Many antineoplastic agents are cytotoxic to the bone marrow and prevent the development of granulocytes necessary to fight infection. Neutropenia is defined as an Absolute Neutrophil Count of less than 500 cells per microliter. When a patient is neutropenic, a fever may be the only sign of infection, which may rapidly progress to sepsis and death if empiric antibiotics are not given. Febrile neutropenia is a medical emergency and carries a substantial increase in morbidity, mortality, hospitalizations, and cost of care. This is a serious complication and avoidance of febrile neutropenia is a meaningful goal of holistic care of the patient with cancer. In the absence of essential medicines to stimulate the proliferation of granulocytes to fight infection, physicians must reduce the dose or delay the timing of chemotherapy delivery.

Discovered in the 1980s, Granulocyte-Colony Stimulating Factor (G-CSF) is a glycoprotein that stimulates the bone marrow to produce granulocytes, and promotes their survival, proliferation, and differentiation. When initiated early in the first cycle of chemotherapy and continued through all cycles of a chemotherapy regimen, CSFs substantially reduce the risk of Febrile Neutropenia. This usage of G-CSF during the first and all subsequent cycles of chemotherapy is called primary prophylaxis. This is an important clinical outcome, regardless of impact on other factors. It has also been shown to reduce the risk of infection-related and early all-cause mortality, while at the same time reducing the need for delays or dose reduction in chemotherapy treatment.¹

Stratifying a Patient's Risk for FN

G-CSFs are expensive agents, but when used in the correct clinical setting can reduce the overall cost of a patient’s care by directly reducing the risk of febrile neutropenia. Thus, use of G-CSFs is justified only in patients deemed to be high risk for developing febrile neutropenia. A patient’s risk is based both on risks inherent to the myelosuppression induced by specific chemotherapy regimens and on the individual’s health factors. The following clinical factors put a patient at a higher risk of developing severe complications from prolonged neutropenia:²

- Patient age greater than 65 years
- Poor performance status
- Prior episodes of FN
- Extensive prior treatment including large radiation ports
- Administration of combined chemotherapy
- Cytopenias due to bone marrow involvement by tumor
- Poor nutritional status
- The presence of open wounds or active infections
- More advanced cancer
- Other serious comorbidities

The prevalence of some of these factors may be increased in low-resource settings and the consequences of febrile neutropenia may be even more striking.
When to Use G-CSF

If a patient’s individual risk of Febrile Neutropenia is estimated to be 20% or greater, CSFs should be used for primary prophylaxis if no other equally effective regimen is possible that would not require the use of CSFs. If a patient has had a neutropenic complication (febrile neutropenia or documented infection during neutropenic episode) from a prior cycle of chemotherapy, he or she should receive secondary prophylaxis beginning during the next cycle. For low-risk patients, those with a less than 20% risk of developing febrile neutropenia, routine use of CSF’s is not considered cost-effective according to a commentary by Smith & Hillner assessing cost-effectiveness literature.

Table 1. Utilization of G-CSF in Pediatric Oncology

<table>
<thead>
<tr>
<th>Status</th>
<th>Disease</th>
<th>Protocol</th>
<th>Institution/Group</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precluded</td>
<td>Standard risk ALL</td>
<td>00 -01 (NCT 00165178)</td>
<td>DFCI* Childhood ALL Consortium</td>
<td>J Clin Oncol 2013; 31: 1202-1210.</td>
</tr>
</tbody>
</table>

*DFCI = Dana Farber Cancer Institute

**Only after an episode of fever and neutropenia

Choosing Regimens relative to risk of causing neutropenia and fever

Treatment with Curative Intent

In certain circumstances dose intensity and schedule impact on long-term survival. There remains a significant amount of variation in the use of G-CSF in cancer treatment among various patient cohorts, as is discussed elsewhere. However, when there is clear evidence that a regimen with sufficient myelosuppression requires primary or secondary prophylaxis with G-CSF, then this would be an appropriate choice of therapy. The incremental benefit of dose intense regimen versus a less intense regimen not requiring G-CSF will factor into this decision.
Treatment with Palliative Intent

In most cases, patients treated with palliative intent should not be treated with intensive regimens that require G-CSF. The primary reason for this is that for most patients with most diseases in this situation, it has not been demonstrated that intensive therapies improve overall survival, nor have dose-dense therapies been associated with gains in quality of life. With breast cancer as an example, ASCO recommends sequential single-agent therapy rather than more intensive multi-agent therapy for patients with metastatic disease.9

Use of G-CSF in treatment of acute leukemia and myelodysplastic syndrome

The considerations are different for the usage of G-CSFs for patients with Acute Myeloid Leukemia (AML), Acute Lymphocytic Leukemia (ALL), and Myelodysplastic Syndrome (MDS). In patients with AML, the priming of leukemia cells with G-CSF is not recommended. CSF use is recommended, however, in patients with AML after the completion of consolidation chemotherapy and has been shown to decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients. CSFs should be used judiciously or not at all in patients with refractory or relapsed myeloid leukemia. The expected benefit of only a few days of shortened neutropenia does not outweigh the cost; CSFs may make it difficult to distinguish between the stimulatory effect of CSFs or drug resistance as the cause of persistent leukemia. CSFs have been shown to increase the absolute neutrophil count in neutropenic patients with MDS. While there is insufficient data that long-term, continuous use of CSFs is beneficial, intermittent administration of CSFs may help in a subset of patients with MDS with severe neutropenia and recurrent infections. There is a potential risk for secondary myeloid leukemia or myelodysplastic syndrome (AML/MDS) associated with CSFs. When given to patients with ALL during the first few days of either the initial induction or of the first post-remission course of chemotherapy, CSFs may shorten the duration of neutropenia. On the other hand, in children with ALL, who would otherwise have an excellent prognosis, the benefits of CSFs may not outweigh the risks of AML/MDS.

How to Use

In general, for primary prophylaxis, G-CSF should be given 24 to 72 hours after the administration of myelotoxic chemotherapy. A dose of 5 mg/kg/day should be continued until a target absolute neutrophil count of at least 2 or 3 x 10^8 cells/L are reached. G-CSF has a short half-life and requires daily subcutaneous injections. A polyethylene glycol conjugated (PEGylated) G-CSF was developed, which only needs to be injected once per chemotherapy cycle. A large, WHO-endorsed study in 2013 established the International Standard for PEGylated G-CSF with an assigned in vitro bioactivity of 10,000 IU per ampoule. PEGylated G-CSF 6 mg should be given once, 24 hours after completion of chemotherapy.

Filgrastim vs Pegfilgrastim

Several studies have shown the comparability in effectiveness of filgrastim (daily subcutaneous injection) and pegfilgrastim (once per cycle subcutaneous injection). The two drugs have similar safety profiles and have been shown to provide similar neutrophil support.10 Several studies have demonstrated the comparability of patient outcomes on the two different forms of G-CSF.11,12,13 A meta-analysis in 2007 analyzing outcomes among patients with different types of cancer (including different chemotherapy regimens) concluded that pegfilgrastim produced moderately better outcomes,14 however in general,
the choice between filgrastim and pegfilgrastim largely concerns individual clinical preference about ease of administration and the difference in cost, with pegfilgrastim being much more expensive. Additionally, there are biosimilars available for filgrastim, allowing for a lower price with comparable clinical efficacy. Several recent studies have determined pegfilgrastim to be more cost-effective or more cost-saving as compared to filgrastim despite the drug being more expensive overall.\textsuperscript{15,16,17} One recent analysis of patients on several regimens in Europe concluded that a filgrastim biosimilar, Zarzio\textsuperscript{®} was more cost-effective than filgrastim and pegfilgrastim.\textsuperscript{18} However, guidelines generally remain accepting of both options depending on patient circumstances and cost considerations within the health system concerned in the analysis.\textsuperscript{19}

Consideration for Afebrile Neutropenia or as Treatment for Febrile Neutropenia

G-CSF has also shown no benefit in patients with afebrile neutropenia or as a treatment for most patients who have already developed febrile neutropenia. However, if a patient has a fever, neutropenia, and is at high-risk for infection-associated complications, CSFs should be considered. These high-risk features include the following:

- Expected prolonged (>10 days) and profound (<0.1 \times 10^9/L) neutropenia
- Age greater than 65 years
- Uncontrolled primary disease
- Pneumonia
- Hypotension and multiorgan dysfunction (sepsis syndrome)
- Invasive fungal infection
- Being hospitalized at the time of development of fever

Use in Autologous Progenitor Cell Transplantation (not applicable in resource constrained settings)

CSFs help mobilize peripheral-blood progenitor cells and the administration of CSFs as adjucnts to autologous progenitor-cell transplantation has become the standard of care. This has been shown to reduce hospital stays and overall medical costs. On the other hand, CSFs should not be used after allogeneic transplant because in this setting they have been shown to increase Graft versus Host Disease, and to decrease overall survival.

Intermediate Risk

NCCN: Individualized consideration of CSF use based on physician-patient discussion of the risk-benefit ratio of the likelihood of developing FN, the potential consequences of a neutropenic event and the implications of reduced chemotherapy dose delivery.
lymphoproliferative disorders and solid tumours preventing febrile neutropenia in breast cancer patients.


