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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  $<100/\mu\text{L}$ ), 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 amphotericin 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.

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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.<sup>1</sup> 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:

<sup>1</sup> 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.

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