Granulocyte colony stimulating factor (G-CSF) (addition) – EML and EMLc

The application requested the inclusion of granulocyte-colony stimulating factor (G-CSF) on the EML and EMLc as supportive treatment alongside myelosuppressive chemotherapy regimens for numerous cancers.

Many antineoplastic agents are cytotoxic to bone marrow and prevent development of the granulocytes necessary to fight infection, resulting in neutropenia. Fever may be the only sign of infection in neutropenic patients, and infection may progress rapidly to sepsis and death if empirical antibiotics are not given. Febrile neutropenia is a medical emergency that gives rise to a substantial increase in morbidity, mortality, hospitalizations and cost of care. In the absence of medicines to stimulate proliferation of granulocytes, physicians must reduce the dose or delay the timing of chemotherapy.

G-CSF is a glycoprotein that stimulates the bone marrow to produce granulocytes and promotes granulocyte survival, proliferation and differentiation. When used as primary prophylaxis (initiated early in the first cycle of chemotherapy and continued through subsequent cycles), G-CSF has been shown to reduce the risk of febrile neutropenia and of infection-related and early all-cause mortality, while also reducing the need for dose reduction or delays in treatment delivery (1, 2).

The Expert Committee noted that American Society of Clinical Oncology (ASCO) guidelines, reviewed and updated in 2005, recommend G-CSF for primary prophylaxis when the risk of febrile neutropenia, secondary to a recommended chemotherapy regimen, is approximately 20% and no alternative, but equal, chemotherapy regimen that does not require G-CSF is available (3).

Because of the high cost, the Expert Committee agreed that use of G-CSF is justified only in patients deemed to be at high risk for developing febrile neutropenia. A patient’s risk is based both on risks inherent in the myelosuppression induced by specific chemotherapy regimens and on individual health factors. The following clinical factors are associated with a higher risk of developing severe complications from prolonged neutropenia (3):

- age greater than 65 years
- poor performance status
- prior episodes of febrile neutropenia
- extensive prior treatment, including large radiation ports
- administration of combined chemotherapy
- cytopenias due to bone marrow involvement by tumour
- poor nutritional status
- presence of open wounds or active infections
- more advanced cancer
- other serious comorbidities.
The Committee accepted that the prevalence of some of these factors may be increased in low-resource settings, when the consequences of febrile neutropenia may be even more striking.

Kuderer et al. conducted a systematic review of 17 randomized controlled trials comparing primary G-CSF prophylaxis with placebo or untreated controls in 3493 adult patients with solid tumours and malignant lymphoma (1). The review found that, compared with controls, patients treated with G-CSF had a 45% lower risk of infection-related mortality (relative risk (RR) 0.55; 95% CI: 0.33–0.90; \( P = 0.018 \)). Similarly, G-CSF treated patients had a 40% lower risk for all-cause mortality during the chemotherapy period (RR = 0.60; 95% CI: 0.43–0.83; \( P = 0.002 \)) and a 46% lower risk of febrile neutropenia (RR 0.54; 95% CI: 0.43–0.67; \( P < 0.01 \)). Significant reductions in febrile neutropenia were also observed in studies that allowed secondary G-CSF prophylaxis in controls.

In the secondary prophylaxis setting, the Expert Committee noted that, for patients who have experienced neutropenic complications from a prior cycle of chemotherapy, and for whom dose reduction or delay might result in adverse treatment outcomes, the ASCO guidelines recommend routine use of G-CSF in subsequent cycles (3).

When treating cancer with curative intent, dose-density of chemotherapy has been shown to have an impact on long-term survival in certain circumstances. For example, randomized controlled trials in breast cancer, non-Hodgkin lymphoma and Ewing sarcoma have demonstrated improvements in clinical outcomes (e.g. event- and disease-free survival) following use of dose-dense regimens compared with standard regimens (4-6). While these data cannot be extrapolated to all disease settings and chemotherapy regimens, the Committee considered that use of G-CSF to enable administration of dose-dense regimens may be appropriate where there is evidence that such regimens produce superior clinical outcomes.

In most cases, patients treated with palliative intent should not be treated with intensive regimens that require G-CSF. For most patients with most diseases in this situation, intensive therapies have not been shown to improve overall survival, nor have dose-dense therapies been associated with gains in quality of life. Dose reduction or dose delay is an appropriate treatment strategy in the palliative setting (3).

With regard to dosage and administration, G-CSF for primary prophylaxis should generally be given 24–72 hours after the administration of myelotoxic chemotherapy. A dose of 5 mg/kg per day should be continued until a target absolute neutrophil count of at least 2 or 3 x 10^9 cells/L is reached. G-CSF has a short half-life and daily subcutaneous injections are required.

Several studies have shown the comparability in effectiveness and patient outcomes of daily filgrastim and once per cycle pegfilgrastim (7-9). A meta-analysis in 2007, analysing outcomes among patients with different types of cancer (and different chemotherapy regimens), concluded that pegfilgrastim produced moderately better outcomes than filgrastim (10). In general, however, the choice between filgrastim and pegfilgrastim largely concerns individual clinical preference, ease of administration and the difference in cost;
pegfilgrastim is much more expensive than filgrastim. Additionally, biosimilars are available for filgrastim, allowing for comparable clinical efficacy at lower cost. Guidelines are generally accepting of both options, depending on patient circumstances and cost considerations within the health system concerned (11).

The Expert Committee noted that G-CSF has not been associated with clinical benefit in patients with afebrile neutropenia or as a treatment for most patients who have already developed febrile neutropenia. Use of G-CSF in these circumstances is not routinely recommended (3).

The Expert Committee acknowledged that avoidance of febrile neutropenia is a meaningful goal of holistic care of patients with cancer undergoing myelosuppressive chemotherapy. On the basis of the available evidence, the Committee recommended addition of filgrastim to the EML and EMLc for use in the following circumstances:

- as primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy;
- as secondary prophylaxis in patients who have experienced neutropenia following prior myelotoxic chemotherapy;
- to facilitate administration of dose-dense chemotherapy regimens.


