



CED-CCO Special Advice Report #14-1

The Prophylactic Use of Filgrastim in Patients with Hematological Malignancies

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Report Date: September 23, 2009

SUMMARY

The full CED-CCO Special Advice Report #14-1 consists of a Summary and a Full Report and is available on the CCO website (<http://www.cancercare.on.ca>)
PEBC CED-CCO page at:
<http://www.cancercare.on.ca/toolbox/qualityguidelines/other-reports/evaldrug-rep/>

QUESTION

Does the use of filgrastim as a primary or secondary prophylaxis in patients with hematological malignancies receiving myelosuppressive chemotherapy improve clinical outcomes? Outcomes of interest include the incidence of febrile neutropenia (FN), death from infection, and maintenance of dose intensity.

TARGET POPULATION

This evidence-based series applies to adult patients receiving myelosuppressive chemotherapy for potentially curative hematological malignancies including non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), acute lymphoblastic leukemia (ALL), and acute myeloid leukemia (AML). We also included chronic lymphocytic leukemia (CLL), hairy cell leukemia and multiple myeloma.

RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report:

- **Filgrastim is recommended as a secondary prophylaxis following an episode of neutropenic fever or neutropenia causing a treatment delay in those patients with potentially curative non-myeloid hematological malignancies who are receiving aggressive chemotherapy.**

Key Evidence

Practice guidelines (1-3) developed by international groups support the use of filgrastim in patients with potentially curative hematological malignancies to maintain dose intensity.

- **Filgrastim is recommended as a primary prophylaxis in patients with potentially curative non-myeloid hematological malignancies where the risk of febrile neutropenia is high (e.g., greater than 20%). Such patients could include those older than 65 years, those with a poor performance status (Eastern Cooperative Oncology Group [ECOG] \geq 2), or those with an infection or neutropenia at the start of treatment.**

Key Evidence

Practice guidelines (1-3) developed by international groups support the use of filgrastim as a primary prophylaxis when the FN rate is at least 20%. Systematic reviews (4) have found that the incidence of FN is effectively reduced with the use of filgrastim as the primary prophylaxis. Based on the opinion of the authors and the Hematology Disease Site Group (DSG) Practice Guideline #6-7 (5), we recommend the use of filgrastim in older lymphoma patients being treated for curative intent if they have a ECOG performance status of at least 2 or if they have an infection or neutropenia at the start of chemotherapy.

- **There is insufficient evidence to recommend the routine use of filgrastim as either a primary or secondary prophylaxis in patients with non-curative hematological malignancies such as multiple myeloma, CLL or indolent NHL. However, the opinion of the authors was that selected patients with recurrent infections who are experiencing some benefit from their chemotherapy may benefit from granulocyte colony-stimulating factor (GCSF) to reduce infectious morbidity.**
- **There is insufficient evidence to recommend the routine use of filgrastim in patients with either AML or ALL. Although some studies have shown a reduction in FN and infectious morbidity with GCSF, there has not been any measured decrease in mortality. A detailed analysis of the acute leukemia literature regarding other outcomes such as the length of hospitalization or cost effectiveness was beyond the scope of this review. The opinion of the authors was that certain patients with leukemia being treated curatively may benefit from GCSF by a reduction in infectious morbidity.**

QUALIFYING STATEMENTS

- **Examples of potentially curative hematological malignancies include aggressive histology NHL, HL, Burkitt lymphoma, and lymphoblastic lymphoma. Such malignancies would be considered potentially curative either at presentation or first relapse. Although ALL would be considered also a potentially curative lymphoid malignancy, it has typically been studied as a leukemia and has been considered as such in this report.**

- The dose of GCSF routinely used is 5 mcg/kg/day subcutaneously, starting at least 24 hrs after chemotherapy and continuing until neutrophil recovery (at least 1.0×10^9 /L for two consecutive days).

RELATED PROGRAM IN EVIDENCE-BASED CARE GUIDELINES

Evidence-based Series

- EBS #6-14: *Treatment of Acute Myeloid Leukemia in Older Patients.*
Available at:
<http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34529>.

Practice Guideline Report

- PG #6-7: *The Use of Chemotherapy and Growth Factors in Older Patients with Newly Diagnosed, Advanced-Stage, Aggressive Histology Non-Hodgkin's Lymphoma.*
Available at:
<http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=14150>.

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Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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FULL REPORT

QUESTION

Does the use of filgrastim as a primary or secondary prophylaxis in patients with hematological malignancies receiving myelosuppressive chemotherapy improve clinical outcomes? Outcomes of interest include the incidence of febrile neutropenia (FN), death from infection, and maintenance of dose intensity.

INTRODUCTION

Common side effects of myelosuppressive chemotherapy include neutropenia and FN. An infection following chemotherapy may be associated with an increased in-hospital resource utilization and infection-related morbidity and mortality, as well as chemotherapy delay and/or dose reduction. In hematological malignancies considered curable, there is a risk that a decrease in dose intensity may impair the antitumour response and possibly compromise response or survival. The risk of FN is related to several factors, including the type of chemotherapy, patient age, comorbidity, and other factors that have been previously reviewed. It is acknowledged that the risk of FN may be higher in practice than that seen in clinical trials, given the selection of more fit patients for trials, in contrast to those seen routinely in clinic.

Filgrastim (granulocyte colony stimulating factor or GCSF) is an effective agent in decreasing the risk of neutropenia and FN. It is administered by daily injection until neutrophil recovery, is well tolerated, and, generally speaking, is free of significant long term effects. A long-acting formulation, pegfilgrastim (Neulasta) can be given once per cycle. Granulocyte-macrophage colony stimulating factor (GM-CSF) has also been studied, but as it is not available in Canada, it is not routinely used.

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 potentially curative non-myeloid hematological malignancies, 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) (2004 to 2009) and the American Society of Hematology 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.
2. Patients who received myelosuppressive chemotherapy for a hematological malignancy.
3. Systematic reviews, meta-analyses, or clinical practice guidelines of the use of filgrastim in patients with non-myeloid hematological malignancies.
4. 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:

5. Letters, comments, books, notes, or editorial publications.
6. Articles published in a language other than English, because of the lack of financial resources for translation.

The eligibility criteria were edited after the literature search and yielded several fully published, mature randomized controlled trials (RCTs) as well as several systematic reviews and meta-analyses. Given the availability of this mature data, studies published in abstract form only were excluded. These studies will instead be included as ongoing studies that will be added to the report when they have been fully published.

Synthesizing the Evidence

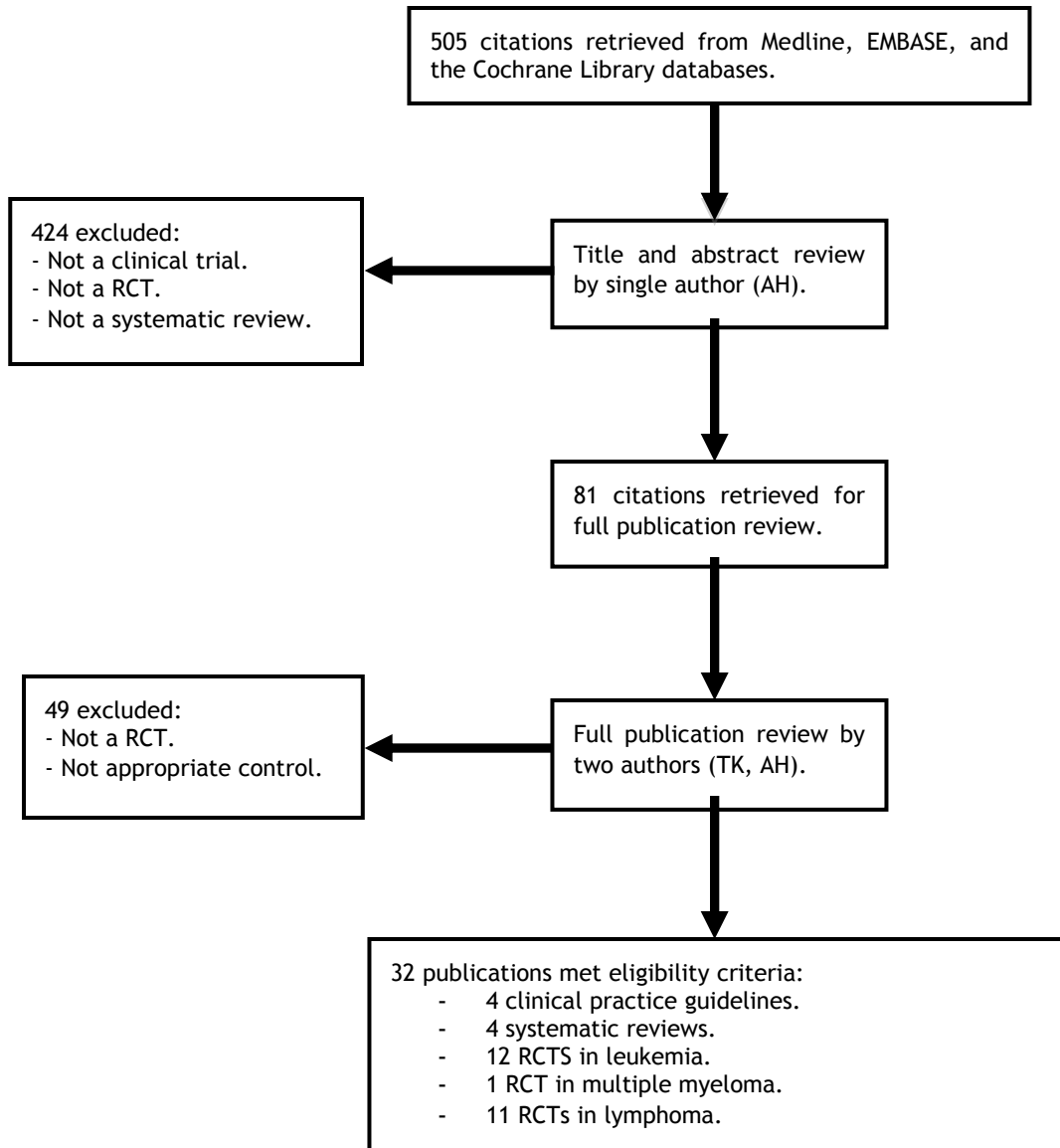
A meta-analysis of trial results will be conducted if sufficient data are available. Outcomes to be considered for meta-analysis include the incidence of FN and death from infection.

RESULTS

Literature Search Results

A total of 505 citations of studies were identified from the MEDLINE, EMBASE, and Cochrane Library databases. From those citations, a total of 32 full publications met the eligibility criteria (Figure 1). Four clinical practice guidelines (1-4), four systematic reviews (5-8), and 24 RCTs were identified. The authors were also aware of one additional relevant practice guideline that was not captured in the literature search. That guideline, produced by the Hematology Disease Site Group (DSG) of the CCO PEBC, was also included (9,10). The Results section has been divided into four sections: clinical practice guidelines, lymphoma, leukemia, and multiple myeloma.

Figure 1. Selection of studies investigating the prophylactic use of filgrastim in patients with non-myeloid hematological malignancies receiving myelosuppressive chemotherapy from the search results of MEDLINE, EMBASE, and the Cochrane Library databases.



Clinical Practice Guidelines

Five clinical practice guidelines were identified that provided advice on the prophylactic use of filgrastim in patients with hematological malignancies.

In 2006, the ASCO guideline on the use of GCSF in cancer patients was updated (2). The conclusion was that the use of GCSF is justified to reduce the incidence of FN when the incidence is at least 20% and there is no other equally effective regimen available that does not require GCSF. Previous versions (11) of this guideline quoted a 40% FN rate as being the deciding factor on offering GCSF primary prophylaxis, based on a pharmacoeconomic analysis of a trial involving lung cancer patients (12). Since then, the committee has adjusted the number downwards, in favour of the clinical benefits of avoiding FN rather than strictly based on cost effectiveness. Primary prophylaxis with GCSF was recommended for the prevention of FN in patients who are at a higher risk, based on age, comorbidity, and disease characteristics in addition to the myelotoxicity of the chemotherapy regimen. GCSF was recommended in those patients in whom a dose-dense chemotherapy regimen has been shown to offer improvements in disease control or survival. Specifically for lymphoma, the guideline suggested the primary use of GCSF in patients with aggressive histology (potentially curative) lymphoma who were at least 65 years of age and who were being treated with aggressive (i.e., cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone, and rituximab [CHOP/R] or more intensive) chemotherapy.

The European Organization for Research and Treatment of Cancer (EORTC) guideline (1) recommendations are very similar to the ASCO guideline, particularly around the use of GCSF in older patients (at least 65 years) and in those with a FN risk of at least 20%.

Both the ASCO and EORTC guidelines suggest that in situations of treatment for non-curative disease, GCSF should be used only where the evidence suggests that the maintenance of dose intensity provides a clinical benefit.

The EORTC in the Elderly Task Force guideline (3) also recommends primary prophylaxis with GCSF in those elderly treated with potentially curative chemotherapy.

In a previous Hematology DSG practice guideline, PG #6-7 (9,10), regarding the optimal therapy for older patients with aggressive histology lymphoma, the DSG determined that patients at least 65 years or older with aggressive histology lymphoma who were being treated with curative intent should receive GCSF if they presented with greater risk factors for FN. These patients are best identified as those with a poor performance status (ECOG 2 or greater), neutropenia prior to therapy, or an ongoing infection. There were insufficient data to recommend the primary use of GCSF for patients whose sole risk factor is bone marrow involvement with lymphoma. The use of GCSF as a secondary prophylaxis is recommended for patients who have previously experienced an episode of neutropenic fever or a treatment delay resulting from persisting neutropenia.

In another Hematology DSG guideline, PG #6-14 (4) regarding the treatment of elderly patients (older than 55 years) with AML, we determined that the routine use of myeloid growth factors (GCSF or GMCSF) as an adjunct to intensive chemotherapy in such patients is not recommended. This finding was based on an aggregate data meta-analysis pooling results of the published studies of GMCSF or GCSF that showed no difference between groups who did or did not receive growth factors with respect to complete response rate, mortality or disease recurrence, overall survival, infection rates, or infectious death. Toxicity data were inconsistently reported and therefore not pooled.

Systematic Reviews

Four publications of systematic reviews were identified (5-8). Two systematic reviews investigated the prophylactic use of filgrastim in patients with cancer (7,8). The remaining two reports were both authored by Bohlius et al (5,6). Because the 2003 publication (6) was an earlier version of the 2008 Cochrane review (5), only the 2008 Cochrane review will be discussed further. Sung et al (8) analyzed the trials of lymphoma and solid tumours together and did not provide separate subgroup data for either type of cancer. Therefore, that systematic review is not discussed further, given the availability of two systematic reviews with meta-analyses that did provide separate data on trials of lymphoma.

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool (13) was used to assess the methodological quality of the systematic review, because the tool has been demonstrated to be both reliable and valid (14,15). The AMSTAR tool consists of 11 items assessing the quality of systematic reviews. Table 1 contains the ratings for each item on the tool for each of the systematic reviews.

Table 1. AMSTAR ratings of included systematic reviews of GCSF in malignant lymphoma.

Item	Bohlius, 2008 (5)	Kuderer, 2007 (7)
A priori design provided?	Y	Y
Duplicate study selection and data extraction?	Y	CA
Comprehensive literature search performed?	Y	Y
Status of publication used as an inclusion criteria?	Y	CA
List of included/excluded studies provided?	Y	N
Characteristics of included studies provided?	Y	Y
Scientific quality of included studies assessed and reported?	Y	N
Scientific quality of included studies used appropriately to form conclusions?	Y	CA
Study findings combined appropriately?	Y	Y
Assessment of publication bias?	Y	Y
Declaration of conflict of interest?	Y	Y

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

Bohlius et al (5) investigated the use of filgrastim as a primary prophylaxis in patients with lymphoma. The systematic review with meta-analysis was high quality and scored 11 out of 11 using the AMSTAR instrument (Table 1). The authors employed a rigorous literature search strategy, and the trial selection and data collection were performed in duplicate. The authors identified 13 RCTs with a total of 2607 patients investigating the use of GCSF or GMCSF in patients with any type of lymphoma. The primary outcomes were overall survival and freedom from treatment failure. Secondary outcomes included, but were not limited to, the risk and duration of neutropenia, risk and duration of FN, infection, and received dose intensity of chemotherapy. The authors performed an individual-patient-data meta-analysis for appropriate outcomes; where individual patient data could not be obtained from the trial authors, summary statistics were obtained using the methods described by Parmar et al (16). Table 2 contains the results of the meta-analysis, with significant differences evident between the prophylactic use of GCSF or GMCSF compared to control for neutropenia, FN, and infection. Compared with no prophylaxis, both GCSF and GMCSF did not improve overall survival (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.87 to 1.09) or freedom from treatment failure (FFTF) (HR, 1.11; 95% CI, 0.91 to 1.35). Prophylaxis significantly reduced the relative risk (RR) for severe neutropenia (RR, 0.67; 95% CI, 0.60 to 0.73), FN (RR, 0.74; 95% CI, 0.62 to 0.89), and infection (RR, 0.74; 95% CI, 0.64 to 0.85). There was no evidence that either GCSF or GMCSF reduced the number of patients requiring intravenous antibiotics (four studies only, RR, 0.82; 95% CI, 0.57 to 1.18); lowered infection-related mortality (RR, 0.93; 95% CI, 0.51 to 1.71); or improved complete tumour response (RR, 1.03; 95% CI, 0.95 to 1.10). One study evaluated quality of life parameters and found no differences between the

treatment groups. Statistical heterogeneity was significant for neutropenia ($p=0.04$, $I^2=53\%$). The authors investigated statistical heterogeneity by use of preplanned sensitivity analyses that revealed significant between-group heterogeneity for prophylactic antibiotic treatment during chemotherapy ($p=0.0022$). The authors reported a stronger treatment effect in trials with antibiotic prophylaxis (RR, 0.43; 95% CI, 0.31 to 0.60; two trials) compared to trials without antibiotic prophylaxis (RR, 0.72; 95% CI 0.65 to 0.79; five trials).

Table 2. Results of select outcomes from identified meta-analyses that reported separate results for studies of colony-stimulating factors in patients with malignant lymphoma.

Study (ref)	Number of RCTs	Neutropenia			Febrile neutropenia			Infection		
		RR (95% CI)	Heterogeneity		RR (95% CI)	Heterogeneity		RR (95% CI)	Heterogeneity	
			p-value	I^2		p-value	I^2		p-value	I^2
Bohlius, 2008 (5)	13	0.67 (0.60-0.73)	0.04	53%	0.74 (0.62-0.89)	0.37	7%	0.74 (0.64-0.85)	0.28	17%
Kuderer, 2007 (7)	6	NR	NR	NR	0.71 (0.59-0.85)	NR	NR	NR	NR	NR

Notes: CI=confidence interval; NR=not reported; RCT=randomized controlled trial; ref=reference; RR=relative risk.

Kuderer et al (7) conducted a systematic review and meta-analysis of GCSF as the primary prophylaxis in adult patients with cancer. The systematic review scored a six on the AMSTAR instrument; however, three of the instrument items could not be determined as the report did provide the necessary information (Table 1). The authors conducted a thorough search and had a priori eligibility criteria. Two reviewers extracted data independently from the eligible RCTs. The primary outcome was FN. Secondary outcomes included infection-related mortality, and relative dose intensity. The authors decided a priori to conduct subgroup analyses including by cancer type (i.e., lymphoma versus [vs.] solid tumours). The authors reported a significant lower risk of febrile neutropenia for GCSF compared to control (RR, 0.71; 95% CI, 0.59 to 0.85). No other significant differences for trials of lymphoma were reported. In both solid tumours and lymphoma, the review found improvements not only in the rate of neutropenia and FN but also in early mortality.

Randomized Trials

Given the availability of two good quality systematic reviews that investigated the use of prophylactic GCSF in lymphoma, the literature search for randomized trials focused on the time period since the date of the last search in the systematic reviews reported by Kuderer et al (7) and Bohlius et al (5). No RCTs, however, have been published since April 2008 that met our eligibility criteria.

Leukemia

Systematic Reviews

One systematic review, reported by Sung et al (8), was identified that included trials of GCSF in patients with leukemia. That systematic review scored nine out of 11 using the AMSTAR instrument. The authors did not provide a list of the excluded studies; however, a list of included studies was provided. The authors did not assess publication bias. The systematic review and meta-analysis was high quality. The authors included only RCTs of either primary or secondary prophylactic GCSF or GMCSF in cancer patients. The eligibility criteria were similar to our own, with the following exceptions: Sung et al included trials in any cancer, trials of GMCSF, and trials with conditioning for stem cell transplantation. The primary outcome was short-term all-cause mortality. Secondary outcomes included, but were not limited to, infections and FN. The authors performed a summary-statistic meta-analysis of the trial results and planned subgroup analyses, including by cancer type (i.e., leukemia, solid tumour or lymphoma, and stem cell transplantation). The authors identified 31 trials of GCSF in adult patients with leukemia and 12 trials of GMCSF in leukemia. The authors reported a significantly lower risk of documented infections (RR, 0.90; 95% CI, 0.82 to 0.98) and FN (RR, 0.81; 95% CI, 0.66 to 0.99) for patients receiving GCSF or GMCSF compared to control.

Table 3. AMSTAR ratings of included systematic reviews of GCSF in leukemia.

Item	Sung, 2007 (8)
A priori design provided?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search performed?	Y
Status of publication used as an inclusion criteria?	Y
List of included/excluded studies provided?	N
Characteristics of included studies provided?	Y
Scientific quality of included studies assessed and reported?	Y
Scientific quality of included studies used appropriately to form conclusions?	Y
Study findings combined appropriately?	Y
Assessment of publication bias?	N
Declaration of conflict of interest?	Y

Abbreviations: N=no, Y=yes.

Of note, the CCO PEBC Hematology DSG Evidence-based Series (EBS) guideline #6-14 *Treatment of Acute Myeloid Leukemia in Older Patients*, included a question on the use of GCSF and GMCSF in older patients with AML (4). The authors identified 10 RCTs and conducted a meta-analysis of infection rates for CSFs versus control. No significant differences in the relative risk of infection or infectious death were reported.

Randomized Trials

Given the availability of one good systematic review (8) as well as the systematic review from the Hematology DSG #6-14 guideline (4), it was decided that RCTs published after the date of the search in Sung et al (8) would be included.

One RCT reported by Sierra et al (17) was identified that was published after April 2007. The authors randomized 84 newly diagnosed AML patients to either pegfilgrastim (single 6 mg dose 24 hours after completing chemotherapy) or to filgrastim (5 mcg daily beginning 24 hours after chemotherapy until the post-nadir absolute neutrophil count was $\geq 1.0 \times 10^9/L$ for three consecutive days or $\geq 10 \times 10^9/L$ for one day). All patients received a matched placebo and standard 3+7 idarubicin (12 mg/m² days 1-3) and cytarabine (100 mg/m² twice daily days 1-7) induction chemotherapy. The primary outcome was time to recovery

from severe neutropenia. The secondary outcomes included absolute neutrophil count, adverse events, and fever. An a priori sample size calculation determined that 120 patients would be required to find a difference of 2-3 days in absolute neutrophil count recovery time between the two groups, with a power of 70%. The two treatment groups were similar in baseline characteristics. No significant difference in the rate of FN was reported for pegfilgrastim (81% of 42 patients) compared to filgrastim (88% of 41 patients).

Multiple Myeloma
Systematic Reviews

No systematic reviews of GCSF in patients with multiple myeloma were identified.

Randomized Trials

One trial randomized 139 patients with multiple myeloma to secondary prophylaxis with lenograstim or to placebo (18). All patients received two cycles of MCNU-VMP (ranimustine 50 mg/m² day 1, vindesine 2 mg/m² days 1 and 22, melphalan 8 mg/m², and prednisolone 40 mg/m² days 1-4 and 22-25). The authors did not report a required sample size. The two treatment groups were well balanced with respect to baseline characteristics. The authors reported that the rate of FN was significantly lower in the lenograstim group (9.2%) compared to the placebo group (30.4%; p=0.003 by Chi-squared test). The authors also reported that the median duration of neutropenia was significantly shorter for lenograstim (two days) compared to placebo (nine days, p<0.001 by Wilcoxon test).

DISCUSSION

Although studies have not demonstrated any impact on overall survival, GCSF is effective in terms of reducing the incidence of neutropenia and FN. FN can be associated with increased in-hospital resource utilization, infectious morbidity, mortality (19) and delays or dose reductions in chemotherapy. A decrease in chemotherapy dose intensity may influence the effectiveness of treatment that may impact on tumour control and mortality in patients with potentially curable lymphomas. Although the available studies have not demonstrated any obvious change in overall mortality, none of them appeared to be powered for that type of endpoint, and some studies censored patients who had multiple neutropenic events. Regarding the importance of dose intensity in potentially curable lymphoma, some of the studies in the Hematology DSG PG #6-7 have indicated a small but statistically significant improvement in received dose intensity for those patients receiving GCSF (9,10). Other non-randomized studies have suggested that the maintenance of dose intensity is important for outcome in patients with potentially curative aggressive histology lymphoma (20-23). Furthermore, examining dose intensity in a different manner, trials designed to compare less intensive chemotherapy to standard CHOP-like chemotherapy have consistently shown inferior outcomes with less intensive chemotherapy. These trials are outlined in the Hematology DSG PG #6-7 (9,10). There are no studies testing standard dose chemotherapy with less than standard dose chemotherapy in the potentially curative setting. Secondary prophylaxis with GCSF has been standard practice in potentially curative lymphomas.

Prevention of febrile neutropenia is a valued outcome. The treatment of FN is associated with in-hospital resource utilization. Costs and morbidity as outlined by American (US) studies have been reported to be significant (19). Although similar studies have not been published in Canada, there is an unseen cost to having inpatient beds occupied by patients whose admission may have been prevented with the use of GCSF. In addition, the reported rates of FN in the randomized studies may underestimate the true rate of FN, as patients seen in clinic may not be as fit as those participating in clinical trials. In the setting of potentially curative lymphoma, primary prophylaxis with GCSF seems reasonable if the FN rate is at least 20%, based on international guidelines but also on the risk of infectious morbidity in higher risk lymphoma patients. In a previous practice guideline by the Hematology DSG, PG#6-7 (9,10), we defined higher risk patients as those with a poor ECOG performance status (≥ 2) or those with neutropenia or infection at the start of chemotherapy. This definition was based largely on consensus of the DSG and a non-randomized study (24) indicating a high infectious morbidity and toxic death rates in such patients.

Regarding the use of GCSF in acute leukemia, based on a meta-analysis, there appears to be a reduction in infections and febrile neutropenia but no reported benefit in survival. The meta-analysis included patients of all ages. Although acute leukemias may be potentially curative malignancies, the decrease in the FN rate may not be associated with the prevention of hospital admission or maintenance of dose intensity. The CCO PEBC Hematology DSG produced an EBS report in December 2008, #6-14 *Treatment of Acute Myeloid Leukemia in Older Patients* (4), that included a meta-analysis of trials investigating the use of GCSF in older patients with AML. The DSG could not find any differences in infections in older patients with AML. We realize, however, that there may be selected patients with acute leukemia who might benefit from a reduction in infectious morbidity, particularly during cycles of consolidation chemotherapy where they may be followed as outpatients.

Regarding non-curative hematological malignancies such as indolent lymphoma, CLL or multiple myeloma, there was a recognized lack of data regarding either primary or secondary prophylaxis. Given the lack of any survival benefits with GCSF in the curative setting, it seems unlikely that there could be any potential survival benefit when using GCSF in the non-curative setting. However, the DSG recognizes that neutropenia or FN may hamper treatment

efforts in the non-curative setting, and, although GCSF might be an option, dose reductions may also be a reasonable option. The use of GCSF in patients with multiple myeloma treated with newer agents such as lenalidomide may also be reasonable for the same reasons but this has not been evaluated prospectively with respect to longer term outcomes compared with dose reduction. Other potential benefits of GCSF in the non-curative setting may involve the reduction in infections or hospitalizations, but these have not been evaluated in any trials.

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.

ACKNOWLEDGEMENTS

The PEBC would like to thank Dr. Tom Kouroukis and Mr. Adam Haynes for taking the lead in drafting this special advice report.

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Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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Appendix 1. Literature search strategies.

Ovid MEDLINE

1. exp granulocyte colony stimulating factor, recombinant/s
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 lymphoma/
10. lymphoma:.tw.
11. Hodgkin: disease:.tw.
12. exp multiple myeloma/
13. multiple myeloma:.tw.
14. exp leukemia, hairy cell/
15. hairy cell leukemia:.tw.
16. exp leukemia, myeloid, acute/
17. acute myeloid leukemia:.tw.
18. AML.tw.
19. exp leukemia, lymphoid/
20. acute lymphocytic leukemia:.tw.
21. acute lymphoblastic leukemia:.tw.
22. chronic lymphocytic leukemia:.tw.
23. chronic lymphoblastic leukemia:.tw.
24. or/9-23
25. 8 and 24
26. meta-analysis as topic/
27. meta analysis.pt.
28. meta analy\$.tw.
29. metaanaly\$.tw.
30. (systematic adj (review\$1 or overview\$1)).tw.
31. or/26-30
32. cochrane.ab.
33. embase.ab.
34. (cinahl or cinhal).ab.
35. science citation index.ab.
36. bids.ab.
37. cancerlit.ab.
38. or/32-37
39. reference list\$.ab.
40. bibliograph\$.ab.
41. hand-search\$.ab.
42. relevant journals.ab.
43. manual search\$.ab.
44. or/39-43
45. selection criteria.ab.
46. data extraction.ab.
47. 45 or 46
48. review.pt.

49. review literature as topic/
50. 48 or 49
51. 47 and 50
52. comment.pt.
53. letter.pt.
54. editorial.pt.
55. or/52-54
56. 31 or 38 or 44 or 51
57. 56 not 55
58. randomized controlled trials as topic/
59. randomized controlled trial.pt.
60. random allocation/
61. double blind method/
62. single blind method/
63. Clinical Trials, phase III as Topic/
64. clinical trial, phase III.pt.
65. clinical trials, phase II as topic/
66. clinical trial, phase II.pt.
67. (clinic\$ adj trial\$1).tw.
68. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
69. placebos/
70. placebo\$.tw.
71. (allocated adj2 random\$).tw.
72. random allocation.tw.
73. randomly allocated.tw.
74. or/58-73
75. case report.tw.
76. letter.pt.
77. historical article.pt.
78. or/75-77
79. 74 not 78
80. 57 or 79
81. practice guideline/
82. practice guideline\$.mp.
83. 81 or 82
84. 80 or 83
85. 25 and 84
86. limit 85 to (English language and humans)