Review article

The role of granulocyte colony-stimulating factors in the prevention of neutropenia and febrile neutropenia – the current state of knowledge

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ABSTRACT

Granulocyte colony-stimulating factors, introduced in the 1990s to prevent neutropenic fever, improve patients' prognosis after myelotoxic chemotherapy. G-CSFs accelerate bone marrow recovery, shortening the duration of neutropenia and reducing its intensity as well as the risk of febrile neutropenia. There are short- and long-acting G-CSFs available these days. This paper is a review of the efficacy, toxicity and indications for short- and long-acting G-CSFs as indicated in the most recent studies.

Key words: neutropenia, neutropenic fever, long- and short-acting granulocyte colony-stimulating factors, guidelines, review

NEUTROPENIA AND FEBRILE NEUTROPENIA

Neutropenia is a drop in neutrophil count to below 1600/μL, with agranulocytosis being a drop below 500/μL. A fall below 1000/μL is believed to be clinically significant, as the condition is associated with a considerable increase in the risk of severe infection of grade 3 or higher in accordance with the Common Terminology Criteria for Adverse Events (CTCAE).

According to the European Society for Medical Oncology (ESMO), febrile neutropenia (FN) is defined as an oral temperature of > 38.3°C or two consecutive readings of > 38.0°C for two hours, and an absolute neutrophil count (ANC) below 500/μL [1–4]. **Development of severe neutropenia and/or FN in cancer patients is a life-threatening situation and is an indication for hospitalization and intravenous broad spectrum antibiotic therapy** [1–4]. Additionally, the above mentioned complications increase the cost of treatment [1–4].

In order to assess the risk of neutropenia-related complications, the MASCC (Multinational Association for Supportive Care in Cancer) risk index score (tab. 1) has been elaborated: in low-risk patients (≥ 21 points) the incidence of severe complications amounts to 6% (with the mortality risk of 1%), while in high-risk patients (< 21 points) it is as much as 39% (with a 14% risk of death) [5].

TABLE 1.
MASCC Risk Index for Febrile Neutropenia.

Characteristic	Weight
Clinical symptoms related to cancer or concomitant diseases • none or mild • moderate	 5 3
Systolic blood pressure > 90 mmHg	5
No chronic obstructive pulmonary disease	4
Solid tumour or haematological malignancy with no previous fungal infection	4
No dehydration	3
Outpatient status	3
Age < 60	2

A frequent clinical problem related to neutropenia and/or FN is the relative dose intensity (RDI). It consists in interrupting and/or delaying chemotherapy and reducing drug doses during consecutive anti-cancer treatment cycles, and it is more frequently associated with elderly patients. A study carried out in 2004–2006 by Pettengell et al. [6], involving two groups of patients (with breast cancer and with lymphomas) indicated that chemotherapy may be delayed (≥ 4 days) in up to 34% of breast cancer patients, 54% of non-Hodgkin lymphoma (NHL) patients, and 40% of HL patients. The dose was found to have been reduced (≥ 10%) in 14.2% of breast cancer patients, and in 33.3% of NHL patients. The study reported RDI reduction of ≤ 85% in 20% of breast cancer patients and in 30% of patients with lymphomas. The main risk factors involved:

- ECOG performance status > 1
- age ≥ 65
- neutropenia with fever in the first cycle of chemotherapy.

It has been demonstrated that even RDI reduction of less than 10% compromises treatment outcomes, including patient survival [7].

COLONY STIMULATING FACTORS

Granulocyte colony-stimulating factors (G-CSF) stimulate the proliferation and differentiation of progenitor cells and neutrophil precursor lines as well as prolong the half-life and improve phagocytic activity of neutrophils [8].

Presently, there are two G-CSF types available on the market: the short-acting G-CSF, including filgrastim, tbo-filgrastim, filgrastim-sndz and lenograstim, and the pegylated long-acting one (pegfilgrastim and lipegfilgrastim).

Filgrastim was the first short-acting G-CSF in clinical practice. It is a recombinant methionyl human granulocyte colony-stimulating factor, produced by recombinant DNA technology in the *Escherichia coli* cells. It is chiefly eliminated via the kidneys, which is why it requires daily administration [9]. According to manufacturer recommendations, filgrastim should be administered once daily, subcutaneously or intravenously, dosed at 5 μg/kg body weight/24 h, to patients who receive cytotoxic drugs, and should be initiated no sooner than 24 hours after chemotherapy. Due to their mechanism of action and a short half-life, all short-acting G-CSF products require daily administration until the neutrophil count returns to normal (around 11 doses per one chemotherapy cycle) [1, 3, 4, 10, 11].

In long-acting G-CSF preparations, plasma clearance has been limited thanks to the development of a recombinant human granulocyte colony-stimulating factor covalently conjugated to a particle of polyethylene glycol (PEG). The long-acting products are mainly eliminated by neutrophils, which renders their concentration high during neutropenia, followed by a gradual decrease as the neutrophil count continues to go up. That mod-

ification has made it possible to reduce the frequency of G-CSF analogue administration to a single dose during one cycle of chemotherapy (24 hours after the completion of chemotherapy according to manufacturer recommendations), while maintaining the same efficacy, and improving the safety profile [1–4, 10–12].

Pegfilgrastim was the first approved long-acting G-CSF product [10–12]. In 2013, the European Medicines Agency (EMA) granted marketing authorization to another long-acting agent, i.e. lipegfilgrastim, which is a conjugate of recombinant human G-CSF covalently conjugated to PEG with the use of a carbohydrate linker, which enhances its receptor binding capacity. In their analysis of randomized clinical trials, Wang et al. demonstrated that lipegfilgrastim is at least as efficacious and safe as pegfilgrastim [13].

USING G-CSF IN ACCORDANCE WITH THE GUIDELINES

In line with their characteristics, G-CSF products should be used in order to shorten the duration and to reduce the incidence of FN in patients treated with cytotoxic chemotherapy for cancer, with the exception of myeloid leukaemia and myelodysplastic syndrome (MDS) [1–4]. G-CSF may be administered as primary and secondary prevention [3].

As part of primary prevention, in accordance with the current guidelines of the European Organisation for Research and Treatment of Cancer (EORTC), American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN), G-CSF is indicated if the chemotherapy regimen in question involves FN risk > 20%. If the risk ranges from 10% to 20%, one should additionally consider the following factors:

- patient age > 65
- advanced underlying condition
- prior episodes of FN
- no antibiotic prophylaxis
- malnutrition or poor performance status
- female sex
- haemoglobin concentration < 12 g/dL
- liver, kidney or heart failure.

Risk assessment should be performed before each consecutive chemotherapy cycle. In the case of FN and/or dose-reducing neutropenia following the previous chemotherapy cycle, the patient is burdened with a high risk, and secondary G-CSF prevention should be included in the subsequent cycle [1–4].

International literature contains relatively few findings on the therapeutic use of G-CSF. A meta-analysis from Cochrane's database, involving 1518 subjects from 13 studies, reported a shorter hospital stay and an increase in the neutrophil count, without improved survival, in patients receiving therapeutic G-CSF [14]. According to the NCCN guidelines, patients who develop FN despite G-CSF prophylaxis should continue receiving the drug at the same dose. However, extra G-CSF doses are not recommended to patients on long-acting G-CSF products. In a group with no prior G-CSF prevention, possible additional risk factors must be considered, including:

- age > 65
- sepsis
- prolonged (> 10 days) neutropenia < 100/μL
- pneumonia
- invasive fungal infection or other infections
- hospital stay
- prior FN episode.

According to the above mentioned principles, FN risk should be assessed anew before each chemotherapy cycle [3]. It should be emphasised here that filgrastim and filgrastim-sndz are indicated for therapeutic use, while pegfilgrastim and lipegfilgrastim have only been studied in the context of preventative use [3].

G-CSF is also used to mobilize the CD34+ stem cells. According to the NCCN guidelines [3], short-acting G-CSF products (filgrastim, filgrastim-sndz and tbo-filgrastim) are indicated for CD34+ harvest, with the recommended dose of 10 μg/kg body weight/24 h sct. Based on the recent findings, though, single-dose long-acting products (pegfilgrastim) are equally efficacious [15].

G-CSF may also be administered to accelerate regeneration following bone marrow transplantation. The NCCN guidelines [3] discuss the use of filgrastim and its derivatives starting from day 5 from autologous (auto-PBSCT) and cord blood transplantation, and the use of pegfilgrastim following autologous transplants solely. The relevant literature includes numerous publications comparing the efficacy of filgrastim and pegfilgrastim in post-auto-PBSCT patients [16]. Frączak et al. observed in their study, involving post-auto-PBSCT patients with multiple myeloma, that lipegfilgrastim was just as efficacious as filgrastim, with the only difference being a shorter hospital stay in the groups of patients receiving lipegfilgrastim [17].

DOSING SCHEDULE ADHERENCE

Adherence, i.e. using G-CSF in line with the above mentioned guidelines is an important issue. Study results indicate that

clinical practice does not fully coincide with the recommendations. One study analysed the degree to which doctors of different specialties (195 of them, including haematologists, pulmonologists, and gynaecologists) adhere to the guidelines involved, also depending on the type of cancer (666 lung cancers, 286 lymphomas, 976 breast cancers). It was revealed that out of 7805 chemotherapy cycles, G-CSF in high-risk patients was administered in accordance with the recommendations in [18]:

- 15.4% of lung cancer patients
- 84.5% of lymphoma patients
- 85.6% of breast cancer patients,

and in the intermediate-risk group in:

- 38.8% of lung cancer patients
- 59.4% of lymphoma patients
- 49.3% of breast cancer patients.

Lugtenburg et al. analysed 1113 patients with diffuse large B-cell lymphoma (DLBCL) undergoing R-CHOP-21 (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy as compared to those treated with the R-CHOP-14 regimen. Also in that case the frequency of G-CSF use in patients with FN risk > 20% was not satisfactory. G-CSF prophylaxis was not offered to:

- in the R-CHOP-14 group – 14% of younger patients, and 19% of elderly patients
- in the R-CHOP-21 group – as much as 61% of younger patients, and 47% of elderly patients.

Older age was associated with a higher probability of G-CSF use [19]. An additional problem was found to be the duration of short-acting G-CSF product use, which was often insufficient. In clinical trials [10, 11] dedicated to the comparable efficacy of pegfilgastrim and filgastrim, the latter was administered for 10–11 days. A similar finding was reported for a paediatric group (61 patients, including 29 treated with filgrastim and 32 treated with pegfilgrastim) after autologous bone marrow transplantation. Filgrastim was found to be used for 7 up to 12 days [20]. However, studies comparing the efficacy of long- and short-acting G-CSF products indicate that a lower efficacy of the latter is often associated with an insufficient duration of their administration, i.e. from 3 to 7 days [12, 19].

G-CSF IMPACT ON THE EFFICACY OF CHEMOTHERAPY

It has been demonstrated that G-CSF reduces the risk of febrile neutropenia, mortality related to infections, and the number of premature deaths [9, 21].

Dose-reducing toxicity, including myelotoxicity, is one of the chief factors impacting the efficacy of anti-cancer treatment [1–4]. Intensified and prolonged neutropenia results in dose reduction and delayed administration of the consecutive cycles of chemotherapy, which in turn reduces its efficacy. Emergence of G-CSF in the 1990s significantly improved patient prognosis [9, 21]. In a systematic review of 59 randomized studies, involving a total number of 25,000 patients with solid tumours and lymphomas, primary G-CSF prevention was found to reduce FN risk, and improve the intensity of chemotherapy. Moreover, the review revealed a considerable reduction of infection-related mortality risk and of early death during chemotherapy [21]. **Therefore, in line with the current guidelines, it is essential to initiate G-CSF prophylaxis as early as the first chemotherapy cycle.**

Introduction of hematopoietic growth factors made it possible to intensify treatment regimens, using standard doses of cytostatics in accelerated protocols, e.g. over periods shorter than 3 weeks [22]. Drullinsky et al. studied breast cancer patients subjected to adjuvant chemotherapy with 2-week breaks, and reported improved progression free survival and overall survival in the group receiving chemotherapy every 2 weeks with simultaneous administration of G-CSF/filgrastim following each cycle in order to enhance bone marrow regeneration [22]. Thanks to the use of G-CSF and the resulting reduction in the duration of neutropenia, it is possible to apply intensive chemotherapeutic regimens like CODOX (cyclophosphamide, doxorubicin) or GMALL in haematological malignancies.

EFFICACY ASSESSMENT OF DIFFERENT G-CSF TYPES

G-CSF is a potent agent that releases mature neutrophils from bone marrow. A single dose (5 µg/kg body weight administered subcutaneously) results in a 5-fold increase in the neutrophil count of healthy persons within 12–24 hours, bringing it up from ca. 4,000/µL to 20,000/µL [23]. Multiple use of G-CSF accelerates production of neutrophils and enhances their migration from bone marrow to peripheral blood [24]. Compared to placebo, as recent study results indicate, G-CSF significantly reduces FN incidence in patients undergoing myelotoxic chemotherapy [9–11, 21].

Together with the development of long-acting products, there came a question about their efficacy as compared to the short-acting ones. Presently, however, it is impossible to establish beyond any doubt what the guidelines should be as regards selection of the available G-CSF drugs. According to ESMO, short-acting G-CSF are equally efficacious provided that the dos-

ing schedule is appropriate, i.e. that they are administered no sooner than 24–72 h following chemotherapy, and for no fewer than 11 days. Those recommendations have been confirmed by two randomized double-blinded clinical studies involving stage II–IV breast cancer patients undergoing myelosuppressive chemotherapy with doxorubicin and docetaxel. The studies demonstrate that long-acting G-CSF shows identical efficacy as the short-acting product on condition that the latter is administered from day 2 following chemotherapy until the level of ANC ≥ 10,000/μL is reached, i.e. for around 10–11 days. In the first of the above mentioned studies, involving 157 patients, the mean duration of grade 4 neutropenia in those receiving pegfilgrastim at a single dose of 6 mg was 1.8 days, and in those on filgrastim it was 1.6 days, with the incidence of febrile neutropenia amounting to 13% and 20% respectively [11]. In the second study, involving 310 patients, pegfilgrastim was administered at a single dose of 100 μg/kg body weight. The mean duration of neutropenia in those on pegfilgrastim was 1.7 days, while in those receiving filgrastim it was 1.8 days, with the incidence of febrile neutropenia totalling 9% and 18% respectively [10]. However, Cooper et al. carried out a meta-analysis comparing 5 studies (n = 606 patients, including 315 treated with pegfilgrastim and 291 treated with filgrastim), in which they determined the relative risk of FN for pegfilgrastim as compared to filgrastim as 0.66% (95% CI: 0.44–0.98%). The result was in line with what was observed in the same review [25]: when comparing the pegfilgrastim group without G-CSF prophylaxis with the filgrastim group without G-CSF prevention, FN risk reduction was higher in the former patient group. It was additionally emphasised in the meta-analysis that patients treated with filgrastim had received the drug in accordance with the recommendations (10–11 days).

An interesting finding was published based on the study carried out by Hershman et al. [26]. Having analysed data pertaining to 10,773 stage I–III breast cancer patients on chemotherapy, they demonstrated than between 2002 and 2005, G-CSF rate of use went up from 36.8% to 73.7% of patients, including an increase in pegfilgrastim use from 4.1% to 83.6%. The increase was related to the findings about improved treatment outcomes associated with intensified chemotherapy regimens, and in the case of pegfilgrastim also to its ease of use. In daily clinical practice, short-acting G-CSF dosing principles are often not adhered to, with treatment initiated too late, and the total dose being too small, possibly affecting the drug's efficacy.

G-CSF TOXICITY PROFILE

The most frequent adverse event related to G-CSF is transient musculoskeletal pain, usually mild or moderate, and managed with standard painkillers [1–4, 9]. No differences have been observed in terms of the pain frequency and intensity between the patients on long-acting and short-acting G-CSF products [1–4, 9, 13].

Individual publications also indicate that long-term administration of recombinant G-CSF may be associated with an increase in the risk of hematopoietic malignancies [27]. However, there is no unequivocal opinion to date on the increased risk of acute myeloblastic leukaemia (AML)/MDS in patients undergoing myelotoxic chemotherapy and G-CSF prophylaxis. Still, G-CSF should be avoided in MDS/AML [3]. It should be emphasised, though, that the higher rate of MDS/AML may result from the intensity of chemotherapy, made possible by the use of G-CSF, and not from the G-CSF itself. So far, no significant differences have been reported in terms of the efficacy and safety profile between the original G-CSF particles and biosimilars.

SUMMARY

G-CSF use in the prophylaxis of chemotherapy-induced neutropenia stems from our understanding of the physiological processes regulating production and distribution of neutrophils under normal conditions and in response to infection. Introduction of G-CSF drugs has improved the efficacy of oncological treatment, making it possible to intensify chemotherapy. Based on the results of randomized clinical studies, G-CSF products (both the long- and short-acting ones) have been proven to be efficacious at enhancing bone marrow regeneration following standard-dose chemotherapy, preventing febrile neutropenia and other neutropenia-related complications. As a result, consecutive chemotherapy cycles may be administered as planned, despite the considerable toxicity of regimens such as GMALL or CODOX.

According to the current guidelines, G-CSF should not be used after myelotoxic chemotherapy, followed by FN risk exceeding 20% or ranging between 10% and 20% with additional risk factors, including:

- advanced age
- advanced stage of disease
- poor performance status
- malnutrition
- prior neutropenia.

Presently, there are no guidelines on the selection of short- or long-acting G-CSF products. Study results are not unequivocal in that matter. Pegylated long-acting agents appear to be more

convenient and easier to dose that the short-acting products, which are often administered at insufficient doses and not long enough to be fully effective. Hence, due to the higher adherence, long-acting G-CSF drugs have been reported as more efficacious in some studies. All in all, G-CSF products are well-tolerated and no differences in terms of their safety profile have been observed between the short- and long-acting ones.

What is most essential is that G-CSF drugs should be administered in accordance with their indications, i.e. to prevent neutropenia and FN in high-risk patients after myeloablative chemotherapy, beginning from the very first treatment cycle. Thanks to such prophylaxis, the patient's quality of life may be improved, and the efficacy of anti-cancer treatment may be maximized.

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