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The Role of Colony-Stimulating Factor (CSF) in Patients Receiving Myelosuppressive Chemotherapy for the Treatment of Cancer

Practice Guideline Report #12-2 (Version 2.2003)

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This practice guideline report replaces an earlier version of the report that was completed in 1997 and published as: Rusthoven J, Bramwell V, Stephenson B and the Provincial Systemic Treatment Disease Site Group. Use of Granulocyte Colony-Stimulating Factor (G-CSF) in Patients Receiving Myelosuppressive Chemotherapy for the Treatment of Cancer. *Canc Prev Control* 1998;2(4):179-90.

SUMMARY

Guideline Questions
Are granulocyte and granulocyte macrophage colony-stimulating factor (G-CSF and GM-CSF, jointly referred to as CSF) effective in the management of adult cancer patients with solid tumours (including lymphomas) who are receiving myelosuppressive chemotherapy, in light of the following clinical questions:

1. Do CSF allow maintenance of chemotherapy dose, reduce important adverse clinical outcomes, and result in improved survival?
2. Do CSF allow dose intensification of chemotherapy and result in improved survival?
3. Do CSF during established episodes of febrile neutropenia improve outcomes such as survival, duration of fever, and days of hospitalization or on antibiotics and thus indirectly affect QOL?
4. Do the CSF currently available for clinical use differ in their efficacies and toxicities?
5. Do the clinically available CSF have differing doses and schedules that not only maintain efficacy but also have benefits in terms of convenience or cost?
6. Do CSF influence the occurrence or resolution of chemotherapy-induced mucositis?

Target Population
These recommendations apply to adult cancer patients with solid tumours receiving myelosuppressive chemotherapy. With the exception of lymphoma, hematologic malignancies are excluded.

Recommendations

1. In the setting of standard-dose chemotherapy for solid tumours the risk of neutropenic fever is insufficient to justify routine use of CSF as primary prophylaxis. If a patient experiences an episode of febrile neutropenia or prolonged neutropenia, dose reductions and/or delays of chemotherapy remain the standard initial approach. It is reasonable to use CSF to avoid multiple dose reductions or delays in circumstances where randomized controlled trials have shown improved survival with maintenance of dose intensity.

2. The use of CSF to support the delivery of dose-intensified chemotherapy regimens can only be recommended in the context of randomized controlled trials evaluating regimens that seek to improve progression-free, disease-free, and/or overall survival.
3. Although data are limited, it is reasonable to use CSF to decrease duration of fever, antibiotic use, or hospitalization in patients with febrile neutropenia. Further studies are warranted to establish specific recommendations in this situation.
4. It is not possible to make firm recommendations for a specific type of CSF. More data are available for G-CSF, but further comparative studies of both agents are warranted.
5. There are insufficient data to support specific recommendations for dose/schedules of CSF that differ from those currently recommended by the manufacturer. However, some schedules in which CSF is delayed or abbreviated are promising and could be cost-effective. Therefore, this issue deserves further study.
6. There is preliminary evidence that CSF helps prevent or treat mucositis. However, the Systemic Treatment Disease Site Group felt there were insufficient data on which to make a recommendation for its use in these settings.

Qualifying Statements

- It is reasonable to suggest that primary prophylaxis with CSF is justified when the anticipated risk of febrile neutropenia is greater than 25-40%. However, such risks are rare with the majority of standard chemotherapy regimens for solid tumours, and evidence comes from cost analysis studies not specific to the Canadian health care system.

  CSF reduces the risk of febrile neutropenia associated with standard-dose chemotherapy; however, data are inconclusive as to whether quality of life is significantly improved by its use. Although reduced hospitalization and antibiotic use may be assumed to improve quality of life, dose maintenance with CSF may allow other significant toxicities to emerge (e.g., mucositis, anemia, thrombocytopenia, neuropathies), which can reduce quality of life. The inconvenience of daily injections of CSF and the cost are additional considerations if the risk of neutropenic fever is low.

  Since many patients still derive clinical benefit from commonly allowed chemotherapy dose reduction/delay, given the available data, it is not possible to define a cut-off point for acceptable dose reduction/delay before introducing CSF as secondary prophylaxis.
- Many patients with febrile neutropenia have a rapid and uncomplicated recovery on intravenous antibiotics. Although it may be reasonable to reserve CSF use for patients not achieving a rapid improvement (i.e., not defervescing within 48 hours on broad spectrum antibiotics or antibiotic therapy based on the sensitivity of the cultured organism), none of the reported trials assessed the use of CSF delayed in this way. Similarly, as recommended in the guidelines produced by the American Society of Clinical Oncology, it may also be most reasonable to reserve CSF for patients with factors predictive of a poor outcome, e.g., profound neutropenia (absolute neutrophil count <100/μL), pneumonia, hypotension, multi-organ dysfunction, or invasive fungal infection.

  The efficacy of CSF may be limited in patients with febrile neutropenia or documented sepsis who have received dose-intensive chemotherapy, which is associated with a high risk of febrile neutropenia.

Methods

The literature was searched using the MEDLINE (Ovid) (1966 through September 2002), CANCERLIT (Ovid) (1983 through July 2002), and Cochrane Library (Issue 3, 2002) databases. In addition, the Physician Data Query clinical trials database and abstracts published in the conference proceedings from the meetings of the American Society of Clinical Oncology (1995-2002), the European Society for Medical Oncology (1998, 2000), and the American Society of Hematology (1997-2002) were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase and the National Guideline Clearinghouse databases were searched for relevant clinical practice guidelines. Reference lists from relevant articles and reviews were searched for additional trials.

Evidence was selected and reviewed by three members of the Practice Guidelines Initiative's Systemic Treatment Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Systemic Treatment Disease Site Group, which comprises medical oncologists, pharmacists, and one patient representative.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report will be obtained from the Practice Guidelines Coordinating Committee.

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

Key Evidence

1. Trials of CSF in which the same starting dose of chemotherapy was used in each treatment arm

A meta-analysis of data from 16 trials showed that CSF reduced the risk of febrile neutropenia by 26% (Risk Ratio 0.74; 95% Confidence Interval, 0.63 to 0.87; p=0.0002). With respect to outcomes related to quality of life, CSF use was associated with a significant reduction in antibiotic usage and duration of hospitalization in two trials and had no effect in the other eight in which it was measured. Twelve trials reported no difference in overall median survival, while two small trials detected a significant increase related to CSF. However, further research is necessary to confirm these results. Dose intensity was significantly improved with CSF in four trials but without a corresponding improvement in response or survival rates.

2. Trials evaluating planned dose intensification of chemotherapy supported by CSF

Dose intensification of chemotherapy with CSF support did not achieve statistically significant differences in overall response rates in any trial. Four trials reported significant increases in progression-free survival with dose intensification of chemotherapy. Three trials reported a significant survival advantage for dose-intensive chemotherapy, while another trial reported a significant survival disadvantage.

3. Trials evaluating the value of CSF in promoting recovery from febrile neutropenia

Of six randomized trials that reported data, CSF was significantly associated with a shorter duration of febrile neutropenia in 1 trial, a shorter duration of hospitalization in 3 trials, a shorter duration of grade 4 neutropenia in 3 trials, and a shorter duration of antibiotic usage in 2 trials.

4. Trials comparing different formulations of CSF

Data from two studies showed significantly faster neutrophil recovery for G-CSF versus GM-CSF, but the mean differences were small (0.5-1.5 days). There were no statistically significant differences between the two CSFs for any other measured clinical outcome.

5. Trials evaluating dose/schedule of G-CSF or GM-CSF

Studies looking at dosing schedules of CSF that may help optimize neutrophil recovery or minimize adverse outcomes have produced mixed results. The results of one study suggest that the presence of monocytopenia can be used to determine the optimal starting time for CSF. Delaying the start of CSF (to day eight) was beneficial in two studies but detrimental (when started at day five) in another study. Priming with CSF was significantly effective in two trials, ineffective in three trials, and produced non-significant benefits in a fourth trial. Administering GM-CSF in the morning versus the evening was associated with a significantly shorter mean duration of grade 3/4 neutropenia in one trial.

6. Randomized trials evaluating the use of CSF in the prevention or treatment of mucositis

In one small study, topical oral G-CSF had a borderline benefit in reducing the incidence of grade 3/4 mucositis, and significantly reduced the duration of hospitalization. In a larger study of G-CSF given by the conventional subcutaneous route, there was significantly less mucositis in the G-CSF arm compared with placebo. In a third study, the duration of established chemotherapy-related mucositis was shorter in patients receiving topical G-CSF compared with povidine-iodine and amphoteracin B. These results are interesting and need to be confirmed in larger randomized studies.

Toxicity

Toxicity of CSF is relatively mild. The most consistent clinical symptom attributed to CSF is bone pain reported in incidence rates ranging from 20% to 50%. With the exception of one case, reported bone pain was mild. Other commonly reported adverse effects include injection-site reactions, low-grade fever, headache, and skin rash. Indirect comparisons suggest that more adverse effects were associated with GM-CSF than G-CSF.

Future Research

It is strongly recommended that patients treated with myelosuppressive therapy be enrolled in randomized trials of CSF designed to better evaluate the effect of treatment on quality of life and health care costs. There are insufficient data to support specific recommendations for doses/schedules that differ from those currently recommended by the manufacturers. However, some schedules in which CSF is delayed or abbreviated are promising, and so this issue deserves further study.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Reports:

- #6-5: *The use of G-CSF for patients undergoing bone marrow and stem cell transplantation*
- #6-7: *The use of chemotherapy and growth factors in older patients with newly diagnosed aggressive histology non-Hodgkin's lymphoma*
- #6-13: *G-CSF/erythropoietin in myelodysplasia*.

Please note that these reports are in progress and are not yet available on the Web site.

For further information about this practice guideline, please contact: Dr. Brent Zanke, Chair, Systemic Treatment Disease Site Group, Cancer Care Ontario, 620 University Avenue Toronto, Ontario, Canada M5G 2L7

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PGI and the Program, please visit the CCO Internet site at:
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FULL REPORT

I. QUESTIONS

Guideline Questions

Are granulocyte and granulocyte macrophage colony-stimulating factor (G-CSF and GM-CSF, jointly referred to as CSF) effective in the management of adult cancer patients with solid tumours (including lymphomas) who are receiving myelosuppressive chemotherapy, in light of the following clinical questions:

1. Do CSF allow maintenance of chemotherapy dose, reduce important adverse clinical outcomes, and result in improved survival?
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4. Do the CSF currently available for clinical use differ in their efficacies and toxicities?
5. Do the clinically available CSF have differing doses and schedules that not only maintain efficacy but also have benefits in terms of convenience or cost?
6. Do CSF influence the occurrence or resolution of chemotherapy-induced mucositis?

II. CHOICE OF TOPIC AND RATIONALE

Patients with cancer who are treated with myelosuppressive chemotherapy experience reduced white blood cell (WBC) counts, which may cause clinically important infections requiring hospitalization and antibiotic therapy. Bone marrow suppression is often the dose-limiting toxicity of chemotherapy treatment; this may compromise the amount of chemotherapy that can be safely administered and potentially reduce antitumour efficacy.

CSFs enhance the activity of normal neutrophils, the production of neutrophils in the bone marrow, and their release into the peripheral blood. By maintaining the level of the neutrophil count in the face of myelosuppressive treatment, CSFs may theoretically reduce the frequency of serious infectious complications. They may also allow for the maintenance of the full doses of chemotherapy and thereby ensure the optimal tumour response and/or overall survival.

Colony-stimulating factors are glycoproteins that act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation, commitment, and some end-cell functional activation. Studies involving two CSFs, G-CSF, and GM-CSF have been considered for this guideline. G-CSF principally affects the proliferation and differentiation of neutrophils within the bone marrow and possibly other sites, e.g., spleen. G-CSF has a minimal effect, which may be dose-dependent, on the production of other hematopoietic cell types. GM-CSF principally affects the proliferation, differentiation, and activation of granulocytes and macrophages by inducing partially committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways. Clinical efficacy has been proven for both agents in cancer patients receiving chemotherapy.

The clinical rationale for the use of CSF is based on its potential benefit to patients through its effects on mature neutrophils and neutrophil progenitors. While the effects of CSF on neutrophil recovery times in chemotherapy-treated patients provide confirmation of a biologic effect, changes in such variables are relevant to clinical recommendations only insofar as they lead to benefits in other outcomes that are considered clinically meaningful. These include outcomes such as improved survival, reduced adverse events, and improved quality of life. Given a large number of randomized trials that investigate the role of CSFs with such outcomes in mind, the Systemic Treatment Disease Site Group (DSG) identified the need to develop a practice guideline on CSFs in the management of patients with cancer receiving mylosuppressive chemotherapy.

III. METHODS

Guideline Development

This practice guideline report was developed by the PGI, using the methods of the Practice Guidelines Development Cycle (1). Evidence was selected and reviewed by three members of the

PGI's Systemic Treatment DSG and methodologists. Members of the Systemic Treatment DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of colony-stimulating factor in patients receiving myelosuppressive chemotherapy for the treatment of cancer developed through systematic review, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report will be obtained from the Practice Guidelines Coordinating Committee.

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

A practice guideline report on colony-stimulating factor was originally completed in 1997 and was published in *Cancer Prevention & Control* (2). The literature search has been updated regularly since the guideline was completed and has uncovered new trials involving colony-stimulating factor. The Systemic Treatment DSG decided to incorporate evidence from the new trials with the evidence used to inform the original practice guideline report and to rewrite the original practice guideline. This document replaces the 1997 report.

Literature Search Strategy

The literature was searched using the MEDLINE (Ovid) (1966 through September 2002), CANCERLIT (Ovid) (1983 through July 2002), and Cochrane Library (Issue 3, 2002) databases. In addition, the Physician Data Query clinical trials database and abstracts published in the conference proceedings from the meetings of the American Society of Clinical Oncology (1995-2002), the European Society for Medical Oncology (1998, 2000), and the American Society of Hematology (1997-2002) were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase and the National Guideline Clearinghouse databases were searched for relevant clinical practice guidelines. In addition, recommendations on the use of G-CSF from the American Society of Clinical Oncology and the Ontario Drug Benefits Program were reviewed. Reference lists from relevant articles and reviews were searched for additional trials.

The literature search combined disease specific terms (neoplasms/ or cancer:.tw. or malignan:.tw. or tumour:.tw.) with treatment specific terms (granulocyte colony-stimulating factor/ or granulocyte colony-stimulating factor.mp. or granulocyte macrophage colony-stimulating factor/ or granulocyte macrophage colony-stimulating factor.mp. or colony-stimulating factors/ or hematopoietic cell growth factors/ or haemopoietic growth factors.mp. or g-csf.tw. or gcsf.tw. or gm-csf.tw. or gmcsf.tw. or filgrastim.tw. or neupogen.tw. or leukine.tw. or sargramostim.tw. or molgramostim.tw. or leucomax.tw. or lenograstim.tw.) with search specific terms for the following study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, controlled clinical trials, and economic evaluations.

Inclusion Criteria

Articles were selected for inclusion if they were randomized trials of CSF in adult cancer patients with solid tumours (including lymphomas) receiving myelosuppressive chemotherapy evaluating:

- the same starting doses of chemotherapy in each arm, comparing CSF to control/placebo.
- the planned dose intensification of chemotherapy supported by CSF.
- the value of CSF in promoting recovery from febrile neutropenia.
- different types of colony-stimulating factors.
- different doses or schedules of CSF.
- the occurrence and/or resolution of chemotherapy-related mucositis with CSF.

Abstract data were excluded from the first and second items in this list because of the number of full-text reports available but were considered for all other sections.

Practice guidelines, meta-analyses, or systematic reviews were eligible for inclusion if they were explicitly based on randomized trials related to one or more of the guideline questions.

Outcomes of interest were events that might affect quality of life and/or resource utilization (febrile neutropenia, antibiotic usage, duration of hospitalization, toxicity, quality of life measurements) and indicators of improved efficacy of chemotherapy related to CSF use (response rates, progression-free and overall survival).

Exclusion Criteria

Articles were excluded from the systematic review of the evidence if they:

- were letters, editorials, or phase I or phase II non-randomized trials.
- included patients with non-lymphoma hematological malignancies ≥ 50% of the patient population.
- evaluated CSF with high-dose chemotherapy and autologous bone marrow or peripheral blood stem cell transplantation.
- evaluated CSF with concurrent chemoradiotherapy.
- evaluated CSF with dual receptor activity (e.g. IL-3 and G-CSF).

Synthesizing the Evidence

To address the first question, results were pooled to determine the effect of CSF on febrile neutropenic events across 16 trials of standard chemotherapy. A sensitivity analysis was performed to restrict the analysis to studies involving only G-CSF. The numbers of events of febrile neutropenia were combined using the meta-analytic software program RevMan 4.1 (Metaview © Update Software). The random effects model was chosen as the more conservative estimate of effect. Results are expressed as the relative risk (RR) of an event in the CSF group compared with the control group with a 95% confidence interval. The significance tests are two-tailed. For the other outcomes of interest in this section, response and survival, the Systemic Treatment DSG determined that the clinical heterogeneity was too great to pool data across trials.

In addressing questions two to five, it was judged inappropriate by the Systemic Treatment DSG to pool response and survival data, as the trials dealt with many different malignancies, chemotherapy regimens, and CFS dose/schedules.

IV. RESULTS

Literature Search Results

A total of 63 randomized trials (3-65) and two clinical practice guidelines (66,67) were identified in the search of the literature and were deemed eligible for review. A classification of the literature search results is found in Table 1. Where the results of a trial have been reported or updated in more than one publication, only the most recent publication is included.

Table 1. Literature search results.

Comparisons	Number of Studies	Reference Numbers	Summary of Results	Outcomes of Interest
1. CSF v. control or placebo with the same starting dose of CT in each arm	19	3-21	Table 2 Figure 1	quality of life, infection rates, episodes of FN, CT dose intensity, response rate, survival
2. Planned dose intensification of CT supported by CSF	14	18,22-35	Table 3	response rates, disease-free survival, progression-free survival, overall survival, CT dose intensity, quality of life
3. Trials evaluating the value of CSF in promoting recovery from FN	9	36-44	Table 4	duration of FN, days of hospitalization, days on antibiotics
4. Trials comparing different formulations of CSF	4	45-48	Page 12	# hospitalizations, duration of fever, duration of antibiotic use, adverse effects of G- and GM-CSF, episodes of FN, # treatment delays
5. Trials evaluating dose/schedule of CSF	14	49-62	Pages 13-15	CT dose intensity, incidence of FN, duration of neutropenia, duration of antibiotics, # hospitalizations, adverse effects
6. Trials involving CSF use in the prevention or treatment of mucositis	3	63-65	Page 15	duration of treatment, duration of oral mucositis, duration of hospitalization, incidence of FN
Clinical Practice Guidelines				
ASCO 2000 (66)	2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines			
ODB 1996 (67)	Guidelines for coverage of Neupogen (filgrastim or G-CSF)			

NOTE: ASCO = American Society of Clinical Oncology; CT = chemotherapy; FN = febrile neutropenia; ODB = Ontario Drug Benefit.

1. When starting with the same dose of chemotherapy, does CSF compared with control/placebo allow maintenance of chemotherapy dose, reduce important adverse outcomes, and result in improved survival?

Literature Search Results

Nineteen randomized controlled trials of CSF using the same starting dose of chemotherapy in each treatment arm were identified (3-21). CSF was compared to observation in 11 trials (4,8,10,11,13-17,20,21), placebo in 7 trials (3,5-7,9,12,18), and to ciprofloxacin and amphotericin B in one trial (19). In these studies, the final dose intensity was often different between the arms because of varying degrees of myelosuppression, and different dose reduction schedules. In all trials, the colony-stimulating factor was used prophylactically to modulate neutropenia. Study descriptions and results are presented in Table 2, and chemotherapy regimens are described in detail in Appendix 1.

Outcomes

CSF had no effect on tumour response rate or progression-free survival in any of the trials where these outcomes were measured. Two small trials reported greater median overall survival with CSF compared with control (10,13).

The proportion of patients with febrile neutropenia was significantly lower in seven of the nineteen trials in which patients received CSF (3-6,13,14,21). The results of 16 trials comparing CSF to observation or placebo were pooled (3-16,18,21). Three trials contributed two treatment groups (15,16,18), thus providing 19 comparisons. Two trials (17,20) did not report the proportion of patients

experiencing febrile neutropenia and therefore could not be included in the meta-analysis. One trial (19) did not compare CSF to observation or placebo and was not included in the analysis. When the results of the 16 trials were pooled, CSF reduced the risk of febrile neutropenia by 26% (RR 0.74; 95% CI, 0.63 to 0.87; p=0.00002) (Figure 1). When the results were restricted to trials involving only G-CSF (3-8,10-17,20-21), G-CSF reduced the risk of febrile neutropenia by 31% (RR 0.69; 95% CI, 0.59 to 0.82; p=0.000020).

The duration of febrile neutropenia was shorter for patients receiving CSF in six out of the seven trials that reported data (3,5-7,13,15,18), however the difference in duration reached statistical significance in only one trial (6). In the seventh trial, a significant difference in duration of febrile neutropenia favouring patients in the control arm was reported (5).

Seven trials reported deaths due to febrile neutropenia (4,5,8,11,16,18,20). The difference in toxic death rates between patients randomized to chemotherapy with or without CSF did not reach statistical significance in any of the trials.

Chemotherapy dose intensity was an endpoint in many of the RCTs (8,9,11-17,20). In most cases, patients in the CSF arm received a higher dose intensity than patients in the control arm. This difference in dose intensity reached statistical significance in four trials (8,9,11,12).

Outcomes related to quality of life, including length of hospital stay and days on antibiotics, were measured in 10 trials (3,6-8,10-12,15,18,19). Chevallier et al (7) reported a significantly shorter mean duration of hospitalization for patients receiving CSF compared to placebo (3.7 days v. 8.3 days; p=0.003). This trial also reported a significantly shorter median number of days on intravenous antibiotics for patients receiving CSF (3.4 v. 6.7; p=0.018). Gisselbrecht et al (12) reported a significant reduction in the mean duration of hospitalization for the treatment of infection in favour of patients receiving CSF versus patients receiving placebo (5.3 v. 10.0 days; p<0.05). Also reported in this trial was a significant reduction in the mean number of days of treatment with intravenous antibiotics, in favour of patients receiving CSF versus patients receiving placebo (6.0 v. 11.8 days; p=0.002). No other significant differences with respect to quality of life-related outcomes were reported.

Adverse Effects

The toxicities of CSF are relatively mild. Nguyen Bui et al reported hyperleukocytosis with back, neck, or extremity pain and pain at injection sites (6). The most consistent clinical symptom attributed to G-CSF is bone pain, which was reported at incidence rates of 20%, 22%, and 50%, respectively, in patients in three trials (3,6,7). Pain tended to be confined to sites containing bone marrow and was mild to moderate. Two patients reported episodes of musculoskeletal pain in the study by Zinzani et al (14). Gisselbrecht et al (12) reported that a greater proportion of patients treated with G-CSF reported bone pain, headache, and injection site reactions but the differences were not significant when compared to patients receiving placebo. Woll et al (8) did not document any bone pain as a result of G-CSF.

In the study by Jones et al (9), the frequency of injection-site reactions (53% v. 14%), low-grade fever (51% v. 26%), and flushing (23% v. 10%) was significantly increased in patients who received GM-CSF versus those who received placebo (p values not reported). Reactions at the site of injections were reported in eight patients receiving GM-CSF in the Steward et al study (18).

Table 2. Trials of CSF versus control/placebo with the same starting dose of chemotherapy.

Study Year (Reference)	# of pts.	Disease Site	Treatment Groups*†	CT Dose median Intensity	% with FN or infection	Response (%)	Survival % or median months	
						Overall	DFS	OS
Crawford	110	SCLC	CAE + placebo	NR	57%‡	80%	8	12
1991 (3)	101		CAE + G-CSF	NR	28%	72%	8	11
Pettengell	39	Non-Hodgkin's	VAPEC-B	NR	44%‡	NR	92%	p=NS
1992 (4)	41	lymphoma	VAPEC-B + G-CSF	NR	23%	NR	90%	
Trillet-Lenoir	64	SCLC	CDE + placebo	NR	53%‡	87%	NR	11
1993 (5)	66		CDE + G-CSF	NR	26%	79%	NR	11
Nguyen Bui	26	Sarcoma	MAID + placebo	NR	58%‡	NR	NR	NR
1995 (6)	22		MAID + G-CSF	NR	23%	NR	NR	NR
Chevallier	59	Breast	FEC + placebo	NR	90%	93%	45%	67%
1995 (7)	61		FEC + G-CSF	NR	77%	89%	54%	62%
Woll	31	SCLC	VICE	1.17	70%	93%	56%	32%
1995 (8)	34		VICE +G-CSF	1.34‡	66%	94%	62%	15%
Jones	72	Breast	FAC + placebo	NR	11%	NR	NR	NR
1996 (9)	70		FAC + GM-CSF	NR‡	9%	NR	NR	NR
Muhonen	15	Breast	MMM	NR	47%	13%	NR	7
1996 (10)	16		MMM + G-CSF	NR	38%	6%	NR	11‡
Fridrik	36	Non-Hodgkin's	CEOP/IMVP-Dexa	76%	58%	67%	p=NS	p=NS
1997 (11)	38	lymphoma	CEOP/IMVP-Dexa + G-CSF	82%‡	42%	83%		
Gisselbrecht	80	Non-Hodgkin's	ACVB/NCVB + placebo	80%	83%	87%	50%	55%
1997 (12)	82	lymphoma	ACVB/NCVB + G-CSF	93%‡	82%	88%	47%	63%
Negoro	32	SCLC	CODE	72%	77%‡	84%	NR	7
1997 (13)	32		CODE + G-CSF	83%	44%	96%	NR	14‡
Zinzani	72	Non-Hodgkin's	VNCOP-B	85%	21%‡	80%	72%	62%
1997 (14)	77	lymphoma	VNCOP-B + G-CSF	95%	5%	83%	76%	64%
Dunlop	12	Hodgkin's	MOPP	82%	36%	NR	NR	NR
1998 (15)	13	Disease	MOPP + G-CSF	84%	8%	NR	NR	NR
	14		MOPP/EVAP	97%	50%	NR	NR	NR
	14		MOPP/EVAP + G-CSF	96%	55%	NR	NR	NR
Fosså	65	Germ cell	BEP/EP	91-99%	13%	NR	53%	75%
1998 (16)	64	tumours	BEP/EP + G-CSF	98-100%	14%	NR	54%	83%
	65		BOP/VIP-B	72-96%	46%	NR		
	65		BOP/VIP-B + G-CSF	71-98%	25%	NR		
Hidalgo	40	Ovarian	CCP	32-94%	NR	54%	p=NS	p=NS
1998 (17)	40		CCP + G-CSF	53-90%	NR	72%		
Steward	76	SCLC	Std. V-ICE + Placebo	NR	51%	77%	NR	13
1998 (18)	77		Std. V-ICE + GM-CSF	NR	53%	78%	NR	12
	74		Int. V-ICE + Placebo	NR	55%	90%	NR	NR
	73		Int. V-ICE + GM-CSF	NR	56%	88%	NR	NR
Schröder	22	Breast	CEF/CMF + CAB	NR	32%	NR	NR	NR
1999 (19)	18		CEF/CMF + G-CSF	NR	39%	NR	NR	NR
Miles	17	SCLC	CEDI	84%	NR	71%	NR	NR
1994 (20)	23		CEDI + G-CSF	82%	NR	74%	NR	NR
Gatzemeier	139	SCLC	ACE	NR	54%‡	80%	8	10
2000 (21)	141		ACE + G-CSF	NR	37%	76%	8	11

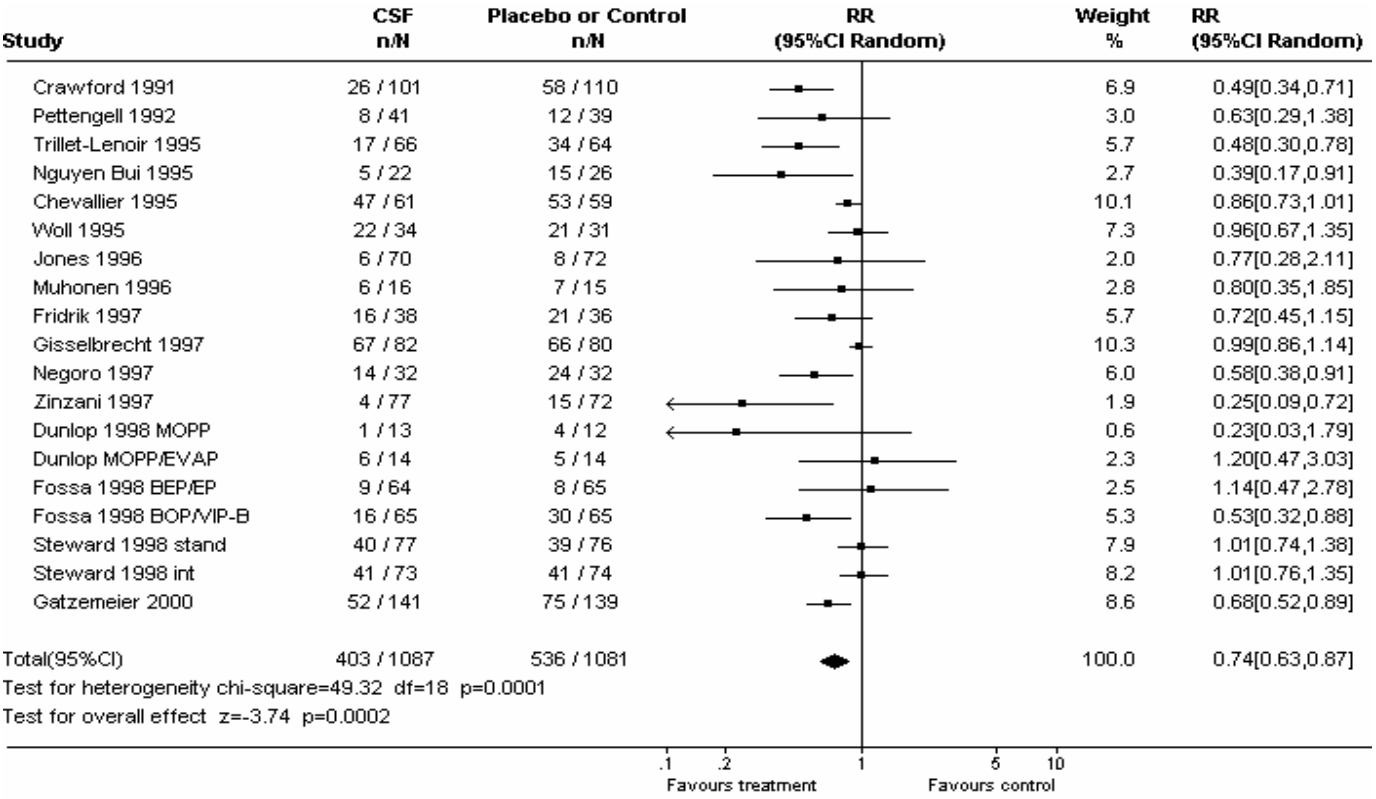
NOTE: # of Pts.= number of patients in group; CT = chemotherapy; FN = febrile neutropenia; DFS = disease-free survival; OS = overall survival; NR = not reported; NS = not significant; Int. = intensified; SCLC = small cell lung cancer; Std. = standard.

* Please see Appendix 1 for detailed chemotherapy regimen information.

† Please see Appendix 2 for glossary of chemotherapy abbreviations/acronyms.

‡ denotes significant differences with $p \leq 0.05$

Figure 1. Risk ratio of trials analyzing the effect of CSF on febrile neutropenia (16 trials with 19 comparisons).



Interpretive Summary

Pooled results across the randomized trials included in the meta-analysis confirm that CSF reduces the risk of febrile neutropenia by 26% when used with standard chemotherapy programs. In five (3,7,13,15,18) of the seven (3,5-7,13,15,18) studies that measured the duration of febrile neutropenia, there were no statistically significant differences despite the use of colony-stimulating factors. Only two of 10 trials (7,12) suggested an improvement in clinical outcomes related to quality of life, showing that CSF reduced the duration of hospitalization and intravenous antibiotic use. Although the meta-analysis showed a significant reduction in the incidence of febrile neutropenia across the studies, this reduction had no impact on quality of life in eight trials (3,6,8,10,11,15,18,19) in which it was formally measured. However, in six of these eight trials (8,10,11,15,18,19), it should be noted that there was no significant reduction in the incidence of febrile neutropenia. Thus, in the absence of conclusive data, it remains a reasonable assumption that a reduction in febrile neutropenic episodes in patients at high risk will improve quality of life.

There is insufficient evidence at this time that the inclusion of CSF in standard chemotherapy regimens results in increased patient survival. In two trials, involving a total of 96 randomized patients, CSF was associated with an increase in overall survival (10,13). These trials should be interpreted with caution. In the trial of breast cancer patients, the increase in the dose intensity of chemotherapy associated with CSF was small and was not associated with an increase in response rate (10). Patients with metastatic breast cancer show a heterogeneous survival pattern, and such a difference may have occurred by chance. In the trial of lung cancer patients, it is not clear that the difference in survival can be attributed to CSF (13). This was a small study and involved a chemotherapy regimen (cyclophosphamide, vincristine, doxorubicin and etoposide [CODE]) not considered standard treatment in Canada. Deaths from other causes were similar in the CSF group compared with the control group, as were response rates. Further research is needed to confirm differences in survival associated with CSF in patients with breast cancer and lung cancer. There were no statistically significant differences in response rates, disease-free survival, progression-free survival or overall

survival between the control and CSF arms in any of the other studies that recorded these outcomes. Dose intensity was significantly improved in four trials (8,9,11,12) with CSF but without a corresponding improvement in response or survival.

2. Trials Evaluating Planned Dose Intensification of Chemotherapy Supported by CSF

Literature Search Results

Fourteen RCTs were located that investigated the role of CSF in dose-intensive chemotherapy regimens (18,22-34). An additional abstract was located (35) that discussed quality of life results of the randomized trial by Bonomi et al (28). Only full reports of trials were considered for this section, with the exception of the quality of life report. The studies involved a variety of disease sites and chemotherapy regimens. The results of the trials are reported in Table 3, and the chemotherapy regimens are described in Appendix 3.

Outcomes

Twelve trials measured overall survival (18,22,23,25-27,29-34), and of these, three trials (18,26,29) reported a significant overall survival difference in favour of patients in the intensified treatment arms versus those in the standard chemotherapy arms. One trial (22) reported a significant survival disadvantage for patients in the intensified regimen compared to the standard regimen.

Disease-free or progression-free survival was measured in 10 trials (18,23,25-27,29,30,32-34). Of the ten trials, four (26,27,30,34) reported a significant difference in disease free or progression-free survival in favour of the intensified treatment regimen compared with the standard treatment regimen. No other significant differences were reported for disease-free/progression-free survival.

Differences in overall response rates between the standard and intensified chemotherapy regimens did not reach statistical significance in any trial. Three trials (22,29,34) reported significantly higher complete response rates in patients receiving intensified chemotherapy compared with patients receiving standard-dose chemotherapy. In contrast, one trial (33) reported significantly higher complete response rates in patients receiving standard-dose versus intensified-dose chemotherapy.

Where reported, chemotherapy dose intensification ranged from 74% to 98% of the planned dose (22-24,27,29,30,32-34). One trial (18) reported a 26% increase in dose intensity and one trial (26) reported a relative dose increase of 1.33 compared with standard dose chemotherapy. Three trials did not report median or relative dose intensity (25,28,31).

Adverse Effects

Three trials reported adverse effects related to CSF (18,23,29). Eight patients receiving GM-CSF in the study reported by Steward et al (18) had reactions at the site of injection. In the study reported by Font et al (23), the main adverse effects related to the use of GM-CSF were hypotension, fever, nausea and vomiting, local reaction, and skin rash. Three patients were removed from this study with symptoms related to GM-CSF use. Three patients reported adverse effects related to G-CSF in the study reported by Thatcher et al (29), including urticaria, asymptomatic hypoglycemia, malaise, nausea, lethargy, and headache.

Quality of Life

In the trial by Riccardi et al (27) quality of life (QOL) was assessed using the Quality of Life Questionnaires QLQ-C30 (compiled by the patient), QLQ-BR23 (specifically for breast cancer patients, compiled by the patient), and the Spitzer's QL-index (compiled by the physician). Quality of life was assessed at baseline, after the third course of chemotherapy, after the sixth course of chemotherapy, and three months after the sixth course of chemotherapy. There were significant differences (from baseline) within each treatment arm, but there were no significant differences between the two treatment arms on any of the quality of life scales.

Quality of life was also measured in the study by Thatcher et al (29) using the Rotterdam Symptom Checklist. Quality of life was assessed through patient questionnaires completed prior to treatment and twice more in an 18 week period. There were no significant differences reported between the two treatment arms on any of the QOL measures.

Cella et al (35) report the QOL results from the Bonomi et al study (28) of advanced non-small cell lung cancer patients. Quality of life was measured using the Functional Assessment of Cancer Therapy-Lung (FACT-L). This instrument provides subscale scores for physical, functional, emotional and social well-being, lung cancer symptoms, a total score, and a Trial Outcome Index (TOI) that combines the scores from the physical, functional, and lung cancer sections. The FACT-L was administered to patients at baseline, six weeks, 12 weeks, and six months. There were no significant differences between the treatment arms for any of the scores.

Interpretive Summary

In general, the results of these randomized studies of dose intensification of chemotherapy using G-CSF or GM-CSF are not encouraging. Dose intensification of chemotherapy with CSF support did not achieve statistically significant differences in overall response rates in any study. In four trials (26,27,30,34), dose intensification was associated with a statistically significant improvement in disease-free survival. The dose intensification of chemotherapy significantly improved overall survival in three studies (18,26,29) but was associated with a significant survival disadvantage in one study (22). The findings of the latter study (22) probably reflected significant toxicity and a high rate of treatment-related deaths in the dose-intensive arm despite CSF use. This also led to significantly improved dose intensity in the standard versus dose-intense arms of this study. Although improved survival was reported in a study (26) involving 100 patients with non-small cell lung cancer, no survival benefit was reported in another study of the same disease (23). The study of Steward et al (18), conducted in patients with small cell lung cancer, showed improved survival for dose-intensified chemotherapy, but this was not dependant on the use of GM-CSF. Interestingly, in this study, the use of GM-CSF did not correlate with reduced incidence of febrile neutropenia or confirmed sepsis. In other studies, dose intensity was improved with CSF use in the intensified arms but reached statistical significance only in one (23).

The heterogeneity of tumour types and chemotherapy regimens limits the value of further analysis. Additional studies of planned dose intensification of chemotherapy using CSF are warranted but only in the context of randomized controlled trials.

Table 3. Description and results of trials of dose intensification.

Study Year (Reference)	# of pts	Disease Site	Treatment Groups*†	CT Dose Intensity‡	Response Rate (%)		Survival % or median months	
					Complete	Overall	DFS/PFS	Overall
Steward, 1998 (18)	76 77 74 73	SCLC	std. V-ICE + placebo std. V-ICE + GM-CSF int. V-ICE + placebo int. V-ICE + GM-CSF	increased 26% over std. CT	54% 44% 59% 42%	77% 78% 91% 88%	6 7§	12 15§//
Pujol 1997 (22)	55 61	SCLC	std. CT int. CT + GM-CSF	83-84% 74-77%	22% 38%//	75% 87%	NR	11// 9
Font 1999 (23)	64 59	NSCLC	std. PE int. PE + GM-CSF	93-94% 93%	2% 8%	32% 27%	6 7	7 9
Kuroda 1998 (24)	29 29	Urothelial	std. MEC int. MEC + G-CSF	95% 90%	3% 14%	52% 76%	NR NR	NR NR
Diehl 1998 (25)	241 213	Hodgkin's disease	std. BEACOPP int. BEACOPP + G-CSF	NR NR	88% 95%	90% 96%	81% 89% (2yr)	94% 96% (2yr)
Masutani 1999 (26)	50 50	NSCLC	std. PVM int. PVM + G-CSF	1.00 1.33	0% 2%	44% 52%	3 6//	9 13//
Riccardi 2000 (27)	38 36	Breast	std. FEC int. FEC + G-CSF	NR 94%	NR NR	50% 51%	13 19//	23 24
Bonomi 1997 (28)	187 190	NSCLC	std. CT int. CT + G-CSF	NR NR	NR NR	26% 31%	NR NR	NR NR
Thatcher 2000 (29)	197 197	SCLC	std. ACE int. ACE + G-CSF	93-95% 81-85%	28% 40%//	79% 78%	p=NS	39% 47%// (1 yr)
Le Cesne 2000 (30)	149 145	STS	std. dox + ifos int. dox + ifos + GM-CSF	97% 98%	3% 3%	21% 23%	4 7//	13 13
Pfreundschuh 2001 (31)	30 30	Hodgkin's	Dexa-BEAM¶ + placebo Dexa-BEAM¶ + GM-CSF	NR NR	57% 47%	57% 57%	NR NR	28 23
Del Mastro 2001 (32)	72 75	Breast	std. CEF int. CEF + G-CSF	93% 86%	15% 20%	49% 51%	14 13	33 27
Forastiere 2001 (33)	98 101	Head and neck	std. pac + CDDP int. pac + CDDP +G-CSF	61% 77%	12%// 4%	36% 35%	4 4	7 8
Sternberg 2001 (34)	129 134	Bladder	std. MVAC int. MVAC + G-CSF	71-88% 90-91%	9% 21%//	50% 62%	8 9//	14 16

NOTE: CT = chemotherapy; DFS = disease-free survival; dox = doxorubicin; eval = number of evaluable patients; ifos = ifosfamide; int. = intensified; mos = months; NR = not reported; NS = not significant; NSCLC = non-small cell lung cancer; pac = paclitaxel; PFS = progression-free survival; rand = number of randomized patients; SCLC = small cell lung cancer; std. = standard; STS = soft tissue sarcoma.

* Please see Appendix 2 for glossary of chemotherapy abbreviations/acronyms.

† Please see Appendix 3 for a detailed description of the chemotherapy regimens.

‡ Delivered dose intensity achieved compared with planned dose expressed as median or relative dose intensity

§ Comparison arms for standard dose and intensified dose chemotherapy were collapsed for outcomes related to survival

// denotes significant differences with $p \leq 0.05$

¶ Patients were randomized to receive Dexa-BEAM chemotherapy with escalating etoposide doses supported by placebo or GM-CSF.

3. Trials Evaluating the Value of CSF in Promoting Recovery from Febrile Neutropenia

Literature Search Results

Eight full reports (36-43) and one abstract (44) of RCTs were located that investigated the role of a CSF in enhancing the recovery of patients diagnosed with febrile neutropenia following chemotherapy. Eight trials are described in Table 4 (36-43), while one (44) is described separately in the Outcomes section.

Outcomes

The median duration of febrile neutropenia was reported in six trials (36-38,40,41,43). Only one trial (41) reported significantly less median time to resolution of febrile neutropenia favouring patients receiving G-CSF.

The median duration of grade 4 neutropenia was reported in three trials (36,37,39). All three trials reported significantly less duration of grade 4 neutropenia with CSF when compared with control. GM-CSF significantly reduced the duration of grade 4 neutropenia from 4.2 to 3.2 days (p=0.024) in the trial by Ravaud et al (37). When patients in this trial were stratified according to the degree of hematologic toxicity associated with their chemotherapy regimen, patients in the low-risk chemotherapy group receiving GM-CSF had a significantly shorter duration of grade 4 neutropenia compared to those in the control group (2.2 days v. 4.6 days; p=0.011). There was no significant difference in the duration of grade 4 neutropenia in patients receiving high-risk chemotherapy (defined as having a 15% or greater absolute risk of inducing febrile neutropenia).

The duration of hospitalization for febrile neutropenia was reported in six trials (36,37,39-41,43). In three trials, treatment with CSF significantly shortened the duration of hospitalization (36,37,39). The difference between the GM-CSF group and the control group in the Ravaud et al study was also significant when patients receiving low-risk chemotherapy were analyzed separately (37). In this group of patients, GM-CSF reduced the duration of hospitalization from 6.9 to 4.2 days (p=0.003). There was no difference in this measure for patients receiving high-risk chemotherapy.

The length of antibiotic therapy was significantly reduced in patients receiving a colony-stimulating factor in two (37,39) of the six trials that measured this outcome (37,39-43).

Infection-related deaths were reported in four trials (36,37,39,42). Mayordomo et al (36) reported two deaths in the G-CSF arm, one death in the GM-CSF arm, and one death in the placebo arm. Ravaud et al (37) reported one death in the control arm. Garcia-Carbonero et al (39) reported 10 deaths–five in each arm. Biesma et al (42) reported one death in the GM-CSF arm.

Arnberg et al (38) measured the total white blood cell (WBC) count and the absolute neutrophil count (ANC). From the third day of GM-CSF or placebo administration, there was a statistically significant difference in the total WBC count between the patients receiving GM-CSF and the patients receiving placebo (2.5 v. 1.0 x 10^9/L; $p<0.05$). The difference between the two study groups was even larger on the final day of treatment administration (18.7 v. 5.1 x 10^9/L; $p<0.01$). A total WBC count of >1.0 X 10^9/L was achieved 1.5 - 2.0 days earlier in the GM-CSF arm. The differences in the ANC of the two groups followed the same pattern as the total WBC count, with patients in the GM-CSF having a significantly larger increase in the ANC, but no values were provided in the study.

Torrecillas et al (44) designed a trial to determine the appropriate ANC level to discontinue colony-stimulating factor treatment. Fifty patients were randomized to receive GM-CSF at a dose of 4-6 µg/kg/day either until the first ANC $\geq$1.5 X 10^9/L or for two to three days after this ANC level was attained, in order to avoid rebound neutropenia. There were no significant differences between the two groups for the duration of fever or ANC levels. There were only three instances of rebound neutropenia. The authors concluded that an ANC of $\geq$1.5 X 10^9/L can be considered a safe cessation level of GM-CSF.

Adverse Effects

Adverse effects attributed to CSF were reported in five trials (36-38,41,43). One patient receiving G-CSF and four patients receiving GM-CSF developed CSF-related fever (defined as fever that disappeared the day after CSF was discontinued) in the study by Mayordomo et al (36). Two patients receiving GM-CSF in the study by Ravaud et al (37) experienced grade 1 erythema at the injection

site, and four patients had mild to moderate bone pain. Two patients in the GM-CSF group in the Arnberg et al study (38) developed fevers after having attained normal temperatures. Maher et al (41) reported a higher proportion of patients with musculoskeletal symptoms receiving G-CSF than placebo, but the difference was not statistically significant. Myalgia and/or rash and/or bone pain and/or edema were observed in 20% of patients treated with GM-CSF versus 6% of patients receiving placebo in the trial by Vellenga et al (43). This difference did not reach statistical significance.

Quality of life

Vellenga et al (43) reported QOL results. The results of the Karnofsky performance index indicated that patients in the placebo group reported fewer complaints than patients who received GM-CSF, but this difference did not reach statistical significance. Mobility and emotional and energy problems were less pronounced in the placebo group than in the GM-CSF group ($p<0.05$). There were no significant differences noticed in the EuroQol instrument. On the Rotterdam Symptom Checklist, patients in the placebo group experienced statistically fewer problems with appetite and energy than patients in the GM-CSF group ($p<0.01$).

Table 4. Results of trials on the role of colony-stimulating factor in recovery from febrile neutropenia.

Study	# of pts.	Treatment Groups*	CSF dose	Median Duration of FN (days)	Median Duration of N (days)	Median Days in Hospital	Median Days on Antibiotics
Mayordomo 1995 (36)	39 39 43	G-CSF GM-CSF placebo	5 µg/kg/d SC 5 µg/kg/d SC	1 2 2	2a† 2a† 3b	5a† 5a† 7b	NR NR NR
Ravaud 1998 (37)	34 34	GM-CSF control	5 µg/kg/d SC	2.3 2.8	3.2† 4.2	4.9† 6.3	5.2† 6.7
Arnberg 1998 (38)	14 15	GM-CSF placebo	5.5 µg/kg/d SC	1 3	NR NR	NR NR	NR NR
Garcia-Carbonero 2001 (39)	104 99	G-CSF control	5 µg/kg/d SC	NR NR	2† 3	5† 7	5† 6
Anaissie 1996 (40)‡	50 50	GM-CSF control	3 µg/kg/d IV	4 4	NR NR	9 10	7 8
Maher 1994 (41) §	109 107	G-CSF placebo	12 µg/kg/d SC	5† 6	NR NR	8 8	p=NS
Biesma 1990 (42) //	15 15	GM-CSF placebo	2.8 µg/kg/d IV	NR NR	NR NR	NR NR	10.8 9.6
Vellenga 1996 (43)¶	65 69	GM-CSF placebo	5 µg/kg/d SC	3 3	NR NR	6 7	5 5

NOTE: # of pts. = number of patients; FN = febrile neutropenia; IV = intravenously; N = Neutropenia; NR = not reported; NS = not significant; SC = subcutaneously.

a, b Where multiple treatment arms exist, a indicates significant differences compared with treatment arms identified with b.

* Please see Appendix 2 for glossary of chemotherapy abbreviations/acronyms.

† denotes significant differences with $p \leq 0.05$

‡ This study included 46 patients with leukemia.

§ This study included 22 patients with acute lymphoblastic leukemia.

// Five patients in the GM-CSF group and 3 patients in the placebo group had received autologous bone marrow transplantation.

¶ This study included 8 patients with acute lymphoblastic leukemia.

Interpretive Summary

The limited available data show that when given during an episode of febrile neutropenia, a CSF may modestly reduce the duration of grade 4 neutropenia, hospitalization for febrile neutropenia, and length of antibiotic use. Some mild to moderate side effects are associated with such therapy, with reductions in some domains of QOL in one study (43). Many patients with febrile neutropenia have a rapid and uncomplicated recovery on intravenous antibiotics. In view of the modest additional benefits of CSF, intuitively it would seem reasonable to reserve CSF use to patients not achieving a rapid response to appropriate broad-spectrum antibiotics. However, none of the trials assessed the use of CSF delayed in this way. It is of note that Ravaud et al (37) failed to demonstrate any benefit for GM-CSF use when patients developed febrile neutropenia after doses of chemotherapy that put them at

higher risk for this complication. Thus, the appropriate use of CSF in febrile neutropenia needs further study.

One study (39) suggests that GM-CSF can be discontinued once the ANC has reached ≥1.5 x 10^9/L. By reducing hospitalization and antibiotic use (results are not definitive), G-CSF could contribute to lower health care costs. A formal cost analysis, involving only direct costs of therapy, was done in only one trial (36), and the savings were small and not statistically significant.

4. Trials Comparing Different Formulations of CSF

Literature Search Results

Four trials were located that compared different types of colony-stimulating factors (45-48). Abstracts were included in this section because only one trial was reported in full.

Outcomes

Beveridge et al (45) compared clinical outcomes in afebrile cancer patients with an ANC <0.5 X 10^9/L. One hundred and eighty-one patients were randomized in a double-blind fashion to receive either GM-CSF 250 µg/m^2 daily (n=79) or G-CSF 5 µg/kg daily (n=102) until an ANC of 1.5 X 10^9/L was attained. The mean number of days to reach an ANC of 1.0 X 10^9/L was significantly lower in patients receiving G-CSF versus GM-CSF (4.5 days v. 5.1 days; p=0.009), as was the mean number of days required to reach an ANC of 1.5 X 10^9/L (4.6 days v. 5.7 days; p=0.0001). Compared to patients receiving G-CSF, patients receiving GM-CSF had fewer hospitalizations, a shorter duration of fever, and a shorter duration of antibiotic use, but none of these differences reached statistical significance.

Regan et al (46) randomized 317 patients to receive either G-CSF or GM-CSF for the prevention of chemotherapy-induced neutropenia. Two hundred and twenty-eight patients received GM-CSF, and 89 received G-CSF. The study measured adverse effects related to treatment, documented infections, hospitalization, delays in chemotherapy, incidence of febrile neutropenia, or ANC. The mean number of days of ANC <1.0 X 10^9/L was lower in the G-CSF group compared to the GM-CSF group (2.2 days v. 3.7 days; p=0.04). There were no other significant differences between the two groups for any outcome measure.

In the study by Mustacchi et al (47), 55 patients were randomized in a single-blind fashion to receive either G-CSF 2.5 µg/kg/day for six days or G-CSF 2.5 µg/kg/day for three days followed by GM-CSF 2.5 µg/kg/day for three days. Patients treated with the combination of G-CSF and GM-CSF were found to have significantly fewer treatment delays and fewer days of delay in relation to the total number of days of observation compared to patients who received G-CSF.

Holmes et al (48) randomized 310 breast cancer patients on a combination of docetaxel and doxorubicin to receive a single subcutaneous injection of pegfilgrastim at 100ug/kg per chemotherapy cycle on day 2 then placebo injections up to 14 days or till the ANC reached ≥10 X 109/L versus filgrastim 5ug/kg/d by subcutaneous injection daily using the same parameters for discontinuation. Pegfilgrastim has a longer half life than filgrastim due to the addition of a polyethylene glycol molecule. There was no significant difference in any of the end points measured between the two groups including incidence of grade 4 neutropenia, mean duration of grade 4 neutropenia, duration of grade 4 neutropenia, depth of ANC nadir, rates of FN, or time of ANC recovery.

Adverse Effects

Adverse effects related to G-CSF or GM-CSF were reported in three trials (45,46,48). Six patients in the Beveridge et al study (45) discontinued treatment because of adverse effects. Two patients receiving GM-CSF reported bone pain and chest pain and discontinued treatment. Four patients receiving G-CSF discontinued treatment because of bone pain. Chills and grade 2 fever were also reported in both study groups. Regan et al (46) measured the incidence of bone pain, myalgia, injection site reaction, and rash in each group of patients. There were no significant differences between the two groups for any treatment-related adverse effect. Holmes et al (48) reported no significant differences in rates of skeletal pain, serious adverse events, and adverse events leading to withdrawal between patients randomized to pegfilgrastim or to filgrastrim.

Interpretive Summary

Data from two of these studies (45,46) showed significantly faster neutrophil recovery for G-CSF versus GM-CSF, but the mean differences were small (0.5 to 1.5 days). There were no statistically significant differences between the two colony-stimulating factors for any other measured clinical outcome. Both colony-stimulating factors appear to have tolerable side effect profiles.

It is not possible, based on the results of these studies, to make firm recommendations for the use of one specific type of CSF. More data are available for G-CSF, but further comparative studies of both agents are warranted.

5. Trials Evaluating Dose/Schedule of G-CSF or GM-CSF

Literature Search Results

Fourteen small trials were located that evaluated the dose or schedule of colony-stimulating factors (49-62). Two trials were available in abstract form only (57,59). Trial descriptions and results are presented in Table 5.

Outcomes

Seven trials (49,51,52,57,58,59,62) reported the percentage of patients with febrile neutropenia or infection. Of these, only one trial (62) reported a significant difference in favour of GM-CSF compared to no GM-CSF support.

Three trials (49,51,55) reported patients with neutropenia as an outcome of interest. One trial (49) detected significantly less neutropenia when G-CSF was started on day eight when compared with patients who received G-CSF at the onset of neutropenia, at day two, or not at all. One trial of G-CSF starting on days six to eight detected significantly less neutropenia when compared to G-CSF at the onset of neutropenia. One trial (51) of G-CSF starting on days one, three, or five did not detect any significant differences between treatment groups.

The mean duration of grade 4 neutropenia was reported in seven trials (49-51,55,58,59,62), Three trials (49,50,55) reported significant differences with the planned administration of G-CSF compared with patients who received G-CSF at the onset of neutropenia. One trial (58) significantly favoured morning administration versus evening administration, and two trials reported superior results when compared to patients with no G-CSF support (49, 62). The remaining trials did not detect any significant differences between treatment groups.

In terms of neutrophil recovery, one trial (50) significantly favoured patients when G-CSF was administered 24 hours after chemotherapy versus delayed administration. There was no difference in the frequency of hospitalization for febrile neutropenia between the two administration schedules.

Crawford et al (51) found that delaying the start of G-CSF treatment to day five provided suboptimal neutrophil recovery; however, this did not result in any differences in the number of episodes of febrile neutropenia among the three schedules. The administration of G-CSF on day three was similar to day one in terms of hematologic recovery. They also found that beginning G-CSF on day three was associated with a decrease in the total dose of G-CSF administered.

In the trial by Kobrinsky et al (54), the times to neutrophil nadir were shorter (13 days v. 15 days; $p=0.0001$) after priming with GM-CSF, however the neutrophil nadir was similar in both groups. The time to platelet nadir was also shorter (10.1 ± 1.9 days v. 11.1 ± 2.2 days; $p<0.05$) and the platelet nadir was higher when compared to the placebo group (166,000/μL v. 151,000/μL; $p=0.007$). The time-to-hemoglobin nadir and the hemoglobin nadir were similar in both groups.

In the trial by Oshita et al (55), the mean neutrophil count nadir was significantly higher in patients receiving G-CSF at the appearance of monocytopenia compared with patients who received G-CSF at the appearance of neutropenia or leukopenia (1,558/μL v. 810/μL; $p=0.032$).

Angietta et al (56) and Juan et al (57) did not detect any statistically significant differences between treatment groups.

In the trial by Fukuda et al (59), the mean neutrophil nadir was significantly higher with CSF on days 8-21 compared with days 2-15 (2465/μl v. 619/μl; p=NR), or when delivered at the onset of neutropenia (2465/μl v. 363/μl; p=NR).

In the trial by Gerhartz et al (61) leukocyte recovery was significantly enhanced with GM-CSF compared with placebo in a dose-dependent manner except for the 22.0 µg/kg dose, which was associated with poor response rates. The middle dose range (5.5 and 11.0 µg/kg) was found to be the most efficient in enhancing the WBC (p=0.004) and the neutrophil (p=0.003) recovery.

Adverse Effects

Adverse effects of G-CSF or GM-CSF were reported in seven of the trials (50-52,54,56,58,60). Mild to moderate bone pain related to G-CSF administration occurred in five patients in the Higa et al study (50). Musculoskeletal pain occurred in 40% of the patients in the study by Crawford et al (51). Major adverse effects attributed to GM-CSF in the Stöger et al study (52) included low grade fever and influenza-like symptoms. GM-CSF was discontinued in four patients in this study due to hypersensitivity reactions and eighteen patients experienced transient erythema and pruritus at the injection site. In the trial by Kobrinsky et al (54), six patients developed anaphylactoid reactions. Headaches, myalgias, itching, tachycardia, heartburn, and dyspepsia were more commonly reported with GM-CSF than with placebo. In the study by Aglietta et al (56), patients in the GM-CSF group experienced adverse events compared with patients in the placebo group (63% v. 38%; p=0.06), and skin rash was significantly more frequent in the GM-CSF group (p=0.02). Dinçol et al (56) reported myalgia (8% v. 18%) and fever (8% v. 0%) in the morning and evening groups respectively. The differences were not significant. Hamm et al (60) reported that injection-site reaction, peripheral edema, asthenia, sensory disturbance, diarrhea, myalgia, musculoskeletal pain, pruritus, and rash occurred more frequently in patients receiving any dosage level of GM-CSF compared to observation.

Table 5. Trials evaluating dose/schedule of G-CSF or GM-CSF.

Study Year (Ref)	Disease Site	# of Pts.	Dose and start day of CSF pre or post Chemotherapy	% pts. with FN or infection	% pts. with neutropenia	Duration of neutropenia days
Soda 1996 (49)	NSCLC	10	No G-CSF support*	24%	94% b	8 bd
		11	G-CSF 2 µg/kg day 2	20%	80% b	3 c†
		11	G-CSF 2 µg/kg day 8	6%	44% a†	0 a†
		11	G-CSF 2 µg/kg at onset of neutropenia	33%	94% b	5 b
Higa 1998 (50)	Solid tumours	25 total	G-CSF 5 µg/kg day 1	NR	NR	0†
			G-CSF 5 µg/kg at onset of neutropenia	NR	NR	3
Crawford 1997(51)	SCLC	14	G-CSF 5 µg/kg day 1	36%	72%‡	3‡
		16	G-CSF 5 µg/kg day 3	38%	75%	3
		15	G-CSF 5 µg/kg day 5	23%	72%	2
Stöger 1998 (52)	Breast	24	No G-CSF	13%	NR	NR
		24	GM-CSF 5 µg/kg days 3-12	21%	NR	NR
		25	GM-CSF 5 µg/kg days 6-3 primer	32%	NR	NR
Langer 1999 (53)	NSCLC	20	G-CSF 5 µg/kg/ days 2-15,23-36	NR	NR	NR
		20	G-CSF 5 µg/kg/ days 6-2 primer, 2-15, 23-36	NR	NR	NR
Kobrinsky 1999 (54)	Breast	10	GM-CSF 250 µg/m^2 days 5-1 primer cycle 1,3	NR	NR	NR
		10	GM-CSF 250 µg/m^2 days 5-1 primer cycle 2,4	NR	NR	NR
Oshita 2000 (55)	Lung	29	G-CSF 2 µg/kg days 6-8 at monocytopenia onset	NR	48%†	1†
		30	G-CSF 2 µg/kg days 6-8 at onset of neutropenia	NR	83%	3
Aglietta 2000 (56)	Hodgkin's	30	No G-CSF (placebo)	NR	NR	NR
		26	GM-CSF 5 µg/kg days 7-4 primer	NR	NR	NR
Juan 2000l (57) abstract	solid tumours	43 total	G-CSF 263 µg/m^2 days 5-14	12%	NR	NR
			G-CSF 131.5 µg/m^2 days 5-14	20%	NR	NR
Dinçol 2000 (58)	soft tissue/ sarcoma	24 total	GM-CSF 5 µg/kg a.m.	64%	NR	5†
			GM-CSF 5 µg/kg p.m.	45%	NR	7
Fukuda 1993 (59) abstract	NSCLC	10	No G-CSF	6%	NR	7
		10	G-CSF 2 µg/kg days 2-15	21%	NR	3
		10	G-CSF 2 µg/kg days 8-21	0%a†	NR	3a†
		10	G-CSF 2 µg/kg at onset on neutropenia	47%b	NR	5b
Hamm 1994 (60)	SCLC	64	No G-CSF	NR	NR	NR
		58	GM-CSF 5 µg/kg days 4-13*	NR	NR	NR
		62	GM-CSF 10 µg/kg days 4-13	NR	NR	NR
		60	GM-CSF 20 µg/kg days 4-13	NR	NR	NR
Gerhartz 1993 (61)	Multiple	60 total	Placebo	NR	NR	NR
			GM-CSF 1.3 µg/kg	NR	NR	NR
			GM-CSF 1.7 µg/kg	NR	NR	NR
			GM-CSF 5.5 µg/kg	NR	NR	NR
			GM-CSF 11 µg/kg	NR	NR	NR
			GM-CSF 22 µg/kg	NR	NR	NR
Janik 2001 (62)	renal cell/ melanoma	28	No GM-CSF	69%	NR	3
		25	GM-CSF 250 µg/m^2 bid day 5 -1 primer	35%†	NR	1†

NOTE: # of Pts. = number of patients in group; FN = febrile neutropenia; NR = not reported.
a,b,c,d Where multiple treatment arms exist, a indicates significant differences compared with treatment arms identified with b, c indicates significant differences compared with treatment arms identified with d.
* denotes comparative treatment group not randomized
† denotes significant differences with $p \leq 0.05$
‡ results reported for the first cycle of chemotherapy.

Interpretive Summary

These small studies have attempted to look at dosing schedules that may help optimize neutrophil recovery or minimize adverse outcomes. The study of Oshita et al (55) suggests that the presence of monocytopenia can be used to determine an optimal starting time for G-CSF. This may also allow for fewer overall doses of CSF administered, which has cost effectiveness benefits, but the monitoring of blood counts to detect the critical time point may be impractical. Delaying the start of CSF to day eight was beneficial in one study (49) but detrimental when started at day 5 in another trial (51). The Fukuda data (59) suggest that some delay in the initiation of CSF to day eight may be beneficial, at least with the type of chemotherapy used in this study but waiting until the development of neutropenia to start CSF may not protect from febrile neutropenia. Priming with CSF pre-

chemotherapy did not appear to be helpful in three studies (52,53,56) but was effective in a third trial (62) and produced non-significant benefits in a fourth trial (54). There was a clinically small but statistically significant benefit for administering GM-CSF in the morning versus the evening (58), but the data are limited and current practice is likely to favour morning administration.

There are insufficient data to support specific recommendations for doses/schedules that differ from those currently recommended by the manufacturers. However, some schedules in which CSF is delayed or abbreviated are promising and could be cost-effective, and so this issue deserves further study.

6. Trials Evaluating the Use of CSF in the Prevention or Treatment of Mucositis

Literature Search Results

The Systemic Treatment DSG located three randomised trials evaluating the effects of G-CSF in preventing mucositis (63-65). The results of these trials are presented below.

Outcomes

In the study by Karthaus et al (63), eight patients with high-grade lymphoma were treated with 32 cycles of chemotherapy containing high-dose methotrexate, which is known to cause severe oral mucositis (grades 1 – 4). Patients were randomly assigned prior to each chemotherapy cycle to receive oral G-CSF 120 µg or placebo four times daily for days 10 to 16 after the start of chemotherapy. World Health Organization (WHO) grades 3/4 mucositis were found in 75% of the cycles in the placebo arm but in only 56% of G-CSF cycles (p=0.058). There were trends in favour of the G-CSF group for healing of erythema and ulceration and improvement of pain and dysphagia, but none of the differences reached statistical significance when compared to the group of patients receiving placebo. The duration of hospitalization was significantly shortened in the G-CSF arm versus the control arm (18.8 days v. 22.2 days; p=0.02). There were fewer febrile events in the group receiving G-CSF compared to the control group, but the difference was not statistically significant.

Hejna et al (64) reported, in abstract form, the results of a randomized trial comparing oral GM-CSF versus povidone-iodine and amphotericin B for the treatment of chemotherapy-induced oral mucositis. Thirty-one patients who developed oral mucositis following chemotherapy with 5-flurouracil were entered into the study. Patients receiving GM-CSF had a significantly shorter duration of oral mucositis when compared to patients receiving the antibacterial regimen (5.3 ± 2.5 v. 8.1 ± 1.5 days; p=0.0008). The required duration of the randomized treatment for mucositis was also shorter in the GM-CSF group (2.8 ± 0.7 v. 6.3 ± 1.1 days; p<0.0001).

Crawford et al (65) randomized patients with newly-diagnosed small-cell lung cancer receiving chemotherapy with cyclophosphamide, etoposide, and doxorubicin to receive either G-CSF (230 $\mu g/m^2$) (n=101) or placebo (n=110) for two weeks following chemotherapy. Patients remained on the blinded study drug until febrile neutropenia occurred. Once patients experienced an episode of febrile neutropenia, they received unblinded G-CSF in subsequent cycles of chemotherapy. During the first cycle of chemotherapy, patients treated with placebo had more episodes of mucositis compared with patients treated with G-CSF (47% v. 28%), corresponding to a relative risk of 1.68 (95% CI, 1.2 to 2.4; p=0.006). Across all cycles of treatment, 70% of patients treated with placebo experienced mucositis compared with 53% of patients treated with G-CSF, corresponding to a relative risk of 1.33 (95% CI, 1.1 to 1.7; p=0.011). For all episodes of mucositis, 79 were grade 1, 73 were grade 2, and 12 were grade 3 among patients randomized to placebo, while 46 were grade 1, 43 were grade 2, and five were grade 3 among patients randomized to G-CSF. The median duration of mucositis over all episodes was eight days in both the placebo and G-CSF arms.

Interpretive Summary

The results of these small studies of oral CSF in the prevention and treatment of mucositis are intriguing, and further trials are needed. No recommendations can be made based on this limited data.

With respect to the Crawford trial (65), use of G-CSF significantly reduced the incidence of mucositis in the first cycle. However, the number of patients developing severe mucositis (≥ grade 3) was small (12 v. 5), and its duration was not reduced. The effects of CSF on mucositis should be further explored in clinical trials using relatively non-myelosuppressive regimens, which are known to cause a high incidence of mucositis.

V. ONGOING TRIALS

Several trials are currently in progress and will likely provide more information on the effect of CSF in various situations. While too numerous to list here, a listing of these trials is available on request or by searching Physician Data Query (PDQ), a bibliographic database provided by the National Library of Medicine. This is accessible on the Internet (http://cnetdb.nci.nih.gov/trialsrch.shtml), or through a health sciences library.

VI. DISEASE SITE GROUP CONSENSUS PROCESS

For Section 1, the results of the meta-analysis confirm the benefits of CSF in reducing the incidence of febrile neutropenia. For this section, the Systemic Treatment DSG also discussed the use of CSF to maintain standard doses of chemotherapy drug regimens where patients are not tolerating them because of neutropenia. This clinical situation is not well informed by the evidence. The argument to use CSF to maintain standard drug doses is indirect and comes from randomized trials in which clinical outcomes have been poorer in patients randomized to receive lower than standard doses compared with conventional doses of chemotherapy. Moreover, there are no trials indicating that the use of CSF to maintain doses in patients who are intolerant actually improves outcome. An alternative hypothesis is that those who do not tolerate standard doses may be the ones who are destined to have a poorer outcome anyway, perhaps because of a larger disease burden. There is no evidence to address this hypothesis either.

Guidelines from the American Society of Clinical Oncology (ASCO) and from the Ontario Drug Benefit (ODB) recommend the use of G-CSF to maintain drug doses in patients with potentially curable tumours who do not tolerate standard-dose chemotherapy because of neutropenia (66,67). Potentially curable patients are defined in the ODB guideline as those patients with testicular cancer, Hodgkin's disease, and pediatric cancers. However, the available evidence does not support this restrictive interpretation. With these caveats, this practice guideline accepts the recommendations of other evidence-based guidelines in the spirit that: i) lack of high quality evidence is an insufficient basis to overturn either a conventional practice or one recommended by another credible guideline, and ii) the hypothesis governing this practice is a reasonable one in light of indirect evidence. However, we support trials that would address the issue specifically.

For Section 2, the available data on the effects of chemotherapy dose intensification supported by CSF on survival showed significantly positive results in four (18,22,26,29) out of fourteen trials (18,22-34). However, a comparison arm of one of the trials also detected a survival benefit for dose intensification without CSF (26). On this basis, the Systemic Treatment DSG felt that the use of CSF to support the delivery of dose-intensified chemotherapy remained experimental.

For Section 3, the available data showed that the use of CSF in established febrile neutropenia produced statistically significant but clinically modest improvements in several measures of recovery from febrile neutropenia. As many patients with febrile neutropenia make a rapid and uncomplicated recovery on intravenous antibiotics, it is unlikely to be cost-effective to use CSF in all cases. Patients not defervescing within 48 hours of starting antibiotics, who remain neutropenic, are at more risk for a complicated and prolonged recovery, and thus might benefit from CSF therapy. However, none of the available trials address this situation. Similarly, as recommended in the guideline produced by ASCO (66), it may also be most reasonable to reserve CSF use for patients with factors predictive of a poor outcome e.g. profound neutropenia (absolute neutrophil count <100/μL),

pneumonia, hypotension, multi-organ dysfunction, or invasive fungal infection. Thus, the Systemic Treatment DSG felt that immediate CSF may be a reasonable option for some patients with febrile neutropenia, but this would depend on the clinical circumstances.

For Section 4, direct comparisons suggested G-CSF and GM-CSF had similar efficacy and did not demonstrate significant differences in side effects. Globally, across all sections of this guideline, the reported incidences of side effects seemed greater in trials using GM-CSF, in contrast with G-CSF, but this comparison is subject to bias. Thus, the Systemic Treatment DSG did not feel it could recommend the use of one specific product.

For Section 5, the available trials evaluated several different approaches to the dose/schedule of CSF. In studies of abbreviated schedules, although neutropenia was more common with short durations of CSF, this did not lead to increased incidences of the clinically most important outcome, i.e., febrile neutropenia. The Systemic Treatment DSG felt that some regimens showed promise, but further study was needed.

For Section 6, there was preliminary evidence from one trial that CSF would help prevent or treat mucositis. However the Systemic Treatment DSG felt there were insufficient data on which to make a recommendation for its use in these settings.

VII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence described above, the Systemic Treatment DSG drafted the following recommendations:

Target Population

These recommendations apply to adult cancer patients with solid tumours receiving myelosuppressive chemotherapy. With the exception of lymphoma, hematologic malignancies are excluded.

Draft Recommendations

Key recommendations

- If a reduction in the number of febrile neutropenic episodes or in the duration of such episodes is expected to improve quality of life, then CSF is a reasonable treatment option in selected patients. A clear justification for the use of CSF should be stated.
- If the objective of using CSF is to maintain the dose intensity of antitumour agents, then CSF can be recommended only where reduction in dose intensity has been shown in randomized controlled trials to reduce survival or disease-free survival.

  Although the evidence is weaker, the Systemic Treatment Disease Site Group (Systemic Treatment DSG) would support the practice endorsed by other guidelines (American Society of Clinical Oncology, Ontario Drug Benefit Plan) and recommend CSF for patients receiving potentially curative chemotherapy:

  i) as primary prophylaxis, that is, when the anticipated risk of febrile neutropenia is greater than 40%, or

  ii) as secondary prophylaxis in patients receiving chemotherapy of established efficacy who have suffered a prior serious episode of febrile neutropenia due to the same chemotherapy regimen or if prolonged neutropenia is causing excessive dose reduction or delay in chemotherapy.

  The exact cut-off for dose reductions is unknown at this time, and ought to be left to the judgement of the clinician. In general, the use of CSF to avoid dose reductions less than 20% is not recommended.
- The use of CSF to support the delivery of dose-intensified chemotherapy regimens can only be recommended in randomized controlled trials evaluating regimens that seek to improve progression/disease-free and/or overall survival.
- For patients with febrile neutropenia or documented sepsis, CSF is a reasonable option if the aim is to reduce the duration of fever, antibiotic use or hospitalization. The efficacy of this therapy may be limited in patients who have received dose-intensive chemotherapy which is associated with a high risk of febrile neutropenia.

Qualifying statements

- Many patients with febrile neutropenia have a rapid and uncomplicated recovery on intravenous antibiotics. Although it may be reasonable to reserve CSF use for patients not achieving a rapid improvement (i.e. not defervescing within 48 hours on broad spectrum antibiotics or antibiotic therapy based on sensitivity of cultured organism), none of the reported trials assess the use of CSF delayed in this way. Similarly, as recommended in the guidelines produced by the American Society of Clinical Oncology, it may also be most reasonable to reserve CSF use for patients with factors predictive of a poor outcome e.g. profound neutropenia (absolute neutrophil count <100/μL), pneumonia, hypotension, multi-organ dysfunction and invasive fungal infection.
- It is not possible to make a firm recommendation for the use of one specific type of CSF. More data are available for G-CSF, which seems to have fewer toxicities than GM-CSF, but further comparative studies of both agents are warranted.
- There are insufficient data to support specific recommendations for doses/schedules of CSF that differ from those currently recommended by the manufacturer. However, some schedules in which CSF is delayed or abbreviated are promising and could be cost-effective. Therefore, this issue deserves further study.

Future Research

- It is strongly recommended that patients treated with myelosuppressive therapy be enrolled in randomized controlled trials of CSF designed to better evaluate the effect of treatment on quality of life and health care costs.
- There are insufficient data to support specific recommendations for doses/schedules that differ from those currently recommended by the manufacturers. However, some schedules in which CSF is delayed or abbreviated are promising, and so this issue deserves further study.

Related Guidelines

For a related guideline, refer to Practice Guidelines Initiative's Practice Guideline #6-5: *The Use of G-CSF for Patients Undergoing Bone Marrow and Stem Cell Transplantation.*

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 138 medical oncologists in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Systemic Treatment DSG reviewed the results of the survey.

Results

Seventy-five responses were received out of the 138 surveys sent (54% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 60 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 6.

Table 6. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	59 (98)	1 (2)	0
There is a need for a clinical practice guideline on this topic.	59 (98)	1 (2)	0
The literature search is relevant and complete.	55 (92)	3 (5)	2 (3)
The results of the trials described in the report are interpreted according to my understanding of the data.	54 (90)	5 (8)	1 (2)
The draft recommendations in this report are clear.	43 (72)	11 (18)	6 (10)
I agree with the draft recommendations as stated.	47 (78)	6 (10)	7 (12)
This report should be approved as a practice guideline.*	45 (75)	9 (15)	5 (8)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?*	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	47 (78)	7 (12)	5 (8)

* Data from one responding practitioner is missing.

Summary of Written Comments

Twenty-eight respondents (47%) provided written comments. The main points contained in the comments were:

1. Many of the responding practitioners who provided comments indicated that they found the draft guideline recommendations vague and ambiguous.
2. Some practitioners questioned the evidence for the statement in the Key Recommendations recommending CSF as primary prophylaxis when the anticipated risk of febrile neutropenia is greater than 40%.
3. Some physicians questioned the evidence behind the statement in the Key Recommendations regarding the use of CSF to avoid dose reductions less than 20%.
4. One practitioner indicated that the proceedings from the meetings of the American Society of Hematology (ASH) should be searched because lymphoma patients have been included.
5. One practitioner indicated that mention should be made of two additional Hematology DSG practice guidelines that are currently in-progress: Practice Guideline #6-7, *The use of chemotherapy and growth factors in older patients with newly diagnosed aggressive histology non-Hodgkin's lymphoma* and Practice Guideline #6-13, *G-CSF/erythropoietin in myelodysplasia*.
6. One practitioner wondered why studies of CSF and stem cell rescue were not commented on.
7. One practitioner indicated that they would be interested in recommendations for CSF in acute myeloid leukemia.
8. One practitioner commented that patients 65 to 70 years of age should also be given G-CSF to avoid toxicity and prolonged hospitalization after chemotherapy.
9. One practitioner commented that it is illogical to conclude that, simply because an "across-the-board" administration of lower-dose chemotherapy gives inferior results, dose reduction in selected patients who develop febrile neutropenia with standard doses is also suboptimal. Overly sensitive patients likely metabolize the drugs in a way that exposes them to a higher effective dose level.

Modifications/Actions

1. Three out of four of the original Recommendations bullets have been modified in an effort to clarify and provide guidance to practitioners. In addition, two additional bullets were added to the Recommendations.
2. This statement came from cost analysis studies not specific to the Canadian health care system. This has been noted in the Qualifying Statements.
3. This statement has been revised to state that it is not possible to define a cut-off point for acceptable dose reductions or delays before introducing CSF.
4. A search of the ASH proceedings was included in the literature search strategy.
5. These guideline titles have been added to the Related Guidelines section in the summary and the full report.
6. No modifications were made to the practice guideline to address this comment. Stem cell rescue studies are listed in the exclusion criteria.
7. No modifications were made to the document to address this comment. This topic would be better addressed by the Hematology DSG.
8. No modifications were made. The recommendations apply to all adult cancer patients.
9. To address this comment, this statement was removed from the Interpretive Summary.

Practice Guidelines Coordinating Committee Approval Process

This Practice Guideline Report was circulated to 13 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eleven members of the PGCC returned ballots. Ten PGCC members approved the practice guideline report as written. Of the ten members, two members approved the practice guideline conditional on the following changes. A rationale for pooling versus not pooling the data was requested; it was suggested that more outcomes be placed into tables as opposed to text; references to the originally published practice guideline were confusing; the reference to non-Ontario based economics was questioned as it was unclear of the value or interpretability of the data; it was requested that two questions (1,3) and two recommendations (2,3) be slightly re-worded for greater clarity.

Modifications/Actions

Based on the comments of the members of the PGCC, the Systemic Treatment DSG modified the practice guideline report to address the above issues. As a result, the following changes to the text of the practice guideline were made:

1. The justification for pooling or not pooling was revised to provide greater clarity for readers.
2. Where possible, text was shortened and the use of tables was employed throughout the document.
3. To avoid confusion, references to the original guideline recommendations were removed. This is in accordance with the current formatting style of the PGI, which is to re-write original guidelines as completely new documents.
4. The non-Canadian based economic data was introduced in response to Practitioner Feedback (comment number two). The DSG discussed whether the indirect evidence should be used and concluded that it was deemed important to provide a frame of reference for establishing an acceptable point in which it would be reasonable to use CSF as primary prophylaxis. The First bullet in the Qualifying Statement was modified such that less emphasis was placed on the economic data.
5. Two questions (1,3) and two recommendations (2,3) were revised to provide greater clarity to readers.

VIII. IMPLICATIONS FOR POLICY

A number of economic analyses of the use of CSF have been published (68-76). As none of these studies were performed in Canada, their relevance to the Canadian health care system is limited. Two studies have suggested that primary prophylaxis with CSF is justified when the anticipated risk of febrile neutropenia is greater than 25-40% (62,73), which is not the case with the majority of standard chemotherapy regimens for solid tumours. Further research is needed to determine the impact of CSF on Canadian health care resources. This should include an assessment of the threshold at which it is cost-effective to utilize CSF relative to the baseline risk of hospitalization for specific malignant neoplasms and according to various chemotherapy regimens. However, ultimately, it would be the responsibility of policy makers in the provincial jurisdiction to define economic questions relevant to the Canadian health care system. Drug acquisition costs in Canada for CSF are shown in Table 7.

Table 7. Acquisition costs per cycle of treatment.

CSF	Dose Schedule	# Vials Needed	Cost per vial	Cost per cycle
G-CSF*	5 µg/kg/d for 10 days	10	$144.54 (CAD)	$1589.94 (CAD)
GM-CSF†	250 ug/m^2/d for 10 days	10	$230.87 (US)	$2539.57 (US)

* Costs are in Canadian dollars. The example of a 70 kg patient is used.
† Costs are in American dollars. The example of a 1.7 m^2 person is used.

IX. PRACTICE GUIDELINE

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process.

Target Population

These recommendations apply to adult cancer patients with solid tumours receiving myelosuppressive chemotherapy. With the exception of lymphoma, hematologic malignancies are excluded.

Recommendations

1. In the setting of standard-dose chemotherapy for solid tumours the risk of neutropenic fever is insufficient to justify routine use of CSF as primary prophylaxis. If a patient experiences an episode of febrile neutropenia or prolonged neutropenia, dose reductions and/or delays of chemotherapy remain the standard initial approach. It is reasonable to use CSF to avoid multiple dose reductions or delays in circumstances where randomized controlled trials have shown improved survival with maintenance of dose intensity.
2. The use of CSF to support the delivery of dose-intensified chemotherapy regimens can only be recommended in the context of randomized controlled trials evaluating regimens that seek to improve progression-free, disease-free, and/or overall survival.
3. Although data are limited, it is reasonable to use CSF to decrease duration of fever, antibiotic use, or hospitalization in patients with febrile neutropenia. Further studies are warranted to establish specific recommendations in this situation.
4. It is not possible to make firm recommendations for specific type of CSF. More data are available for G-CSF, but further comparative studies of both agents are warranted.
5. There are insufficient data to support specific recommendations for dose/schedules of CSF that differ from those currently recommended by the manufacturer. However, some schedules in which CSF is delayed or abbreviated are promising and could be cost-effective. Therefore, this issue deserves further study.
6. There is preliminary evidence that CSF helps prevent or treat mucositis. However, the Systemic Treatment DSG felt there were insufficient data on which to make a recommendation for its use in these settings.

Qualifying Statements

- It is reasonable to suggest that primary prophylaxis with CSF is justified when the anticipated risk of febrile neutropenia is greater than 25-40%. However, such risks are rare with the majority of standard chemotherapy regimens for solid tumours, and evidence comes from cost analysis studies not specific to the Canadian health care system (62,73).

  CSF reduces the risk of febrile neutropenia associated with standard-dose chemotherapy; however, data are inconclusive as to whether quality of life is significantly improved by its use. Although reduced hospitalization and antibiotic use may be assumed to improve quality of life, dose maintenance with CSF may allow other significant toxicities to emerge (e.g., mucositis, anemia, thrombocytopenia, neuropathies), which can reduce quality of life. The inconvenience of daily injections of CSF and the cost are additional considerations if the risk of neutropenic fever is low.

  Since many patients still derive clinical benefit from commonly allowed chemotherapy dose reduction/delay, given the available data, it is not possible to define a cut-off point for acceptable dose reduction/delay before introducing CSF as secondary prophylaxis.
- Many patients with febrile neutropenia have a rapid and uncomplicated recovery on intravenous antibiotics. Although it may be reasonable to reserve CSF use for patients not achieving a rapid improvement (i.e., not defervescing within 48 hours on broad spectrum antibiotics or antibiotic therapy based on the sensitivity of the cultured organism), none of the reported trials assessed the use of CSF delayed in this way. Similarly, as recommended in the guidelines produced by the American Society of Clinical Oncology, it may also be most reasonable to reserve CSF for patients with factors predictive of a poor outcome, e.g., profound neutropenia (absolute neutrophil count <100/μL), pneumonia, hypotension, multi-organ dysfunction, or invasive fungal infection.

  The efficacy of CSF may be limited in patients with febrile neutropenia or documented sepsis who have received dose-intensive chemotherapy, which is associated with a high risk of febrile neutropenia.

Future Research

- It is strongly recommended that patients treated with myelosuppressive therapy be enrolled in randomized controlled trials of CSF designed to better evaluate the effect of treatment on quality of life and health care costs.
- There are insufficient data to support specific recommendations for dose/schedules that differ from those currently recommended by the manufacturers. However, some schedules in which CSF is delayed or abbreviated are promising, and so this issue deserves further study.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Reports:

- #6-5: *The use of G-CSF for patients undergoing bone marrow and stem cell transplantation*
- #6-7: *The use of chemotherapy and growth factors in older patients with newly diagnosed aggressive histology non-Hodgkin's lymphoma*
- #6-13: *G-CSF/erythropoietin in myelodysplasia*.

Please note that these reports are in progress and are not yet available on the Web site.

X. JOURNAL REFERENCE

Campbell C, Bramwell V, Charette M, Oliver T. Role of colony-stimulating factor in patients receiving myelosuppressive chemotherapy for treatment of cancer. *Curr Oncol* 2003;10(2):102-26.

XI. ACKNOWLEDGEMENTS

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For a full list of members of the Systemic Treatment Disease Site Group and the Practice Guidelines Coordinating Committee, please visit the CCO Web site at http://www.cancercare.on.ca/access_PEBC.htm.

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Appendix 1. Administration and dosage schedules of randomized controlled trials comparing CSF to control or placebo that used the same starting dose of chemotherapy.

Study	Dosage schedule
Crawford 1991 (3)	**CAE:** cyclophosphamide 1000mg/m^2, day 1; doxorubicin 50 mg/m^2, day 1; etoposide 120 mg/m^2, days 1-3. G-CSF 230 µg/m^2 s.c. daily versus **CAE** + placebo.
Pettengell 1992 (4)	**VAPEC-B:** doxorubicin 35 mg/m^2 i.v.; cyclophosphamide 350 mg/m^2 i.v.; vincristine 1.4 mg/m^2 i.v.; bleomycin 10 mg/m^2 i.v.; toposide 100 mg/m^2 po daily for 5 days; prednisolone 50 mg daily for 5 weeks; cotrimoxazole 960 mg b.i.d.; ketoconazole 200 mg b.i.d. G-CSF 230 µg/m^2 s.c. daily for 13 weeks versus **VAPEC-B.**
Trillet-Lenoir 1993 (5)	**CDE:** cyclophosphamide 1 g/m^2 on day 1; doxorubicin 50 mg/m^2 on day 1; etoposide 120 mg/m^2 days 1-3, for up to 6, 21 day cycles. G-CSF 230 µg/m^2 s.c. daily for a maximum 14 days during each cycle versus **CDE** + placebo.
Nguyen Bui 1995 (6)	**MAID:** doxorubicin 60 mg/m^2; ifosfamide 7.5 g/m^2; dacarbazine 900 mg/m^2, days 1 to 3. G-CSF 5 µg/kg/d s.c., days 4 to 13 versus **MAID** + placebo.
Chevallier 1995 (7)	**FEC:** fluorouracil 750 mg/m^2 (CI.V.), days 1 to 4; epirubicin 35 mg/m^2, day 2 to 4; cyclophosphamide 400 mg/m^2, days 2 to 4 for 4 cycles. G-CSF 5 µg/kg/d s.c., day 6 to 15. Radiotherapy 60 Gy to the tumour, the whole breast and the axilla, 50 Gy to the internal mammary chain, and 46 Gy to the supra clavicular area; 10 Gy/wk in 5 fractions. Epirubicin 75 mg/m^2, fluorouracil 500 mg/m^2, cyclophosphamide 500 mg/m^2; 4 cycles q 4 weeks versus **FEC** + placebo + radiation.
Wollt 1995 (8)	**VICE:** carboplatin 300 mg/m^2 over 1 hour I.V. on day 1; ifosfamide 5 g/m^2 with mesna 5g/m^2 over 24 hours I.V. on day 1; etoposide 120 mg/m^2 over 1 hour I.V. on days 1 and 2; etoposide 240 mg/m^2 on day 3; vincristine 1 mg I.V. on day 15 (VICE). G-CSF 5 µg/kg s.c. daily. 6 cycles + prophylactic cranial irradiation 8 Gy, day 5 or 7 of 1st chemotherapy cycle. Thoracic irradiation 12.5 Gy, day 5 or 7 of 3rd chemotherapy cycle versus **VICE** + radiation.
Jones 1996 (9)	**FAC:** fluorouracil 600 mg/m^2; doxorubicin 60 mg/m^2; cyclophosphamide 750 mg/m^2 day 1 + placebo 250 µg/m^2 s.c. days 3-15 versus **FAC** + GM-CSF 250 µg/m^2 s.c. days 3-15.
Muhonen 1996 (10)	**MMM:** mitomycin 8 mg/m^2/day; mitoxantrone 8 mg/m^2, days 1 and 22; methotrexate 35 mg/m^2 days 1 and 22. Repeated every 42 days, for maximum of 6 courses. G-CSF 5 µg/kg s.c., days 4 to 17 and 24 to 37 versus **MMM.**
Fridrik 1997 (11)	**CEOP/IMVP-Dexa:** cyclophosphamide 750 m/m^2 i.v. day 1; epirubicin 70 mg/m^2 i.v. day 1; vincristine 1.4 mg/m^2 i.v. days 1 and 8; prednisolone 100 mg orally days 1-5; ifosfamide 2000 mg/m^2 i.v. days 15-17; uromitexane 400 mg/m^2 i.v. days 15-17; VP-16 100 mg/m^2 i.v. days 15-17; dexamethasone 40 mg orally days 15-19; methotrexate 800 mg/m^2 i.v. day 22; Ca-folinate 15 mg/m^2 orally days 23-25.G-CSF 5 µg/kg daily s.c. days 2-7, 9-12, 18-21, 23-27 versus **CEOP/IMVP-Dexa**
Gisselbrecht 1997 (12)	**ACVB**: cyclophosphamide 1200 mg/m^2 i.v. day 1; vindesine 2 mg/m^2 i.v. days 1 and 5; bleomycin 10 mg i.v. days 1 and 5; prednisone 60 mg/m^2 orally days 1-5; intrathecal methotrexate 15 mg day 1; doxorubicin 75 mg/m^2 i.v. day 1. G-CSF 5 µg/kg/d s.c. days 6-13 versus **ACVB** + placebo days 6-13 versus **NCVB**: chemotherapy regimen as above, with mitoxantrone 12 mg/m2 i.v. day 1 substituted for doxorubicin + G-CSF 5 µg/kg/d s.c. days 6-13 versus **NCVB** + placebo days 6-13.
Negoro 1997 (13)	**CODE:** cisplatin 25 mg/m^2 weekly for 9 weeks; vincristine 1 mg/m^2 weeks 1,2,4,6,8; doxorubicin 40 mg/m^2 for 3 days during weeks 1,3,5,7,9; etoposide 80 mg/m^2 for 3 days during weeks 1,3,5,7,9. G-CSF 50 µg/m^2 daily s.c. except on treatment days versus **CODE**
Zinzani 1997 (14)	**VNCOP-B:** cyclophosphamide 300 mg/m^2 i.v. weeks 1,3,5,7; mitoxantrone 10 mg/m^2 i.v. weeks 1,3,5,7; vincristine 2 mg i.v. weeks 2,4,6,8; etoposide 150 mg/m^2 i.v. weeks 2,6; bleomycin 10 mg/m^2 i.v. weeks 4,8; prednisone 40 mg daily intramuscular, dose tapered over the last 2 weeks versus **VNCOP-B** + G-CSF 5 µg/kg daily s.c. starting on day 3 of every week for 5 consecutive days.
Dunlop 1998 (15)	**MOPP:** mustine 6 mg/m^2 i.v. days 1 and 8; vincristine 1.4 mg/m^2 i.v. days 1 and 8; procarbazine 100 mg/m^2 orally days 1-14; prednisolone 25 mg/m^2 orally days 1-14 versus **MOPP** + G-CSF 5 µg/kg daily s.c. days 15 – 28 versus **MOPP/EVAP:** mustine 6 mg/m^2 i.v. day 1; vincristine 1.4 mg/m^2 i.v. day 1; procarbazine 100 mg/m^2 orally days 1-7; prednisolone 25 mg/m^2 orally days 1-14; etoposide 75 mg/m^2 i.v. days 8-10; doxorubicin 25 mg/m^2 day 8; vinblastine 6 mg/m^2 day 8 versus **MOPP/EVAP** + G-CSF 5 µg/kg daily s.c. days 11 – 28.
Fosså 1998 (16)	**BEP/EP:** 4 three-weekly cycles of cisplatin 20 mg/m^2 days 1-5; etoposide 100 mg/m^2 days 1-5; bleomycin 30 U days 2,9,16; followed by 2 three-weekly cycles of EP (BEP without bleomycin) versus **BEP/EP** + G-CSF 5 µg/kg daily s.c. days 6-19. **BOP/VIP-B:** 3 cycles every 10 days of bleomycin 30 U days 1 and 2; vincristine 2 mg days 1 and 2; cisplatin 50 mg/m^2 days 1 and 2; followed by 3 cycles every 21 days of cisplatin 20 mg/m^2 days 1-5; ifosfamide 1000 mg/m^2 days 1-5; etoposide 100 mg/m^2 days 1,3,5; bleomycin 30 U days 8 and 15 versus **BOP/VIP-B** + G-CSF 5 µg/kg daily s.c. days 6-19 for VIP-B cycle and days 3-9 for BOP cycle.
Hidalgo 1998 (17)	**CCP:** cyclophosphamide 750 mg/m^2 day 1; carboplatin 350 mg/m^2 day 1; cisplatin 75 mg/m^2 day 14 versus **CCP** + G-CSF 5 µg/kg daily s.c. days 2-13.
Steward 1998 (18)	**V-ICE:** carboplatin 300 mg/m^2 i.v. day 1; etoposide 120 mg/m^2 i.v. days 1,2 240 mg/m^2 orally day 3; ifosfamide 5 g/m^2; mesna 5 g/m^2; vincristine 0.5 mg/m^2 i.v. day 15. Chemotherapy every 28 days. Placebo 250 µg/m^2 s.c. for 14 days between chemotherapy cycles versus **V-ICE** + GM-CSF 250 µg/m^2 s.c. for 14 days between chemotherapy cycles versus **V-ICE** every 22 days + placebo 250 µg/m^2 s.c. for 14 days between chemotherapy cycles versus **V-ICE** every 22 days + GM-CSF 250 µg/m^2 s.c. for 14 days between chemotherapy cycles.
Schröder 1999 (19)	**CEF+CMF**: three courses of cyclophosphamide 1500 mg/m^2 i.v. day 1; epirubicin 80 mg/m^2 i.v. day 1; 5-fluorouracil 1500 or 1000 mg/m^2 i.v. day 1; followed by three courses of cyclophosphamide 1500 mg/m^2 i.v. day 1; 5-fluorouracil 600 mg/m^2 i.v. day 1; methotrexate 1500 mg/m^2 i.v. day 2.G-CSF 263 µg s.c. days 3-12 versus **CEF + CMF + CAB:** oral ciprofloxacin 250 mg twice daily days 3-17; oral amphotericin B 5 ml four times daily days 3-17.
Miles 1994 (20)	**CEDI:** Twelve weekly courses of: cisplatin 50 mg/m2 i.v. day 1; etoposide 75 mg/m2 i.v. days 1 and 2; alternating weekly with ifosfamide 2 g/m2 i.v. day1; doxorubicin 25 mg/m2 i.v. day 1; G-CSF 5 µg/kg s.c. for 5 days after the cisplatin/etoposide cycles, and 6 days after the ifosfamide/doxorubicin cycle versus as above, without G-CSF.
Gatzemeier 2000 (21)	**ACE:** etoposide 100 mg/m^2 i.v. day 1, 240 mg/m^2 orally or 100 mg/m^2 i.v. days 2,3; cyclophosphamide 1000 mg/m^2 i.v. day 1; doxorubicin 45 mg/m^2 i.v. day 1. Chemotherapy repeated every 3 weeks for 6 cycles versus **ACE** + G-CSF 150 µg/m^2 s.c. days 4-13.

*neutropenia defined as neutrophil count <1000/µ; i.v. = intravenously; s.c. = subcutaneously.

Appendix 2. Glossary of chemotherapy abbreviations/acronyms.

ACE	etoposide, cyclophosphamide, doxorubicin
ACVB	cyclophosphamide, vindesine, belomycin, prednisone, intrathecal methotrexate, doxorubicin, G-CSF
BEACOPP	cyclophosphamide, vincristine, etoposide, procarbazine, prednisone, doxorubicin, bleomycin
BEP/EP	cisplatin, etoposide, bleomycin/cisplatin etoposide
BOP/VIP-B	bleomycin, vincristine, cisplatin/cisplatin ifosfamide, etoposide, bleomycin
CAE	cyclophosphamide, doxorubicin, etoposide
CCP	cyclophosphamide, carboplatin, cisplatin
CDE	cyclophosphamide, doxorubicin, etoposide
CEDI	cisplatin, etoposide, ifosfamide, doxorubicin
CEF	cyclophosphamide, epirubicin, fluorouracil
CEF+CMF	cyclophosphamide, epirubicin, 5-fluorouracil + cyclophosphamide, 5-fluorouracil, methotrexate
CEF+CMF+CAB	cyclophosphamide, epirubicin, 5-fluorouracil + cyclophosphamide, 5-fluorouracil, methotrexate, G-CSF, oral ciprofloxacin, oral amphotericin
CEOP/IMVP-Dexa	cyclophosphamide, epirubicin, vincristine, prednisolone, ifosfamide, uromitexane, dexamethasone, methotresate, Ca-folinate
CODE	cisplatin, vincristine, doxorubicin, etoposide
Dexa-BEAM	dexamethasone, carmustine, melphalane, cytosin arabinoside, etoposide
FAC	fluorouracil, doxorubicin, cyclophosphamide
FEC	5-fluorouracil or fluorouracil, epirubicin, cyclophosphamide
I-MEC	methotrexate, epirubicin, cisplatin
MAID	doxorubicin, ifosfamide, dacarbazine
MMM	mitomycin, mitoxantrone, methotrexate
MOPP	mustine, vincristine, procarbazine, prednisolone
MOPP/EVAP	mustine, vincristine, procarbazine, prednisolone, etoposide, doxorubicin, vinblastine
MVAC	methotrexate, vinblastine, doxorubicin, cisplatin
NCVB	cyclophosphamide, vindesine, belomycin, predisone, intrathecal methotrexate, mitoxantrone
PE	cisplatin, etoposide
PVM	cisplatin, vindesine, mitomycin
MEC	methotrexate, epirubicin, cisplatin
VAPEC-B	doxorubicin, cyclophosphamide, vincristine, bleomycin, etoposide, prednisolone, cotrimoxazole, ketoconazole
VICE	carboplatin, ifosfamide, etoposide, vincristine
VNCOP-B	cyclophosphamide, mitoxantrone, vincristine, etoposide, belomycin, prednisone

Appendix 3. Chemotherapy administration and dosage schedules of dose intensity trials.

Study	Treatment Description
Steward 1998 (18)	**V-ICE:** carboplatin 300 mg/m^2 IV day 1; etoposide 120 mg/m^2 IV days 1,2 240 mg/m^2 orally day 3; ifosfamide 5 g/m^2; mesna 5 g/m^2; vincristine 0.5 mg/m^2 IV day 15. Chemotherapy every 28 days. Placebo 250 µg/m^2 s.c. for 14 days between chemotherapy cycles. **V-ICE.** GM-CSF 250 µg/m^2 s.c. for 14 days between chemotherapy cycles. **V-ICE** every 22 days. Placebo 250 µg/m^2 s.c. for 14 days between chemotherapy cycles. **V-ICE** every 22 days. GM-CSF 250 µg/m^2 s.c. for 14 days between chemotherapy cycles.
Pujol 1997 (22)	Epirubicin 40 mg/m^2 day 1; cyclophosphamide 400 mg/m^2 days 1-3; cisplatin 100 mg/m^2 day 2; etoposide 75 mg/m^2 days 1-3. Epirubicin 60 mg/m^2 day 1; cyclophosphamide 600 mg/m^2 days 1-3; cisplatin 120 mg/m^2 day 2; etoposide 110 mg/m^2 days 1-3. GM-CSF 5 µg/kg s.c. days 4-13.
Font 1999 (23)	**PE:** cisplatin 35 mg/m^2 days 1-3; etoposide 200 mg/m^2 days 1-3. Chemotherapy administered every 4 weeks. **PE** every 3 weeks. GM-CSF 5 µg/kg s.c. days 4-13.
Kuroda 1998 (24)	**S-MEC:** methotrexate 30 mg/m^2 days 1,15; epirubicin 50 mg/m^2 day 1; cisplatin 100 mg/m^2 day 2. **I-MEC:** methotrexate 36 mg/m^2 days 1,15; epirubicin 60 mg/m^2 day 1; cisplatin 120 mg/m^2 day 2. G-CSF 2 µg/kg days 3-12.
Diehl 1998 (25)	**BEACOPP:** cyclophosphamide 650 mg/m^2 i.v. day 1; vincristine 1.4 mg/m^2 i.v. day 1; etoposide 100 mg/m^2 i.v. days 1-3; procarbazine 100 mg/m^2 orally days 1-7; prednisone 40 mg/m^2 orally days 1-14; doxorubicin 25 mg/m^2 i.v. day 1; bleomycin 10 mg/m^2 i.v. day 8. **Intensified BEACOPP:** cyclophosphamide 1250 mg/m^2 i.v. day 1; vincristine 1.4 mg/m^2 i.v. day 1; etoposide 200 mg/m^2 i.v. days 1-3; procarbazine 100 mg/m^2 orally days 1-7; prednisone 40 mg/m^2 orally days 1-14; doxorubicin 35 mg/m^2 i.v. day 1; bleomycin 10 mg/m^2 i.v. day 8. G-CSF 300 µg or 480 µg s.c. day 8 until leukocyte recovery.
Masutani 1999 (26)	**PVM:** Cisplatin 80 mg/m^2 day 1; vindesine 3 mg/m^2 days 1,8; mitomycin C 8 mg/m^2 day 1. Chemotherapy administered every 4 weeks for 2 cycles. **PVM** every 3 weeks for 3 cycles. G-CSF 2 µg/kg s.c. when blood cell count ≤ 2000/µl.
Riccardi 2000 (27)	**FEC:** 5-fluorouracil 600 mg/m^2 i.v. day 1; cyclophosphamide 600 mg/m^2 i.v. day 1; epirubicin 60 mg/m^2 i.v. day 1. **FEC:** 5-fluorouracil 600 mg/m^2 i.v. day 1; cyclophosphamide 600 mg/m^2 i.v. day 1; epirubicin 120 mg/m^2 i.v. day 1. G-CSF 5 mg/kg/day s.c. days 4-13.
Bonomi 1997 (28)	Paclitaxel 135 mg/m^2 i.v. day 1; cisplatin 75 mg/m^2 i.v. day 2. Paclitaxel 250 mg/m^2 i.v. day 1; cisplatin 75 mg/m^2 i.v. day 2. G-CSF 5 µg/kg orally day 3 until granulocyte count > 10,000/cells/mm^3.
Thatcher 2000 (29)	**ACE:** doxorubicin 40 mg/m^2 i.v. day 1; cyclophosphamide 1 g/m^2 i.v. day 1; etoposide 120 mg/m^2 i.v. day 1, 240 mg/m^2 orally days 2,3. Chemotherapy administered every 2 weeks for 6 cycles. G-CSF 263 µg s.c. days 4-14. **ACE** chemotherapy every 3 weeks for 6 cycles.
Le Cesne 2000 (30)	Doxorubicin 50 mg/m^2 i.v. day 1; ifosfamide 5 g/m^2 i.v. day 1. Chemotherapy administered every 3 weeks. Doxorubicin 75 mg/m^2 i.v. day 1; ifosfamide 5 g/m^2 i.v. day 1. Chemotherapy administered every 3 weeks. GM-CSF 250 µg/m^2 s.c. days 3-16.
Pfreundschuh 2001 (31)	**Dexa-BEAM**: dexamethasone 8 mg orally three times daily days 1-10; carmustine 60 mg/m^2 day 2; melphalane 20 mg/m^2 day 3; cytosin arabinoside 100 mg/m^2 every 12 hours days 4-7; etoposide days 4-7 75 mg/m^2 (level 1), 100 mg/m^2 (level 2), 150 mg/m^2 (level 3), 250 mg/m^2 (level 4), 250 mg/m^2 (level 5), 300 mg/m^2 (level 6), 400 mg/m^2 (level 7), 500 mg/m^2 (level 8). Placebo 250 µg/m^2 s.c. day 8 until neutrophil recovery. **Dexa-BEAM** as above with GM-CSF 250 µg/m^2 s.c. day 8 until neutrophil recovery.
Del Mastro 2001 (32)	**CEF:** Cyclophosphamide 600 mg/m^2 i.v. day 1; epirubicin 60 mg/m^2 i.v. day 1; fluorouracil 600 mg/m^2 i.v. day 1. Chemotherapy administered every 3 weeks. **CEF:** Cyclophosphamide 1,000 mg/m^2 i.v. day 1; epirubicin 80 mg/m^2 i.v. day 1; fluorouracil 600 mg/m^2 i.v. day 1. Chemotherapy administered every 2 weeks. G-CSF 263 µg/day days 4-11.
Forastiere 2001 (33)	Paclitaxel 135 mg/m^2 i.v. (24 hours); cisplatin 75 mg/m^2. Chemotherapy administered every 3 weeks. Paclitaxel 200 mg/m^2 i.v. (24 hours); cisplatin 75 mg/m^2. Chemotherapy administered every 3 weeks. G-CSF 5 µg/kg/d s.c. from day 3.
Sternberg 2001 (34)	**MVAC:** methotrexate 30 mg/m^2 days 1,15,22; vinblastine 3 mg/m^2 days 2,15,22; doxorubicin 30 mg/m^2 day 2; cisplatin 70 mg/m^2 day 2. Chemotherapy administered every 4 weeks. **MVAC:** methotrexate 30 mg/m^2 day 1; vinblastine 3 mg/m^2 day 2; doxorubicin 30 mg/m^2 day 2; cisplatin 70 mg/m^2 day 2. Chemotherapy administered every 2 weeks. G-CSF 240 µg/m^2 s.c. days 4-10.

i.v. = intravenously; s.c. = subcutaneously.