The Use of Prophylactic Granulocyte-colony Stimulating Factor for Chemotherapy-induced Febrile Neutropenia

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Abstract

Febrile neutropenia (FN) is a common and serious complication of cytotoxic chemotherapy. It impairs the immune system, placing the cancer patient at risk of infection and is a key contributor to chemotherapy-associated morbidity and mortality. Factors including therapeutic regimen, tumour type and individual characteristics influence susceptibility to myelosuppression. Over the years, several granulocyte-colony stimulating factors (G-CSFs) have been developed for primary prophylaxis of FN including filgrastim, lenograstim and pegfilgrastim. These agents have demonstrated safety and efficacy in reducing FN in patients allowing for administration of optimal treatment and thereby improving clinical outcomes. They also support the use of dose-dense and dose-intense chemotherapy regimens found to be beneficial in some patients. Recently, the introduction of biosimilars of G-CSFs with proven comparability with the originator filgrastim has expanded the prophylactic therapies available. Effective use of these drugs by physicians early in the chemotherapy schedule may lead to fewer adverse events and improved survival.

Keywords

Granulocyte-colony stimulating factor, febrile neutropenia, cytotoxic chemotherapy, myelosuppression, filgrastim, biosimilars, primary prophylaxis, lenograstim, pegfilgrastim, dose-dense, dose-intense

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Febrile neutropenia (FN) is a serious and potentially fatal complication of cytotoxic cancer chemotherapy.[1] In general, neutropenia severely impairs the immune system and places cancer patients at a high risk of developing major infections.[2] Indeed, FN is a major contributor to chemotherapy-associated morbidity and mortality.[3] Using data from a large US survey, a retrospective study looking at mortality risk associated with FN found overall in-hospital mortality in patients with FN to be 9.5 %.[4] This rate was dependent on, and increased with, the presence of comorbidities in subjects. In those without any major comorbidity the mortality rate was 2.6 %, whereas this value increased to 10.3 and >21 % in patients with one and more than one major comorbidity, respectively. Moreover, in the systemic use of chemotherapy, myelosuppression and its subsequent complications are the most common dose-limiting toxicities. As such, FN can have a substantial impact on the ability to deliver full-dose chemotherapy on schedule imposing a significant burden and challenge to oncologists.[5,6] This may increase the risk of disease recurrence and disease-related mortality, especially in those individuals where reduction of dose or density of treatment is associated with poor prognosis. FN may also result in longer hospital stays and increased monitoring, diagnostic and treatment costs while reducing quality of life.

Neutropenia is often avoidable and this would reduce hospital admissions, antibiotic usage and the need for dose reductions and delays in chemotherapy administration.[6] Effective management of FN embraces prevention of the condition with prophylactic measures, such as the use of granulocyte colony-stimulating factor (G-CSF) as well as the appropriate management of FN and FN-related events as they occur. It may also be feasible to lower the dose or frequency of therapy to control the incidence of asymptomatic neutropenia and FN. In this article, an up-to-date review of the use of G-CSF for the prevention of chemotherapy-induced FN is provided.

Definition and Risk Factors

In healthy individuals, the lower limit of the blood neutrophil count is approximately 2,000 cells/mm^3. Values below this indicate neutropenia and are classified according to severity where 1,500–2,000 cells/mm^3 is grade 1 neutropenia, 1,000–1,500 cells/mm^3 grade 2, 500–1,000 cells/mm^3 grade 3 and <500 cells/mm^3 is grade 4, the most severe.[7] More specifically, FN is defined as a rise in body temperature to >38.0° C for a duration of >1 hour or a single temperature reading of >38.5° C, while having an absolute neutrophil count of <500/mm^3.[1] Both the duration and severity of chemotherapy-induced neutropenia (CIN) are factors that lead to FN.[7] FN is also most often seen during the initial cycles of myelosuppressive therapy.[8,9] While all patients receiving chemotherapy are at risk for developing CIN and FN, a number of factors including current and prior treatment regimens have been implicated in the development of chemotherapy-induced FN.

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The intensity (including the frequency and/or total dose) of a chemotherapy regimen is a primary determinant of risk for neutropenia and some regimens are more myelosuppressive than others.[10] For example, doxorubicin plus docetaxel in patients with metastatic breast cancer has been associated with a high risk of FN.[11,12] Similarly, patients with non-Hodgkin's lymphoma (NHL) that are treated with high doses of cyclophosphamide or etoposide are more likely to develop FN.[13,14] The same outcome is observed with high doses of anthracycline in early breast cancer patients.[15]

The type of tumour may also be a predictor of FN. Patients with haematological malignancies are at greater risk of experiencing FN than those with solid tumours owing to the nature of the underlying disease process and the intensity of the required treatment.[16] However, after controlling for the type of cancer, advanced and uncontrolled diseases are significant predictors of neutropenic complications.[16,17]

Aside from factors relating to the cancer and its treatment, patient characteristics including age, poor performance status, poor nutritional status as well as the presence of comorbidities such as renal disease and heart disease are significant risk factors for the development of FN.[13,15,18] Female sex[15,19] and low baseline blood cell counts[20] also contribute to an increased risk of FN.

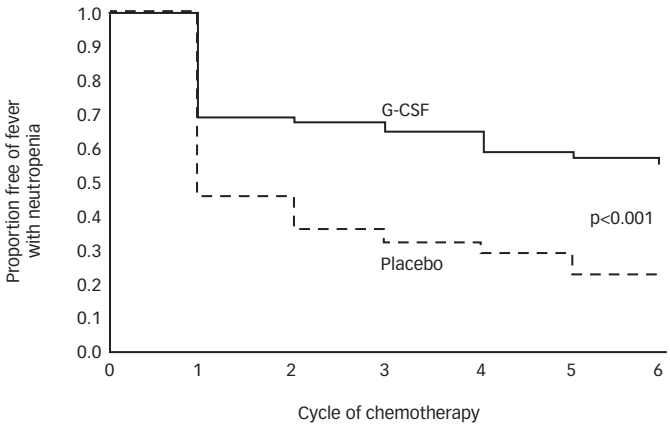
Considering the number of factors that influence susceptibility to FN, it is not surprising that there is a high variability of neutropenic events among cancer patients. Furthermore, there is a small proportion of individuals that have a very low risk of serious complications or death from chemotherapy-induced FN.[21] Risk factor scoring systems such as those developed by the Multinational Association for Supportive Care in Cancer can be used to identify low-risk patients and will aid in the development of new therapeutic strategies.[22] This index identifies low-risk patients with a positive predictive value of 91 % at 68 % specificity and 71 % sensitivity.

Granulocyte-colony Stimulating Factor

One method by which to manage FN is through the use of haematopoietic growth factors such as G-CSF. These agents work to stimulate haematopoietic progenitors thereby increasing the number of functional neutrophils.[23] A recombinant human G-CSF, filgrastim (Neupogen®), was first purified from human cell lines and placenta, and cloned in the mid-1980s.[24–26] An early Phase I/II clinical study with filgrastim demonstrated its ability to stimulate production of neutrophils in patients receiving melphalan therapy for advanced malignancy.[27] Administration of this G-CSF before and after chemotherapy resulted in a reduced period of neutropenia caused by melphalan. Overall, G-CSF was well tolerated with minimal adverse effects.[27] In addition, registration trials of filgrastim in patients with small-cell lung cancer (SCLC) receiving cyclophosphamide, doxorubicin and etoposide demonstrated a reduction in the incidence, duration and severity of FN with G-CSF use.[23,28]

Based on these positive findings, filgrastim received US and European approval for clinical use in cancer patients treated with chemotherapy in 1991.[29] Approval of a glycosylated recombinant G-CSF (lenograstim [Granocyte®]) and a pegylated form of G-CSF (pegfilgrastim [Neulasta®]) followed shortly thereafter in 1993 and 2002, respectively.[30]

Figure 1: Kaplan–Meier Curve of the Proportion of Patients who Remained Free of Febrile Neutropenia According to Treatment Cycle



G-CSF = granulocyte-colony stimulating factor. Source: reproduced from Crawford et al., 1991.[23]

In recent years, three biosimilar filgrastim molecules have been introduced and approved in the EU: XM02 (Tevagrastim®, Ratiograstim® and Biograstim®); EP2006 (Zarzio® and Filgrastim Hexal®); and Hospira filgrastim (Nivestim®). Biosimilars are biologically similar versions of a drug and have been approved for use for the same disease following patent expiry on the original product. These drugs undergo their own strict regulatory pathway to gain approval that is separate from the generic-drug regulatory scheme. In the EU, the European Medicines Agency outlines the standards that biosimilars must meet prior to approval:[31] clinical trials are required to demonstrate the comparability of the biosimilar with the originator product in terms of quality, safety and efficacy. In the cases of the G-CSF biosimilar molecules, the reference drug was the Amgen filgrastim (Neupogen) and only when these molecules have a proven similar nature to their originator are they then approved for use.

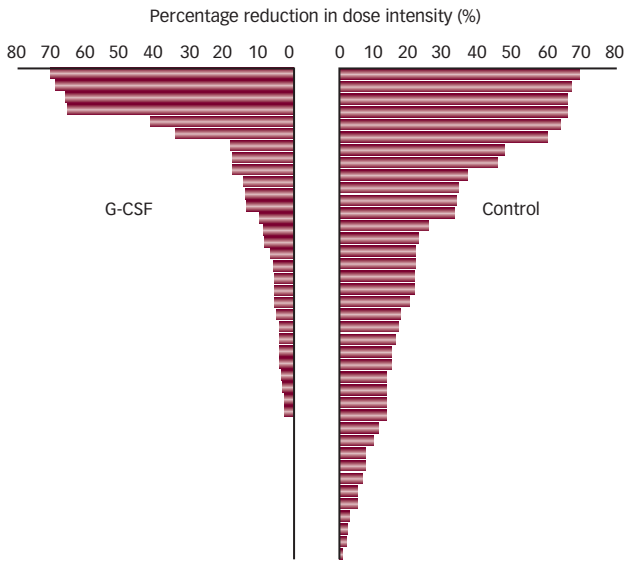
Primary Prophylaxis of Chemotherapy-induced Febrile Neutropenia with Granulocyte-colony Stimulating Factor

Since their introduction over two decades ago, G-CSF treatments have been used in the primary prophylactic treatment of FN in patients receiving chemotherapy. Results from multiple randomised controlled trials, across a range of settings, have confirmed that filgrastim reduces the risk of FN.[23,28,32,33] Crawford et al.[23] illustrated the efficacy of prophylaxis with filgrastim in patients with SCLC in a multicentre, randomised double-blind, placebo-controlled trial. Using G-CSF led to decreases in the incidence of FN and infections as well as lowering the total number of days of treatment with antibiotics. *Figure 1* presents the proportion of patients that remained free of FN according to treatment cycle illustrating the significant improvement ($p<0.001$) observed in patients receiving G-CSF versus those receiving placebo.

Similarly, randomised controlled trials of lenograstim[34–36] and pegfilgrastim[9,37,38] have provided substantial evidence that their prophylactic use reduces the incidence of chemotherapy-induced FN.

Several high-quality meta-analyses, in haematological malignancies and solid tumours, support the use of G-CSF to prevent chemotherapy-induced FN.[39–41] Indeed, G-CSF use has been shown to be effective in accelerating neutrophil recovery in patients with acute

Figure 2: Percentage Reduction in Cyclophosphamide Dose Intensity for Non-Hodgkin's Lymphoma Patients Receiving Chemotherapy with or without Granulocyte-colony Stimulating Factor (Each Bar Represents one Individual Patient)



G-CSF = granulocyte-colony stimulating factor. Source: reproduced from Pettengell et al., 1992.[33]

myeloid leukaemia (AML) who are receiving intensive chemotherapy.[42,43] Several studies in adult AML patients demonstrated the benefits of primary prophylaxis with 5 µg/kg of G-CSF given daily following induction and consolidation therapy.[44–46] G-CSF reduced the duration of neutropenia as well as the duration of infections and antibiotic use. However, no improvements in the frequency of reported infections and overall survival were found. At present, there is great variation in the use of G-CSF in AML both within the UK and globally. Current guidelines from some UK cancer networks recommend considering the use of G-CSF after initial induction therapy for AML and similarly, G-CSF may be used following completion of consolidation chemotherapy to decrease the frequency of infection.[47] Comparable guidelines are given by the British Committee for Standards in Haematology.[48]

G-CSF was also shown to have a favourable risk/benefit profile with only mild-to-moderate musculoskeletal pain being a characteristic adverse event associated with G-CSF treatment.

As mentioned earlier, FN is reported more often during the first cycle of chemotherapy, underscoring the need to initiate G-CSF from the beginning of cancer treatment in appropriate patients.[49] Prophylactic pegfilgrastim administered during cycle 1 reduced the incidence of FN by approximately 60 % compared with when treatment was initiated after cycle 1 at the discretion of the physician in patients aged 65 years or older receiving a variety of mild to moderately myelosuppressive chemotherapy regimens for solid tumours and NHL.[50]

The Impact of Granulocyte-colony Stimulating Factor on Chemotherapy Administration and Clinical Outcomes

Maintenance of Full-dose Chemotherapy on Schedule

When strict chemotherapy schedules are required for survival benefits, it becomes important that treatment is delivered on time and at the optimal dosage. Indeed, dose reductions and delays in chemotherapy are associated with poorer outcomes in many cancers including NHL, breast cancer, non-SCLC and colorectal cancer.[51–54] The use of prophylactic G-CSF can help avoid potentially detrimental disruptions to standard chemotherapy regimens. Patients with NHL treated with filgrastim received a greater dose intensity of cytotoxic chemotherapy than control patients.[33] Here, patients were randomised to receive either VAPEC-B (vincristine, Adriamycin®, prednisolone, etoposide, cyclophosphamide and bleomycin) therapy alone or therapy with G-CSF administered subcutaneously daily. *Figure 2* illustrates the finding that subjects using G-CSF had a lower percentage reduction in dose intensity relative to controls.

Similarly, a recent prospective observational study in patients with breast cancer or lymphoma showed that FN was associated with low relative dose intensity chemotherapy (i.e. reductions and/or delays) for both malignancies.[55] Prophylactic G-CSF in turn had a strong protective effect against dose modifications in lymphoma patients. Finally, a systematic review and meta-analysis established that patients who received prophylactic G-CSF had significantly fewer dose reductions and delays in cytotoxic chemotherapy than those who received placebo or no supportive care.[41]

Support of Dose-dense and Dose-intense Chemotherapy Regimens

There are instances where an increased frequency or dose of chemotherapy is found to be beneficial. As a result, dose-dense or dose-intense regimens are increasingly being incorporated into the therapeutic algorithm by oncologists in an attempt to improve clinical outcomes in cancer patients.[56,57] This approach is likely to be particularly relevant where treatment is intended to be curative or to prolong survival[1] and numerous studies support the use of prophylactic G-CSF to facilitate the delivery of dose-dense or dose-intense chemotherapy. The incidence of grade 3/4 neutropenia was lower in SCLC patients treated with dose-intense carboplatin plus etoposide (CE) with lenograstim G-CSF support versus conventional CE without G-CSF (37.5 versus 69.4 %; p=0.009).[58] Furthermore, a regimen of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone at 14-day intervals (R-CHOP-14) plus G-CSF produced fewer episodes of neutropenia compared with R-CHOP-21 (21-day intervals) without G-CSF (31 versus 57 %) in patients with diffuse B-cell lymphoma.[59] In a meta-analysis of seven lymphoma trials involving G-CSF, all but one study showed a higher dose intensity in the G-CSF-treated arm compared with the control arm.[40]

Effect of Prophylactic Granulocyte-colony Stimulating Factor use on Survival Outcomes

With the use of G-CSF reducing the incidence of FN and allowing optimal treatment, it is possible that this could result in improved survival outcomes.[41] Several meta-analyses have recently investigated this hypothesis with conflicting results.[40,41,60] A meta-analysis compared prophylactic G-CSF (filgrastim, lenograstim or pegfilgrastim) with placebo or no treatment in 3,493 patients treated for solid tumours or lymphoma. It was found that G-CSF reduced the risk of infection-related mortality by 45 % (1.5 versus 2.8 %; p=0.018) and all-cause early mortality by 40 % (3.4 versus 5.7 %; p=0.002).[41] The studies in this analysis consisted of relatively young and fit patient populations and an even larger benefit of G-CSF may be observed in older populations. By contrast, a meta-analysis using data from 148 studies of prophylactic G-CSF or granulocyte-macrophage

colony-stimulating factor (GM-CSF) in a wide range of settings showed little to no mortality benefit with CSFs compared with placebo or no treatment.[60] Similar results were reported in a Cochrane database review of 13 trials in patients with lymphoma.[40] This disparity may be attributed to the heterogeneity of the studies analysed. Furthermore, the two meta-analyses showing no effect on mortality endpoints included studies of GM-CSF, which is thought to be less effective than G-CSF at reducing FN.[61]

Comparisons Between Different Formulations of Granulocyte-colony Stimulating Factor

Filgrastim and Lenograstim

Evidence from a meta-analysis suggests that filgrastim and lenograstim have comparable efficacy with regards to FN and FN-related endpoints.[39] Eight studies of prophylactic G-CSF administered prior to the onset of FN in patients with solid tumours or malignant lymphomas receiving systemic chemotherapy were included in this analysis: five trials of filgrastim and three of lenograstim. Findings demonstrated that both these products were effective in reducing the risk of FN as well as infections associated with chemotherapy regimens. Bone pain was the only adverse effect reported, where the mean frequency of complaints among patients receiving growth factor was 21 % compared with 6 % in control subjects.[39] A recent systematic review further confirms the comparability of lenograstim and filgrastim.[62]

Comparability of Biosimilars XM02 (Tevagrastim®, Ratiograstim® and Biograstim®) and EP2006 (Zarzio® and Filgrastim Hexal®) with Originator Product

In order for biosimilars to be approved, they must undergo numerous trials that prove their similarity to the originator product in terms of efficacy and safety. A meta-analysis of three clinical studies involving a total of 608 breast cancer, lung cancer and NHL patients investigated the comparability of the G-CSF biosimilar XM02 with its originator filgrastim.[63] Patients were treated with prophylactic G-CSF during the first cycle of chemotherapy and the incidence of FN was determined. The collective results indicated the non-inferiority of XM02 relative to filgrastim with respect to the incidence of FN and this was seen regardless of the myelotoxicity of the chemotherapy regimen.

Similarly, the biosimilar EP2006 was evaluated in Phase I and III studies in healthy volunteers and neutropenic patients.[64] The studies in healthy volunteers confirmed the biosimilarity of EP2006 with its reference product filgrastim with regards to pharmacodynamics and pharmacokinetics. The open Phase III study included 170 breast cancer patients undergoing four cycles of doxorubicin and docetaxel chemotherapy. Primary prophylaxis of severe neutropenia using EP2006 demonstrated its efficacy and safety. It was therefore concluded that this biosimilar had sufficient comparability with its originator filgrastim.[64]

Hospira Filgrastim (Nivestim™)

A further biosimilar molecule developed by Hospira based on the originator filgrastim was approved in June 2010. A study was designed to evaluate the similarities of this Hospira filgrastim with the reference filgrastim from Amgen.[65] This was an extensive characterisation study that assessed and compared the physiochemical properties of the two products. Both drugs were evaluated using state-of-the-art analytical methods and no significant differences were found regarding their physiochemical properties, molecular characteristics, purity and biological activity. Furthermore, when subjected to stress conditions (storage at 40º C), product-related impurities were similar between the two drugs for up to 12 weeks.[65] However, in terms of stability, Hospira filgrastim has an out of refrigerator stability of up to seven days allowing it to be used in an ambulatory setting, whereas Amgen filgrastim can only be left at room temperature for a maximum of 24 hours before it must be discarded. This suggests an improvement in the quality of product available in later generation formulations while retaining the fundamental biological aspects.

Additional Phase I and III studies further support the equivalence of the Hospira filgrastim and Amgen filgrastim in healthy volunteers and 282 patients with breast cancer.[66–68] These randomised trials demonstrated that Hospira filgrastim was comparable in pharmacokinetic properties, pharmacodynamic profile, efficacy and safety to filgrastim.

Pegfilgrastim

With its approval in 2002, pegfilgrastim had overtaken filgrastim as the standard of care for cancer patients undergoing chemotherapy owing to its convenient dosing schedule. As its name suggests, pegfilgrastim is pegylated and therefore has a longer half-life than filgrastim within the body. As a result, only a single dose of pegfilgrastim is required per cycle of chemotherapy versus daily filgrastim injections. A meta-analysis of five studies with a total of 617 patients receiving myelosuppressive therapy was conducted to investigate the relative efficacies of pegfilgrastim and filgrastim.[69] The pooled findings of the trials suggest that one dose of pegfilgrastim is significantly more effective at reducing the rate of FN in patients than a median of 10–14 days of filgrastim (pooled relative risk of 0.64; 95 % CI, 0.43–0.97). Similarly, the rate of grade 4 neutropenia was also significantly reduced using pegfilgrastim compared with filgrastim. While these findings may reflect the sustained activity of pegfilgrastim, trial heterogeneity was an acknowledged limitation of this meta-analysis and may have influenced the results. The trials included varied in the type of cancer, chemotherapy regimen and trial design.[69] At present, biosimilars of pegfilgrastim are in development and will soon be entering the market.

Current Use of Prophylactic Granulocyte-colony Stimulating Factor for Chemotherapy-induced Febrile Neutropenia

With the number of G-CSF products available, it is important to develop comprehensive guidelines to ensure consistency in their application across different institutions and that all appropriate patients are considered for these drugs. Prior to 2006, primary G-CSF prophylaxis was only recommended for cancer patients receiving chemotherapy regimens associated with a 40 % risk of FN or higher.[70] However, later evidence suggested a clinical benefit at much lower levels of risk. Data showed that G-CSF prophylaxis confers positive results to patients with a FN risk of 20 % or higher.[9,71] The European Organisation for Research and Treatment of Cancer guidelines have since been updated to reflect this change stating that primary prophylaxis with any of the available G-CSF formulations should be given to adult cancer patients receiving cytotoxic chemotherapy when the overall FN risk is ≥20 % to prevent FN and FN-related complications.[1,72] Further to risks associated with chemotherapy regimens, individual patient factors need to be taken

into account such that, for regimens with intermediate (10–20 %) FN risk, patient characteristics such as old age and the presence of comorbidities may increase the overall risk of FN to warrant G-CSF use.[1,73] Similarly, the most recent guidelines from the American Society of Clinical Oncology recommend that G-CSFs be used when the risk of FN reaches approximately 20 %.[43] Patients at high risk of FN based on factors including age, medical history and disease characteristics should also be considered for primary prophylaxis with a G-CSF.

G-CSF should also be used to support dose-dense or dose-intense chemotherapy as well as to help maintain the dose intensity or dose density of standard regimens, especially when the treatment intent is curative or to prolong survival.[1] Despite these guidelines, in real-world clinical practice settings, patients often receive inconsistent and suboptimal courses of G-CSF treatment highlighting the need for better knowledge of these recommendations.[55,74]

Summary and Conclusions

Over the years, several G-CSF drugs have been developed that have shown efficacy in preventing FN in cancer patients receiving myelosuppressive chemotherapy. Recent introductions of biosimilar products have expanded the choices available to clinicians. Proper administration of these treatments to appropriate individuals will help reduce the incidence of FN, thereby promoting optimal therapy and better prognosis. Moreover, this will likely result in cost savings for healthcare systems, as the number of complications will be reduced. It therefore becomes important that physicians and patients are aware of these products and their potential benefits in cancer treatment. ■

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