5-yr DFS from 70% to 80% with 80% power at $\alpha=0.05$.	Toxicity, OS	NR	NR	NR	NR	Yes	No	1.8%	Yes
Citron, 2003 (11)	DFS	1584 pts req'd to detect a 33% difference in hazard for DFS or OS with 90% power; $\alpha=NR$.	OS	NR	NR	NR	Yes	Yes	No	NR	Yes
Holmes, 2002 (12)	Duration of G4 Neut in cycle 1	Non-inferiority study: differences in duration of G4 Neut assessed by confidence intervals using upper 97.5% confidence intervals.	Duration of G4 Neut in cycles 2-4; FN, ANC	Stratified permuted-block ^A	NR	Double-blind	Yes	Yes	No	NR	Yes
Abstracts											
Satheesh, 2009 (13)	NR	NR	Duration of G4 Neut; FN, G4 Neut	NR	NR	NR	NR	NR	NR	NR	NR
Brugger, 2007 (15)	NR	NR	ANC	NR	NR	No	NR	NR	NR	NR	NR
Moebus, 2006 (14)	NR	NR	Neut, anemia, FN	NR	NR	NR	NR	NR	NR	NR	NR

Notes: abs=abstract; ANC=absolute neutrophil count; DFS=disease-free survival; FN=febrile neutropenia; G=grade; GF=growth factor; ITT=intention-to-treat; LND=lonidamine; Neut=neutropenia; NR=not reported; OS=overall survival; pts=patients; ref=reference; req'd=required; w=week(s).

^AStratified by center and previous chemotherapy.

Table 4. Randomized trials of G-CSF in breast cancer.

Study (ref)	Breast stage	cancer	Chemotherapy	G-CSF use by arm	N	Dose intensity	Grade Neutropenia	3-4	Febrile Neutropenia	Grade Infection	3-4
Full Publications											
Liu, 2008 (7)	Early		dd AC → T	F 5 mcg/kg vs. F 10 mcg/kg	NR	NR	99%; p=ns		NR	NR	
Papaldo, 2003, 2005, 2006 (8-10)	Early		EC	none	124	NR	81.6%		NR	NR	
			vs. EC + LND	none	125						
			vs. EC	primary F	129						
			vs. EC + LND	primary F	128						
Citron, 2003 (11)	Early		AT → C	none	484	NR	Gran: 24%		NR		3%
			vs. A → T → C	primary F	493						
			vs. AC → T	none	501						
			vs. AC → T	primary F	495						
Holmes, 2002 (12)	Early		AD	primary PEG	147	NR	NR		9%	NR	
				vs. primary F	149						
Abstracts											
Satheesh, 2009 abs (13)	Early	- pts receiving adjuvant or neoadjuvant chemotherapy?	ACD	F vs. PEG	43	NR	NR		18.6%	NR	
					28						
Brugger, 2007 abs (15)	Early		FEC100	primary PEG vs. secondary PEG	31 29	NR	Abstract has a chart of mean ANC values		NR		NR
Moebus, 2006 abs (14)	Early		E → T → C EC → T	primary F none	1284	NR	NR		7% 2%; p<0.0001		NR

Notes: A=doxorubicin; Adv=advanced; C=cyclophosphamide; D=docetaxel; dd=dose dense; E=epirubicin; F=filgrastim; FEC=fluorouracil, epirubicin, cyclophosphamide; FN=febrile neutropenia; Gran=granulocytopenia; IBCSG=International Breast Cancer Study Group; L=lenograstim; LND=lonidamine; Neut=neutropenia; PEG=pegfilgrastim; T=paclitaxel (Taxol®); →=followed by (absence of arrow between chemotherapy agents indicates concurrent administration).

^aProtocol was changed three times with respect to the agent used for primary prophylaxis.

^bVersus both ciprofloxacin alone and daily G-CSF.

^cVersus TAC with ciprofloxacin alone prophylaxis.

Table 5. Rates of FN, neutropenia, and infection for chemotherapy regimens commonly used in Ontario.

Chemotherapy regimen	Study (ref)	Prophylactic growth factor	Prophylactic antibiotics	N	Febrile neutropenia (%)	Grade 3 or 4 neutropenia (%)	Grade 3 or 4 infection (%)
First Generation Regimens							
CMF x 6	Fisher, 2001 (21)	NR	NR	499	NR	Gran G3: 13 G4: 4	G3: 3 G4: 0
	Levine, 1998 (22) Levine, 2002 (23) abs	NR	No	359	1.1	NR	NR
	Hutchins, 2005(24)	No	NR	673	NR	Gran G3: 25 G4: 37	Leuk G3: 49 G4: 7
AC x 4	Fisher, 1990 (25)	NR	NR	1492	NR	NR	Systemic: 0.9 Shock, sepsis: 1.5
	Fisher, 2001 (21)	NR	NR	495	NR	Gran G3: 6 G4: 1	G3: 3 G4: 1
	Jones, 2006 (26)	No	No	510	NR	55	8
	Nabholtz, 2003 (27)	No	No	210	10	88	2
FEC50 x 6	Fumoleau, 2003 (28)	No	No	207	NR	13.3	NR
Second Generation Regimens							
FEC100 x 6	FASG, 2001 (29)	No	No	268	2.6	25.2	3.4
	Coombes, 1996 (30)	NR	NR	364	NR	NR	G1-4: 17
FAC x 6	Martin, 2005 (31)	No	Secondary	736	4.4	49.3	2.2
	Martin, 2003 (32)	NR	NR	480	NR	3	NR
CEF x 6	Levine, 1998 (22)	NR	Primary	351	8.5	Gran G3: 8 G4: 89.7	NR
	Levine, 2002 (23) abs						
CAF x 6	Hutchins, 1998 (33) abs	No	NR	652	NR	Gran G3: 21 G4: 53	Leuk G3: 52 G4: 21
	Hutchins, 2005 (24)						
E x 4 → CMF x 6/8	Poole, 2006 (34)	NR	NR	1157	NR	1.5	6.3
AC x 4 → T x 4	Mamounas, 2005 (35) Mamounas, 2003 (36) abs	Secondary-filgrastim	Secondary	1531	3	Gran: 3	2
TC	Jones, 2006 (26)	No	No	506	NR	61	7
Third Generation Regimens							
TAC	Nabholtz, 2001 (37) abs	NR	NR	238	30	94	3
	Martin, 2005 (31)	Secondary-filgrastim	Primary	744	28.8	65.5	3.9
	Nabholtz, 2002 (38) abs						
	Martin, 2005 (39) abs	Primary	NR	416	24.6	NR	NR
FEC-D	Roche, 2003 (40) abs	Secondary	NR	1000	2.5	7.0	NR
dose dense AC-T	Citron, 2003 (11)	Primary-filgrastim	NR	501	NR	Gran G3: 0 G4: 43	G3: 5 G4: 0

Notes: abs=abstract; FASG=French Adjuvant Study Group; FN=febrile neutropenia; Gran=granulocytopenia; Leuk=leucopenia; NR=not reported; ref=reference; T=paclitaxel (Taxol).

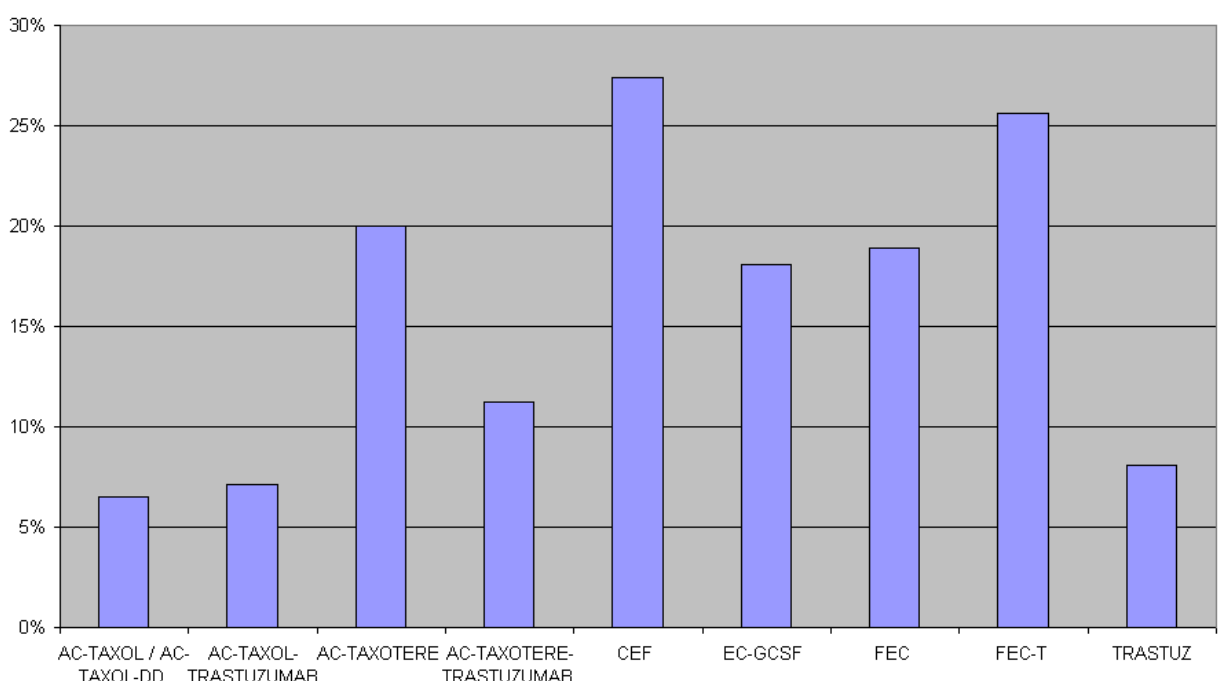
DISCUSSION

FN is a serious and potentially life-threatening complication of chemotherapy, dependent not only on the regimen used, but also on a variety of patient related factors. The incidence and severity of neutropenia, as well as the rate of complications due to neutropenia can be significantly reduced with the use of CSFs. Unfortunately a reliable model to predict who will develop FN is lacking. While there is a considerable body of data supporting the use of CSFs as primary and secondary prophylaxis for patients with breast cancer receiving myelotoxic chemotherapy, there remain a number of unanswered questions that are not likely to be addressed in future clinical trials.

Clinical trials addressing all of the possible regimens and scenarios in clinical practice are lacking. In addition, elderly patients and patients with comorbidities, routinely excluded from clinical trials, are increasingly prevalent in clinical practice. Furthermore, patients in clinical trials are highly selected and receive very stringent supportive care, resulting in a care package which is often not generalizable to the general population in routine clinical practice. There is also heterogeneity across the reported clinical trials, with heterogeneous patient populations, variable definitions of FN, variable use of prophylactic antibiotics, and other poorly defined variables that likely contribute to some degree of underreporting of event rates of interest.

The Breast DSG is aware of a considerable body of unpublished data from current clinical practice in Ontario demonstrating significantly higher toxicity rates for certain regimens than that reported in the literature. In particular, several regional cancer centres in Ontario have reported FN rates for fluorouracil, epirubicin, and cyclophosphamide (FEC/CEF)-docetaxel (FEC-D) in excess of 24%: 29% Cancer Centre of Southeastern Ontario (CCSEO) (personal communication, Y. Madarnas, 2009 Sep 29), 33% Sudbury (personal communication, A. Robinson, 2009 Sep 29), 29% Ottawa Regional Cancer Centre (ORCC) (personal communication, S. Dent, 2009 Sep 29), 24% Toronto-Sunnybrook Regional Cancer Centre (TSRCC) (personal communication, M. Trudeau, 2009 Sep 29); and in excess of 30% for taxotere (TC): London Regional Cancer Centre (LRCC) reported 33% overall, 40% for age >65, 100% for age >65 with comorbidity (personal communication, T. Vandenberg, 2009 Sep 29); Credit Valley Hospital (CVH) reported 50% overall (personal communication, R. Myers, 2009 Sep 30). In support of these reported rates, the centrally collected Cancer System Quality Index (CSQI) data demonstrate a $\geq 20\%$ incidence of emergency room visits and/or admissions for FN for commonly used second- and third-generation regimens: actinomycin-D (AC-D), FEC/CEF, or FEC-D (Figure 2).

Figure 2. Rates of patients in emergency room or admitted to hospital for neutropenia/fever/infection by regimen for patients treated in Ontario 2006/07 to 2007/08. Source: NDFP and NACRS.



As is evident from an increasing body of data, FN rates in routine, contemporary, and local clinical practice are greater than those reported in clinical trials. Given the unquestionable efficacy of CSFs in this context, methods to assist clinicians in optimal patient selection are needed.

CONCLUSIONS

Until a reliable, prospectively validated predictive model for neutropenic events is developed, a risk-adapted strategy that takes into consideration patient and treatment-related factors is the most comprehensive way to guide prophylactic CSF use in routine clinical practice.

CONFLICT OF INTEREST

The authors of this special advice report were asked to disclose potential conflicts of interest related to the topic of this special advice report and reported no conflicts of interest.

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Appendix 1. Literature search strategies.

Ovid MEDLINE

1. exp granulocyte colony stimulating factor, recombinant/
2. neupogen.tw.
3. filgrastim.tw.
4. pegfilgrastim.tw.
5. neulasta.tw.
6. granulocyte colony stimulating factor.tw.
7. g-csf.tw.
8. or/1-7
9. exp breast neoplasms/
10. breast cancer:.tw.
11. 9 or 10
12. 8 and 11
13. meta-analysis as topic/
14. meta analysis.pt.
15. meta analy\$.tw.
16. metaanaly\$.tw.
17. (systematic adj (review\$1 or overview\$1)).tw.
18. or/13-17
19. cochrane.ab.
20. embase.ab.
21. (cinahl or cinhal).ab.
22. science citation index.ab.
23. bids.ab.
24. cancerlit.ab.
25. or/19-24
26. reference list\$.ab.
27. bibliograph\$.ab.
28. hand-search\$.ab.
29. relevant journals.ab.
30. manual search\$.ab.
31. or/26-30
32. selection criteria.ab.
33. data extraction.ab.
34. 32 or 33
35. review.pt.
36. review literature as topic/
37. 35 or 36
38. 34 and 37
39. comment.pt.
40. letter.pt.
41. editorial.pt.
42. or/39-41
43. 18 or 25 or 31 or 38
44. 43 not 42
45. randomized controlled trials as topic/
46. randomized controlled trial.pt.
47. random allocation/
48. double blind method/

49. single blind method/
50. Clinical Trials, phase III as Topic/
51. clinical trial, phase III.pt.
52. clinical trials, phase II as topic/
53. clinical trial, phase II.pt.
54. (clinic\$ adj trial\$1).tw.
55. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
56. placebos/
57. placebo\$.tw.
58. (allocated adj2 random\$).tw.
59. random allocation.tw.
60. randomly allocated.tw.
61. or/45-60
62. case report.tw.
63. letter.pt.
64. historical article.pt.
65. or/62-64
66. 61 not 65
67. 44 or 66
68. practice guideline/
69. practice guideline\$.mp.
70. 68 or 69
71. 67 or 70
72. 12 and 71
73. limit 72 to (English language and humans)
74. (199: or 20:) .ed.
75. 73 and 74