# Prophylaxis of chemotherapy-induced febrile neutropenia with granulocyte colony-stimulating factors: where are we now?

**Matti Aapro · Jeffrey Crawford · Didier Kamioner**

**Abstract** Updated international guidelines published in 2006 have broadened the scope for the use of granulocyte colony-stimulating factor (G-CSF) in supporting delivery of myelosuppressive chemotherapy. G-CSF prophylaxis is now recommended when the overall risk of febrile neutropenia (FN) due to regimen and individual patient factors is ≥20%, for supporting dose-dense and dose-intense chemotherapy and to help maintain dose density where dose reductions have been shown to compromise outcomes. Indeed, there is now a large body of evidence for the efficacy of G-CSFs in supporting dose-dense chemotherapy. Predictive tools that can help target those patients who are most at risk of FN are now becoming available. Recent analyses have shown that, by reducing the risk of FN and chemotherapy dose delays and reductions, G-CSF prophylaxis can potentially enhance survival benefits in patients receiving chemotherapy in curative settings. Accumulating data from 'real-world' clinical practice settings indicate that patients often receive abbreviated courses of daily G-CSF and consequently obtain a reduced level of FN protection. A single dose of PEGylated G-CSF (pegfilgrastim) may provide a more effective, as well as a more convenient, alternative to daily G-CSF. Prospective studies are needed to validate the importance of delivering the full dose intensity of standard chemotherapy regimens, with G-CSF support where appropriate, across a range of settings. These studies should also incorporate prospective evaluation of risk stratification for neutropenia and its complications.

**Keywords** Cancer treatment · Colony-stimulating factors · Neutropenia · Guidelines

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## Introduction

Neutropenia is a major dose-limiting toxicity of myelosuppressive chemotherapy that predisposes patients to serious infections. Febrile neutropenia (FN), generally defined as fever (single oral temperature ≥38.3°C or ≥38.0°C for >1 h) with grade 3/4 neutropenia (absolute neutrophil count [ANC] <1.0 or <0.5×10$^9$/l), is associated with substantial morbidity, escalation of costs and mortality risk [1–5]. Severe neutropenia and FN episodes are also major drivers of chemotherapy dose delays and reductions [6–8], which have been shown to compromise survival outcomes in various curative settings [7, 9–13].

Prophylaxis with recombinant granulocyte colony-stimulating factors (G-CSFs) reduces the severity and duration of chemotherapy-induced neutropenia and the consequent risk of FN [14, 15] and is playing an increasingly broad role in supporting the delivery of myelosuppressive chemotherapy [16–18].

The aim of this article is to review recent developments in the use of G-CSFs in this setting. A literature search was conducted using the search terms "granulocyte colony-stimulating factor", "leukaemia", "lymphoma" and "solid

tumours". Additional studies were identified by hand-searching reference lists of retrieved papers. Conference websites were searched for recent reports (2006 onwards) not covered by published literature, using the search terms "G-CSF", "granulocyte colony-stimulating factor", "neutropenia", "filgrastim", "lenograstim" and "pegfilgrastim".

## Who should receive G-CSFs?

Official guidelines from Europe and the USA now agree that primary G-CSF prophylaxis should be given when the overall risk of FN due to regimen and patient factors is ≥20% [16–20]. Prior to 2006, primary G-CSF prophylaxis was recommended for chemotherapy regimens associated with a relatively high FN risk of 40% [21]. However, data showed that clinical benefit was obtained at a much lower threshold of risk [22, 23], and the importance of individual patient risk factors was also recognised [16, 17].

Regimens with an overall risk of FN of ≥20% include anthracycline/taxane regimens that are used for treatment of breast cancer, cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)-like regimens used for non-Hodgkin's lymphoma (NHL) [16, 18] and the docetaxel, cisplatin and 5-fluorouracil (DCF/TPF) regimen used for gastric [24] and head and neck [25, 26] cancer.

Immunomodulatory derivatives of thalidomide such as lenalidomide have shown promise for the treatment of myeloma [27, 28]. These agents appear to induce neutropenia by transiently blocking the maturation of granulocytes, rather than via stem cell toxicity, suggesting that this might be prevented by G-CSF administration [29]. Further work is required to define the risk of FN with these agents.

For regimens that are associated with a 10–20% risk of FN, individual patient factors must also be considered when determining the need for G-CSF support (Fig. 1). There is high-level evidence for older age, advanced-disease stage and FN occurrence in a first or previous chemotherapy cycle as risk factors for FN [16]. Other factors that have been reported to increase risk include the presence of comorbidities and poor performance/nutritional status [16–18]. As age >65 years is consistently shown to be associated with increased FN risk, G-CSF prophylaxis should be considered for supporting chemotherapy delivery in all elderly patients receiving myelotoxic chemotherapy [30].

Historically, it was common practice to reduce the chemotherapy dose instead of administering G-CSF in at-risk patients, but this strategy risks obtaining suboptimal results. Rather, G-CSF use should be guided by the intent of treatment (i.e., whether curative or for prolonging survival as opposed to palliative). If reduction in chemotherapy dose intensity or density is associated with poor prognosis or where dose-dense or dose-intense chemotherapy regimens have survival benefits, G-CSF prophylaxis should be used. Where this is not crucial, use of a less myelosuppressive chemotherapy regimen or dose/schedule modification can be considered [16].

## G-CSF to support chemotherapy: new data

Anthracycline/taxane regimens, particularly doxorubicin-containing regimens, have become a standard of care in breast cancer. Docetaxel, doxorubicin and cyclophosphamide (TAC) is a combination regimen that has high efficacy in the adjuvant setting, reducing the risk of death by 30% compared to fluorouracil, doxorubicin and cyclophosphamide (FAC) [31]. While TAC is associated with a relatively high risk of FN (>20%) and other toxicities, delivery is feasible with effective growth factor support [32, 33]. As well as reducing the risk of FN, G-CSF prophylaxis has also been reported to attenuate non-haematological toxicities such as aesthenia/anorexia, stomatitis/mucositis and diarrhoea in TAC recipients [32, 33]. It is unknown whether this is a direct protective effect or related to decreased cytokine release via the reduced risk of infection.

Elderly patients have often not been considered as candidates for full-dose aggressive chemotherapy, but there is a growing body of evidence to show that, with adequate G-CSF support, delivery of myelosuppressive chemotherapy [34–37], including taxane-containing (neo)adjuvant regimens [36, 37] and dose-dense CHOP (discussed in a later section), is feasible in this population.

Recent prospective data from a large community-based study have confirmed previous observations that FN is most common in the first cycle of chemotherapy [38], and this underlines the need to start G-CSF from the first cycle in appropriate patients. Prophylactic use of G-CSF (pegfilgrastim) from cycle 1 was shown to reduce the incidence of FN by approximately 60% compared with reactive use (initiated after cycle 1 at the physician's discretion) in elderly patients (aged ≥65 years; $n$=852) receiving a range of mild to moderately myelosuppressive chemotherapy regimens for solid tumours (lung, breast or ovarian cancer) or NHL [35]. Among those with solid tumours, FN occurred in 10% (95% confidence interval [CI] 7–14%) of the reactive-use group versus 4% (95% CI 2–6%) of the pegfilgrastim primary prophylaxis group ($p$= 0.001). Among NHL patients, FN occurred in 37% (95% CI 26–49%) of the reactive-use versus 15% (95% CI 8–25%) of the pegfilgrastim primary prophylaxis group ($p$=0.004).
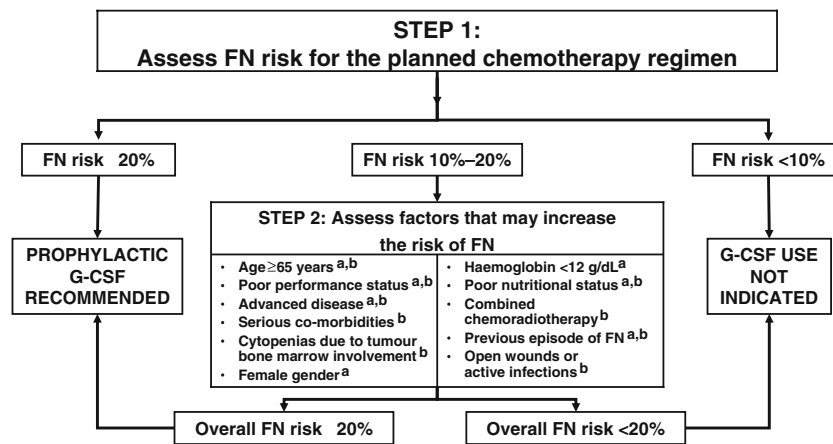
**Fig. 1** Algorithm for determining whether granulocyte colony-stimulating factor (*G-CSF*) prophylaxis is indicated in patients undergoing chemotherapy (represents a combined interpretation of the 2006 G-CSF guidelines of the European Organisation for Research and Treatment of Cancer and the American Society of Clinical Oncology [16, 17]). *FN* febrile neutropenia. Adapted from (a) Aapro et al. [16], with permission from Elsevier. Incorporating data from (b) Smith TJ et al. [17]

## Development of risk models

A number of groups have been developing predictive models to identify patients at increased risk of severe myelosuppression, low dose intensity and/or FN during chemotherapy for breast cancer [8, 39–42], NHL [8, 43, 44] or various cancer types [45–47]. The models are based on traditional risk factors such as age, gender, bodyweight and performance status, as well as disease type and stage, haematology/clinical chemistry, chemotherapy, whether G-CSF was given and a previous history of FN (Table 1). A

number of these have been validated retrospectively using existing patient datasets [43, 46].

Jenkins et al. demonstrated that patients receiving adjuvant 5-fluorouracil, epirubicin, cyclophosphamide (FEC) chemotherapy for breast cancer could be divided into five risk groups, in which the risk for neutropenic events ranged from 18% to 52%, the risk of receiving suboptimal (<85%) chemotherapy dose intensity from 9% to 36% and the risk of FN from 4% to 21%, based only on their pretreatment absolute neutrophil and lymphocyte counts [40].

**Table 1** Risk models for febrile neutropenia (FN) or severe haemotoxicity in patients receiving myelosuppressive chemotherapy

|  | Dranitsaris et al. [39] | Pettengell et al. [44] | Ziepert et al. [43] | Lyman et al. [46] |
|---|---|---|---|---|
| Regimen/disease | Doxorubicin or liposomal doxorubicin/ metastatic breast cancer | Various/NHL | CHOP-like regimens/ NHL | Various |
| Risk assessed by model | Neutropenic complications[a] | FN | Anaemia; leucocytopenia; thrombocytopenia | Neutropenia |
| Basic characteristics | Age ≥59 years; performance status | Age; bodyweight | Gender; bodyweight; performance status | Older age |
| Disease characteristics |  |  | Disease stage; bone marrow involvement |  |
| Haematology/clinical chemistry | Neutrophils $\leq 2 \times 10^9$/l in previous cycle | Baseline albumin | Baseline haemoglobin; leucocytes; thrombocytes; GGT; LDH | WBC; abnormal hepatic or renal function |
| Treatment factors | Whether first cycle, doxorubicin or liposomal doxorubicin | Planned cyclophosphamide, cytarabine, etoposide dose; G-CSF use | Chemotherapy cycle length; etoposide use; vincristine dosage; G-CSF use | Various chemotherapy agents; prior chemotherapy; immunosuppressive agents; G-CSF use |
| History |  | Previous chemotherapy; recent infection | First cycle FN |  |

*CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone, *GGT* gamma glutamyltransferase, *LDH* lactate dehydrogenase, *NHL* non-Hodgkin's lymphoma

[a] Absolute neutrophil count $\leq 1.5 \times 10^9$ cells/l, FN or neutropenia with a documented infection

Ziepert et al. [43] have developed a validated web-based tool for predicting the grade of haematological toxicity (leucopenia, thrombocytopenia and anaemia, but not specifically neutropenia) in lymphoma patients treated with CHOP-like therapies in clinical practice (www.toxcalculator.com). It was calculated that use of these models, which again stratify patients into five risk groups, could potentially spare intensive prophylactic strategies in 10–38% or 16–38% of patients, depending on whether cycle 1 data are available. Pettengell et al. [44] found that their model had high sensitivity (81%) and specificity (80%) for predicting cycle 1 FN in patients with NHL, with a 28% positive and 98% negative predictive value.

Lyman et al. [46] developed a predictive model for neutropenic events that they retrospectively validated, using data from 4,458 patients treated for various cancers in clinical practice. The model demonstrated good discrimination, predicting cycle 1 neutropenic events in 34% of high-risk and 4% of low-risk patients, with a sensitivity and specificity of 90% and 59%, respectively. G-CSF primary prophylaxis was confirmed as a protective factor, and almost two thirds of patients in the validation dataset who were classified as high risk but did not receive primary G-CSF prophylaxis subsequently received secondary G-CSF prophylaxis in later cycles.

Once prospectively validated, such models will be a valuable resource for helping to target G-CSF support.

Dose-dense/intense treatment

Shortening the time interval between chemotherapy cycles from the conventional 3-week, to a 2-week, cycle—dose densification—is thought to maximise tumour cell kill and minimise regrowth between cycles [48, 49]. Moreover, completion of chemotherapy within a shorter time frame may allow patients to resume their normal activities sooner. Earlier landmark studies with anthracycline/taxane regimens in breast cancer [50], CHOP-like regimens in aggressive lymphomas [51, 52] and doxorubicin/cyclophosphamide/etoposide (ACE) chemotherapy in the small cell lung cancer (SCLC) setting [53] showed that dose densification significantly improves response and survival outcomes.

G-CSF has been central to the paradigm of dose-dense chemotherapy, as the short treatment cycle of 14 days would not otherwise allow sufficient time for bone marrow recovery between cycles. There is now a large body of new evidence for the efficacy of G-CSF (filgrastim or pegfilgrastim) in supporting delivery of dose-dense CHOP with or without rituximab, at full dose, on time in patients with NHL [54–57], including the elderly [54, 58, 59]. For instance, younger patients with intermediate-risk aggressive NHL were able to receive a dose-intense and dose-dense CHOP regimen (cyclophosphamide 1,000 mg/m$^2$, doxoru-

bicin 70 mg/m$^2$, vincristine 2 mg and prednisone 100 mg× 5, delivered in 6×14-day cycles) with G-CSF support (filgrastim) [55]. G-CSF (pegfilgrastim) also supported delivery of dose-dense cyclophosphamide, doxorubicin, etoposide, vincristine, bleomycin, procarbazine and prednisone at full dose, on time in patients with Hodgkin's lymphoma [60].

In the breast cancer setting, several recent reports have documented the efficacy of pegfilgrastim in supporting delivery of dose-dense anthracycline/taxane regimens, including docetaxel followed by epirubicin/cyclophosphamide (T→EC) or the reverse sequence (EC→T) [61] and fluorouracil, epirubicin, cyclophosphamide→docetaxel (FEC→Doc) [62], as well as FEC alone [63]. Dose-dense sequential doxorubicin plus cyclophosphamide followed by paclitaxel (AC→T) was well tolerated when administered with pegfilgrastim and additional red cell support (darbepoetin alfa) in patients with haemoglobin ≤12 g/dl, with few chemotherapy dose reductions or episodes of FN (<2% of patients) [64].

In patients with SCLC, full-dose, on-schedule, dose-dense ACE chemotherapy was found to be feasible with pegfilgrastim support [65].

Use of G-CSF has also allowed investigation of higher chemotherapy dosages, but the benefits of dose escalation alone are presently unclear, suggesting that currently used dosages may already be optimal in most settings, provided that they can be delivered safely. For instance, significant dose escalations of cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide (CHOEP) were possible with G-CSF support (filgrastim or lenograstim) in young patients with lymphoma [66], but this strategy did not enhance clinical benefits compared with standard CHOEP-21 [67].

Impact of G-CSF on chemotherapy delivery and survival outcomes

Recent data from a large US survey (41,779 patients with FN treated at 115 medical centres) have highlighted the mortality risk associated with FN. Overall, in-hospital mortality was 9.5% and increased with the number of comorbidities: 2.6% in those without any major comorbidity, 10.3% in those with one major comorbidity and >21% in those with more than one major comorbidity [3].

There are now much data to show that reduced chemotherapy dose intensity due to delays and dose reductions can potentially compromise survival outcomes in patients receiving curative treatment [7, 9–13, 68]. Even moderate reductions can negatively impact survival. For instance, in NHL patients treated with CHOP-like chemotherapy (n=210), failure to achieve a relative dose intensity

(RDI; the ratio of actual dose to planned dose of chemotherapy over the same time interval) of >90% resulted in significantly shorter mean overall survival (2.24 vs. 5.38 years; *p*=0.002) [7].

The prospective Impact of Neutropenia in Chemotherapy-European observational study in breast cancer (*n*=444) and lymphoma (*n*=305) patients undergoing chemotherapy found that first-cycle FN, age ≥65 years and Eastern Cooperative Oncology Group (ECOG) performance score >1 were associated with low RDI in both groups of patients, with G-CSF primary prophylaxis protecting against low RDI in the lymphoma patients [8]. A meta-analysis of ten studies that reported RDI as an outcome found that average RDI in patients treated for solid tumours or lymphoma ranged from 91.0% to 99.0% (mean 95.1%) in patients who received G-CSF, compared with only 71.0 to 95.0% (mean 86.7%) in those who did not [69].

There is now a growing body of evidence that improved chemotherapy delivery and reduction in FN with G-CSF [8, 69] may translate into better survival outcomes. Three meta-analyses of randomised studies comparing prophylactic G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF) with placebo or no treatment have been conducted recently [69–71].

A meta-analysis of 17 studies compared primary prophylactic G-CSF (filgrastim, lenograstim or pegfilgrastim) with placebo or no treatment in 3,493 patients treated for solid tumours or lymphoma. In addition to improving RDI, G-CSF reduced the risk of infection-related mortality by 45% (1.5% vs. 2.8%: relative risk [RR] 0.55, 95% CI 0.33–0.90; *p*=0.018) and early mortality (all-cause, during chemotherapy) by 40% (3.4% vs. 5.7%: RR 0.60, 95% CI 0.43–0.83; *p*=0.002; Fig. 2). As the patient populations in the studies included in this analysis tended to be relatively young and fit, it is possible that greater benefit of G-CSF might be seen in older populations [69].
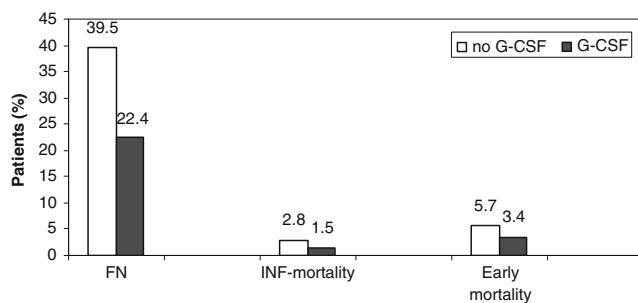


**Fig. 2** Efficacy of primary prophylactic granulocyte colony-stimulating factor (*G-CSF*; pegfilgrastim, filgrastim or lenograstim) versus placebo or no treatment in preventing febrile neutropenia (*FN*), infection-related mortality (*INF* mortality) and early mortality (all-cause, during chemotherapy) in 3,493 patients treated with chemotherapy for solid tumours or lymphoma. Results of a meta-analysis of 17 studies [69]

However, a meta-analysis of 148 studies in a broad range of settings, including adults and children with cancer or undergoing stem cell transplantation, found prophylactic G-CSF or GM-CSF to have little or no effect on early mortality (7.6% vs. 8.0% of patients) or infection-related mortality (3.1% vs. 3.8%) versus placebo/no treatment [70]. Nevertheless, G(M)-CSF did reduce the risk of documented infections (median 38.9% vs. 43.1%; rate ratio 0.85, 95% CI 0.79–0.92) and microbiologically documented infections (median rate 23.5% vs. 28.6%; rate ratio 0.86, 95% CI 0.77–0.96) [70]. Similarly, a recent Cochrane database review of 13 trials in patients treated for lymphoma (*n*=2,607) did not find any benefit of G-CSF or GM-CSF on overall survival (HR 0.97, 95% CI 0.87–1.09), freedom from treatment failure (HR 1.11, 95% CI 0.91–1.35), complete response (RR 1.03, 95% CI 0.95–1.10) or infection-related mortality (RR 0.93, 95% CI 0.51–1.71) [71].

The reasons for the differences between results of these three meta-analyses are not clear but probably relate to differences in individual study methodology and endpoints, as well as criteria for inclusion of studies. Both analyses that failed to show an effect of CSFs on mortality endpoints included studies that used GM-CSF (sargramostim or molgramostim) [70, 71], whereas the meta-analysis that demonstrated a survival benefit was restricted to studies of G-CSF [69]. It is thought that GM-CSF may be less effective than G-CSF in reducing FN and fever [72], and its use has been discontinued in Europe. In the USA, GM-CSF is not FDA-approved as an adjunct to standard myelosuppressive chemotherapy regimens in patients with solid tumours and lymphoma and has limited off-label use in this setting. Indeed, 61 of the 148 studies included in the Sung analysis used GM-CSF [70]. This analysis included transplant patients receiving high-dose chemotherapy, a different scenario from use of CSFs to support standard-dose chemotherapy. Moreover, only the Kuderer analysis [69] was restricted to trials in which daily CSFs were to be given continuously until neutrophil recovery.

Nevertheless, all three meta-analyses confirmed a substantial FN risk reduction in patients receiving G-CSF/GM-CSF support [69–71]. For instance, Kuderer et al. found that FN was reduced by 46% (22.4% vs. 39.5%: RR 0.54, 95% CI 0.43–0.67; *p*<0.001) [69].

Exploratory data from a prospective observational study conducted at 115 US practices (*n*=4,458 patients) showed that pegfilgrastim significantly improved survival endpoints in patients with comorbidities who were receiving chemotherapy [73]. Of these patients, 41% were aged >65 years, 46% had ECOG performance score >1 and 38% had stage 4 disease. Patients receiving primary pegfilgrastim prophylaxis (*n*=620) had better progression-free survival than those who did not, even after adjustment for other significant covariates. This study was not randomised,

which limits firm conclusions, but these results are consistent with the G-CSF meta-analysis [69].

## Are the G-CSFs different?

The non-PEGylated G-CSFs, standard G-CSF (filgrastim) and glycosylated G-CSF (lenograstim) appear to be broadly comparable in efficacy [16]. However, a growing body of evidence suggests that pegfilgrastim—a PEGylated formulation of filgrastim with neutrophil-regulated pharmacokinetics that is given as a single dose once per cycle [57, 74]—is more effective than filgrastim. A meta-analysis of five studies in a total of 617 patients treated for breast cancer or lymphoma showed that a single dose of pegfilgrastim was significantly more effective than 10–14 days of filgrastim in reducing FN (RR 0.64, 95% CI 0.43–0.97) [75]. Data from the larger meta-analysis by Kuderer et al. [69] also suggest that pegfilgrastim was more effective than either lenograstim or filgrastim, although it must be noted that the pegfilgrastim data came from a single study (Fig. 3). These findings might reflect the sustained stimulation of bone marrow by pegfilgrastim throughout the period of neutropenia.

Moreover, the way that filgrastim is administered in real-world clinical practice (and some clinical trials) may compromise its efficacy. It should be given daily, until ANC returns to the normal range; data from registrational trials indicate that this requires approximately 9–14 injections per chemotherapy cycle [14, 76]. However, it is common practice to administer fewer doses than this and/or to start treatment relatively late after chemotherapy [77–79]. Several analyses have shown that, when used in this manner, filgrastim may provide suboptimal protection against FN [33, 78, 79]. For instance, the Gepartrio study evaluated four different supportive regimens in consecutive cohorts of patients (n=1,256 total) receiving adjuvant TAC for breast cancer. FN occurred in 18% of patients who received an abbreviated course of daily G-CSF administered from days 5 to 10. However, a single dose of pegfilgrastim on day 2 reduced the incidence of FN to 7%; if ciprofloxacin was also incorporated into the prophylactic regimen, the risk was reduced to 5% (Fig. 4) [33].

An integrated analysis of data from 2,282 breast cancer patients compared pegfilgrastim primary prophylaxis with current-practice neutropenia management (a: no G-CSF or b: any G-CSF use other than protocol-specified pegfilgrastim
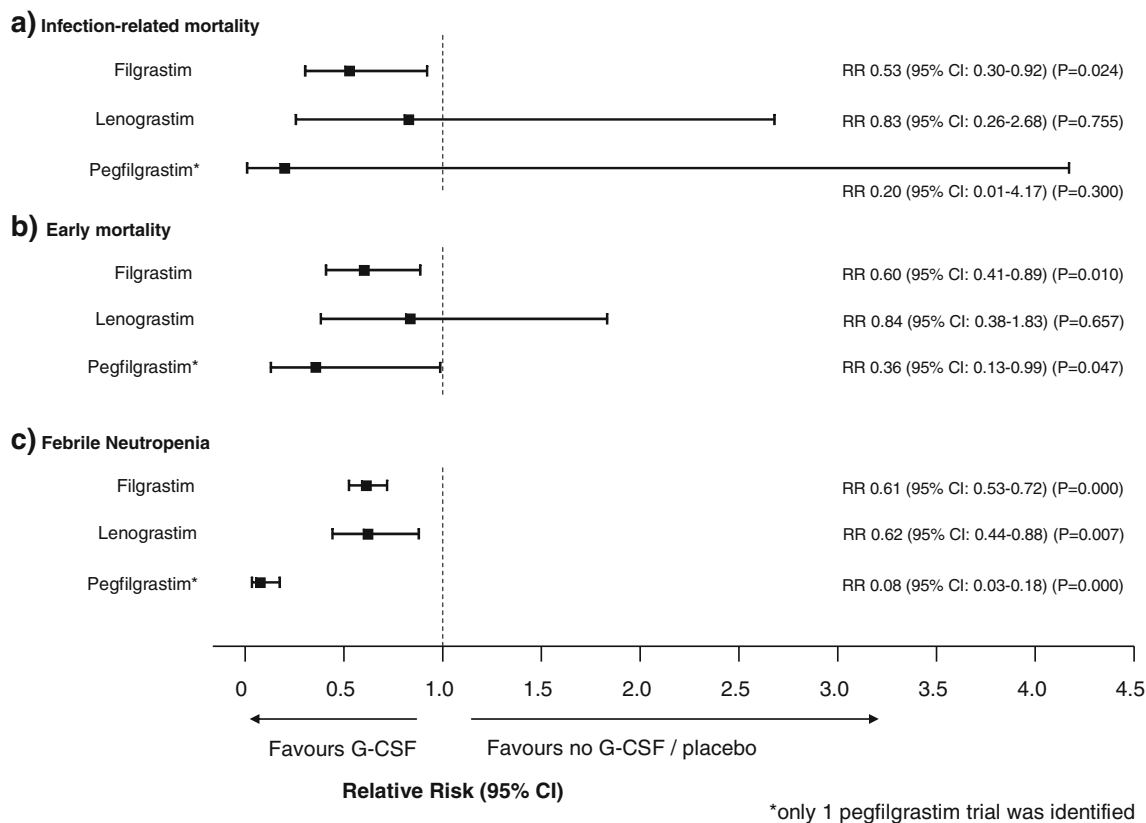


Fig. 3 Efficacy of different granulocyte colony-stimulating factors in preventing infection-related mortality, early mortality and febrile neutropenia in 3,493 patients treated with chemotherapy for solid tumours or lymphoma. Forest plot of data from a meta-analysis of 17 randomised controlled studies comparing G-CSF primary prophylaxis with placebo or no treatment [69]
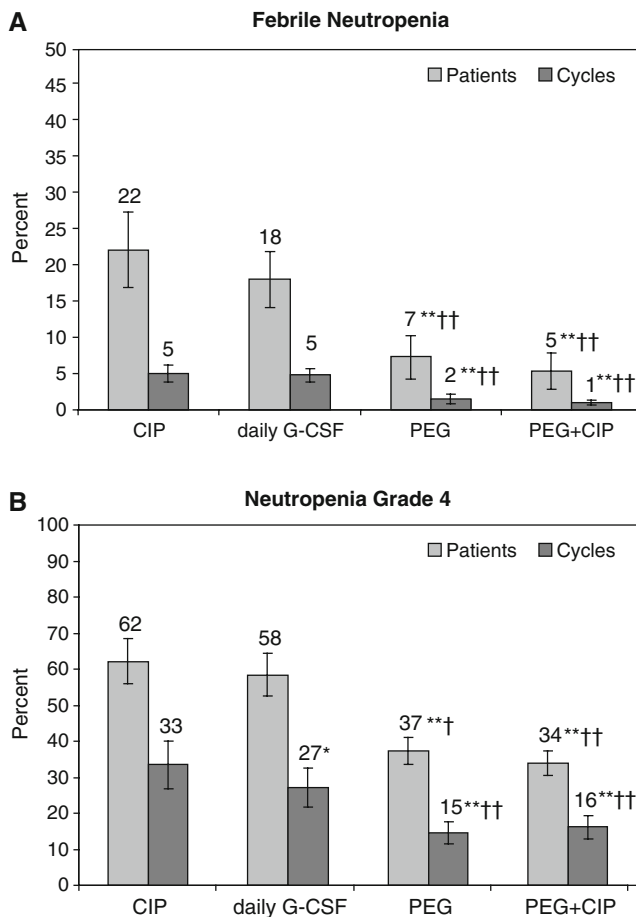
**Fig. 4** Comparison of febrile neutropenia and grade 4 neutropenia incidence per patient and per cycle in patients receiving TAC chemotherapy for early breast cancer, supported by different primary prophylactic regimens: ciprofloxacin 500 mg orally twice daily on days 5–14 ($n$=253 patients), daily granulocyte colony-stimulating factor (*G-CSF*; filgrastim 5 µg/kg per day or lenograstim 150 µg/m$^2$ per day) on days 5–10 ($n$=374), pegfilgrastim (*PEG*) 6 mg on day 2 ($n$=303) or pegfilgrastim plus ciprofloxacin (PEG+CIP; $n$=314) [33]. *$p$<0.01, **$p$<0.001 versus CIP; †$p$<0.01, ††$p$<0.001 versus daily G-CSF. Reprinted from von Minckwitz et al. [33]. By permission of Oxford Journals/European Society for Medical Oncology

primary prophylaxis) for supporting chemotherapy regimens associated with a moderately high/high FN risk [80]. The most common chemotherapy regimens were docetaxel or taxane/anthracycline combinations. Usage of primary G-CSF prophylaxis was low in the current-practice group: 75% of these patients did not receive any G-CSF prophylaxis in the first cycle. FN was markedly less frequent in the pegfilgrastim group compared with the current-practice group (5% versus 29%, adjusted for age, disease stage and study; adjusted odds ratio [OR] 0.124, 95% CI 0.08–0.194; $p$< 0.0001). A subanalysis in elderly patients ($n$=285, aged ≥65 years) showed similar results: FN occurred in 6% (95% CI 2–10%) of the pegfilgrastim group versus 24% (95% CI 16–32%) of the current-practice group, while dose reductions occurred in 15% versus 29% of patients [37].

A retrospective US survey [77] of patients ($n$=6,148) treated in 99 community oncology practices for various cancers also found that FN was more common in those who received filgrastim (6.5%) than in those who received pegfilgrastim (4.7%) [adjusted OR 1.41, 95% CI 1.02–1.96; $p$=0.040]. However, whereas pegfilgrastim was administered within approximately 2 days after chemotherapy, filgrastim was started much later (mean >7 days and >5 days after chemotherapy in first and subsequent cycles, respectively), suggesting that filgrastim was used reactively instead of proactively. A similar analysis found that in community-based patients receiving various chemotherapy regimens (total of 15,763 cycles), the risk of hospitalisation was approximately 30% lower with pegfilgrastim support than with daily G-CSF [81].

Alternative versions of many innovative biopharmaceuticals, including G-CSF [82], are being developed. These "biosimilars" will not be identical to the corresponding original products because of differing protein sources and difficulties in replicating the complex proprietary manufacturing processes involved. While biosimilars may cost less, it is possible that small differences in biochemical and biophysical characteristics might translate into differences in potency and immunogenic potential [83].

## Tolerability issues

### Bone pain

Bone or musculoskeletal pain is a characteristic adverse event associated with G-CSF treatment. This is generally mild to moderate and can be managed with standard analgesics [84–86]. A large meta-analysis [69] found that bone or musculoskeletal pain was reported in approximately 20% of patients who received G-CSFs compared with approximately 10% of controls (RR 4.023, 95% CI 2.156–7.52; $p$<0.0001). Arthralgia is also an adverse effect of taxane chemotherapy [87], which is often administered with G-CSF support. Filgrastim and pegfilgrastim were associated with similar incidences of bone pain in another large analysis (RR 0.95, 95% CI 0.76–1.19) [75]. Although administering a lower-than-recommended dose of G-CSF (pegfilgrastim) was reported to be successful in reducing bone pain [88], this strategy obviously risks achieving suboptimal protection against FN [89], and it is at yet unclear whether bone pain is dose-related.

### Other short-term adverse events

A proportion of patients may experience leucocytosis (white blood cell count >100×10$^9$/l) after receiving G-CSFs [64, 84, 90]. At ANC recovery, pegfilgrastim

clearance increases, resulting in a rapid decrease in serum concentrations. This resulted in less "overshoot" of ANC post-nadir compared with daily filgrastim [91]. Pegfilgrastim concentrations are negligible by day 12 and therefore unlikely to overstimulate neutrophil production [92].

G-CSFs can induce elevation of cancer antigen 15-3, a circulating marker of secreted products of the polymorphic MUC1 gene used for monitoring breast cancers, in breast cancer patients [93–96]. Physicians should be aware of the potential for this "false-positive" effect, which may occur via an increase in neutrophil counts or induction of MUC1 antigen [95]. There is no evidence that this is due to tumour stimulation.

Secondary malignancies

On the basis of retrospective data, it has been suggested that G-CSF/GM-CSF use might lead to a small increase in the risk of secondary malignancies. In patients treated with adjuvant chemotherapy for breast cancer, acute myeloid leukaemia or myelodysplastic syndrome (AML/MDS) occurred in 1.77% of those who had received G-CSF or GM-CSF ($n=906$) compared with 1.04% of those who had not ($n=4,604$; HR 2.14, 95% CI 1.12–4.08) [97]. However, as acknowledged by the investigators, anthracyclines and cyclophosphamide may increase the risk of second malignancies in a dose-related manner [98–100]; administration of G-CSF may have allowed higher chemotherapy doses to be delivered, thereby confounding the analysis. Moreover, data from other studies, including a very large observational study ($n=64,715$) [100], have not indicated an increased risk of secondary AML/MDS with G-CSF use [50, 100, 101].

A recent meta-analysis found that although intensified chemotherapy with G-CSF support slightly increased the risk of second malignancies compared with standard chemotherapy without G-CSF, this was more than offset by the survival benefits [102]. Thus, the overall risk/benefit ratio continues to favour G-CSF use [103], as it facilitates chemotherapy delivery and prevents life-threatening FN.

**Clinical implications of new data**

Guidelines published from 2006 onwards have broadened the scope of G-CSF use for supporting chemotherapy delivery. There is now a large body of evidence for the efficacy of pegfilgrastim, as well as filgrastim, in supporting dose-dense chemotherapy and facilitating delivery of the full dose on time. Importantly, recent data have provided further (albeit indirect) evidence that appropriate primary G-CSF prophylaxis can potentially confer survival benefits in patients receiving chemotherapy in the curative setting.

FN risk should be assessed on an individual patient basis, taking into account the regimen, patient- and disease-related factors and treatment intent. Predictive tools that will help clinicians to identify which patients are most likely to benefit from G-CSF prophylaxis are now starting to become available, and these will allow more efficient targeting of patients at high risk.

Several studies have documented the considerable cost burden of FN in patients receiving chemotherapy [1, 3]. An analysis in >40,000 US patients found that, on average, an FN episode resulted in a median hospital stay of 6 days and a median cost of $8,376, with 35% of patients being hospitalised for at least 10 days [3]. Smaller studies from various western European countries have provided estimates of the average charge for FN-related hospitalisation ranging from €2,619 in Spain to €4,931 in France [4, 104, 105]. These findings highlight the need to implement official guidelines for preventing FN. A number of economic analyses have indicated that the costs of G-CSFs can be at least partially offset by reduction of FN and its associated costs [106–108]. It should be noted that results of cost-effectiveness studies are dependent on the costs considered by each study, and such costs may differ between countries.

It is important that G-CSFs are used according to recommendations in order to gain the maximum benefit. In real-world clinical practice settings, patients often receive abbreviated courses of daily G-CSF treatment and this can reduce the level of FN protection obtained. Use of a single dose of pegfilgrastim per cycle in appropriate patients assures the delivery of adequate CSF support, providing a more convenient and potentially more effective strategy for assisting neutrophil recovery.

Prospective studies are needed to validate the importance of delivering the full dose intensity of standard chemotherapy regimens, integrated with G-CSF support where appropriate, across a range of tumour types. This will allow better quantification of the impact of both chemotherapy dose and supportive care in improving outcomes in cancer patients. These studies should also incorporate prospective evaluation of risk stratification for neutropenia and its complications, so that the use of both chemotherapy and G-CSFs can be optimised in the most cost-effective way.

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