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SYSTEMATIC REVIEW

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Clinical role of filgrastim in the management of patients at risk of prolonged severe neutropenia: An evidence-based review

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Abstract

Background: Patients undergoing chemotherapy are at risk of toxicity, especially of haematological origin. Granulocyte depletion, although often underestimated, can lead to the occurrence of an event defined as febrile neutropenia (FN). Neutropenic fever syndromes are dangerous because they cause major complications in around 25%-30% of patients and have a mortality rate of up to 11%. Treatment for FN was limited to antibiotics and supportive therapies until filgrastim was approved for use in the 1990s.

Objectives: The present systematic review focuses on the efficacy and safety of this haematopoietic growth factor.

Data Sources and Methods: For this review, a systematic literature search of electronic databases and references from recent reviews up to December 2018 was carried out to identify clinical trials, observational studies and case reports evaluating filgrastim efficacy and safety. English language was defined as a restriction. Published randomised controlled trials (RCTs), case reports and reviews analysing the effects of filgrastim on severe neutropenia and its limits were considered. Four review authors independently selected the studies, assessed the risk of bias and extracted study data.

Results: As reported in ASCO guidelines, the efficacy of filgrastim with respect to placebo or no treatment in RCTs is based on its prevention of FN. A recent meta-analysis analysed nine RCTs with 2197 patients, revealing a reduction in the incidence of FN with filgrastim (risk ratio [RR] 0.63, 95% CI 0.53-0.75). These findings were further confirmed in two observational studies. Bone pain is the most commonly reported adverse event with filgrastim, while other toxicities are associated with filgrastim efficacy and with an increased neutrophil count.

Key Findings: In conclusion, our findings attest to the previous results on the efficacy and safety of filgrastim.

1 | INTRODUCTION

A major issue in patients undergoing chemotherapy is the risk of toxicity, especially of haematological origin. In particular, granulocyte depletion, although underestimated, can lead to a reduction in the neutrophil count associated with fever, known as febrile neutropenia (FN).[1] Neutrophils play a critical role in the innate immune system, providing powerful defence against bacterial and fungal infections. The severity and duration of a reduced neutrophil count are the most important risk factors in patients with prolonged neutropenia, especially after induction chemotherapy or transplantation for haematological malignancies.[2] Although fever is a potential symptom of infection, patients experiencing protracted neutropenia are sometimes anergic and may also be afebrile or hypothermic because of the steroids and nonsteroidal anti-inflammatory drugs used as supportive therapy for the side effects of chemotherapy. FN is an important syndrome because of major associated complications such as hypotension, acute renal, respiratory and heart failure in 25%-30% of patients, and a mortality rate of up to 50% in patients affected by severe sepsis or septic shock.[3-5]

In 2011, Lyman et al performed a study on 3760 patients to identify risk factors for FN. Among those identified were reduced hepatic and renal function, preexisting bone marrow suppression and previous chemotherapy. Specifically, anthracyclines, alkylating agents and topoisomerase I and II inhibitors were among the most neutropenising drugs. The risk of FN further increased when more than one chemotherapeutic agent was used in association.[6]

The same authors published another paper showing that the adjusted mortality risk in patients with FN was 15% higher than in those without FN.[7] These findings confirm the importance of systemic complications as a result of neutropenia after myelosuppressive therapy.[2]

Granulocyte colony stimulating factors (G-CSF) induce the proliferation, differentiation and activation of neutrophils in bone marrow, increasing the number of circulating neutrophils.[4] The treatment of FN was limited to antibiotic treatment and other support therapies until the early 1990s when the recombinant human G-CSF, filgrastim, was introduced into clinical practice. The risk of developing fever in patients undergoing chemotherapy is the most important factor to determine the indication for the use of prophylactic G-CSFs. This risk is related to the intensity of chemotherapy, setting (palliative vs adjuvant), schedule (eg dose-dense), the presence and degree of injury to the gastrointestinal mucosa, the underlying damage caused to the patient's haematopoietic stem cells, the concurrent use of radiation and the overall clinical status of the patient (ie age and comorbidities).[8] The Multinational Association for Supportive Care in Cancer risk index score could be a useful tool to identify patients with FN at different risk of developing serious medical complications or of death.[9] However, it should be used with caution in patients with haematologic malignancies.[10]

The latest key recommendations from ASCO guidelines[5] on the use of G-CSFs include:

Review criteria

- Searches updated to December 2018 were conducted independently in the following electronic databases: Medline via PubMed, EMBASE and Cochrane Central Register of Controlled Trials. Keywords used were: "Filgrastim", "NEUPOGEN®", "Neutropenia" and "Febrile Neutropenia".

Message for the clinician

- This systematic review provides an overview of filgrastim dose, timing and duration in chemotherapy-induced neutropenia in the "biosimilars and pegfilgrastim era". Our aim was to help clinicians optimise their use of filgrastim and facilitate decision-making for patients with severe neutropenia. We also wanted to underline the potential for filgrastim repurposing.

- "Primary prophylaxis" when a patient undergoing chemotherapy has not experienced neutropenia but has a 20% chance of developing it on a given regimen and another equally safe or effective regimen not requiring the use of G-CSFs is not available.
- "Secondary prophylaxis" to prevent FN in a patient who has already experienced it in order to maintain the dose density. A prior episode of fever during neutropenia is a risk factor for developing fever during neutropenia in later treatment cycles, with a 50%-60% incidence of recurrence.
- "Supportive care" to reduce the severity and duration of chemotherapy-induced neutropenia in afebrile patients.

Of note, G-CSFs should be not routinely administered in patients with established neutropenia and fever.[3]

Biosimilar medicines were first used in Europe in 2005. Once the patent for a pharmacological product has expired, a biosimilar drug can be produced by other companies. Biosimilars must be equivalent to their reference products from a biological, pharmacokinetic and pharmacodynamic point of view. The concept of biosimilarity refers to the ability of these drugs to be similar to the original product in terms of quality, safety and efficacy.[11,12]

The aim of the present systematic review was to summarise current literature data on the mode of action, pharmacology, pharmacokinetics, efficacy and safety of filgrastim and related biosimilars.

2 | METHODS

Four authors of this review carried out an independent literature search in the following electronic databases updated to December 2018: Medline via PubMed, EMBASE and Cochrane Central Register of Controlled Trials. The keywords "Filgrastim", "NEUPOGEN®", "Neutropenia" and "Febrile Neutropenia" were used for the search. An additional analysis of the safety profile, especially in relation to

adverse events (AEs) of special interest, was performed on the basis of pooled data from the main clinical trials and Summary of Product Characteristics. Abstracts with results not published in manuscript form were avoided. A hand search of bibliographies was also performed for systematic reviews identified as containing relevant information in the initial search. A flow diagram of the literature search is shown in Figure 1.

2.1 | Pharmacology, mode of action, pharmacokinetics and dosing strategies of filgrastim

Granulocyte colony stimulating factors promote the growth of neutrophils from human bone marrow progenitor cells.[13]

Biotechnological drugs such as G-CSFs are obtained using recombinant technology, implanting genetic material (eg DNA) into the living organisms and converting them into "industries" of the substance needed, usually a pharmacologically active protein. The recombinant haematopoietic colony-stimulating factor, filgrastim, is a potent promoter of the maturation of neutrophil cells, boosting proliferation and survival. This glycoprotein plays a key role in increasing bone marrow granulopoiesis and is frequently used to reduce neutropenia in solid tumours and haematological malignancies.[14] In addition, filgrastim exhibits non-linear pharmacokinetics. It is cleared by the kidneys and its clearance depends on the concentration used and the neutrophil count at the time. Filgrastim, administered subcutaneously at a dose of 3.45 μg/kg or 11.5 μg/kg, results in maximum serum concentrations of 4 ng/mL and 49 ng/mL within 2 and 8 hours, respectively. If intravenously administered, the volume of distribution reaches 50 mL/kg and the half-life elimination is around 3.5 hours. Filgrastim clearance rates are about 0.5-0.7 mL/min/kg. Single parenteral doses or daily intravenous doses over a 14-day period have similar half-lives. Both subcutaneous and intravenous administration have comparable half-lives; 210 minutes following a dosage of 3.45 μg/kg in the former and 231 minutes following a dosage of 34.5 μg/kg in the latter. A continuous 24-hour infusion of 20 μg/kg over an 11- to 20-day period produces a steady-state concentration of filgrastim without drug accumulation during this period. Filgrastim bioavailability after subcutaneous administration ranges from 60% to 70%.[3] Two meta-analyses showed that the use of filgrastim primary prophylaxis (PP) vs no G-CSF PP or placebo was associated with a significant reduction in the risk of FN.[15,16]

Granulocyte colony stimulating factors should be started at least 48 hours after intense chemotherapy with a high risk of leukopenia to maximise bone marrow stimulation. Although there is no hard and fast rule about when to stop treatment, it is generally done after complete neutrophil recovery to avoid an overlap with the subsequent treatment cycle as this could lead to increased myelotoxicity.[17]

A recent paper by Schirm et al focused on G-CSF schedules using a biomathematical model of human granulopoiesis for different chemotherapy regimens to optimise filgrastim and pegfilgrastim administration. The authors reported that, for the highest risk group, filgrastim should begin 6-8 days after the start of therapy, cycle with at least eight injections. Timing is less important for medium- and low-risk groups, with six and four injections, respectively, obtaining sufficient neutrophil recovery.[18]

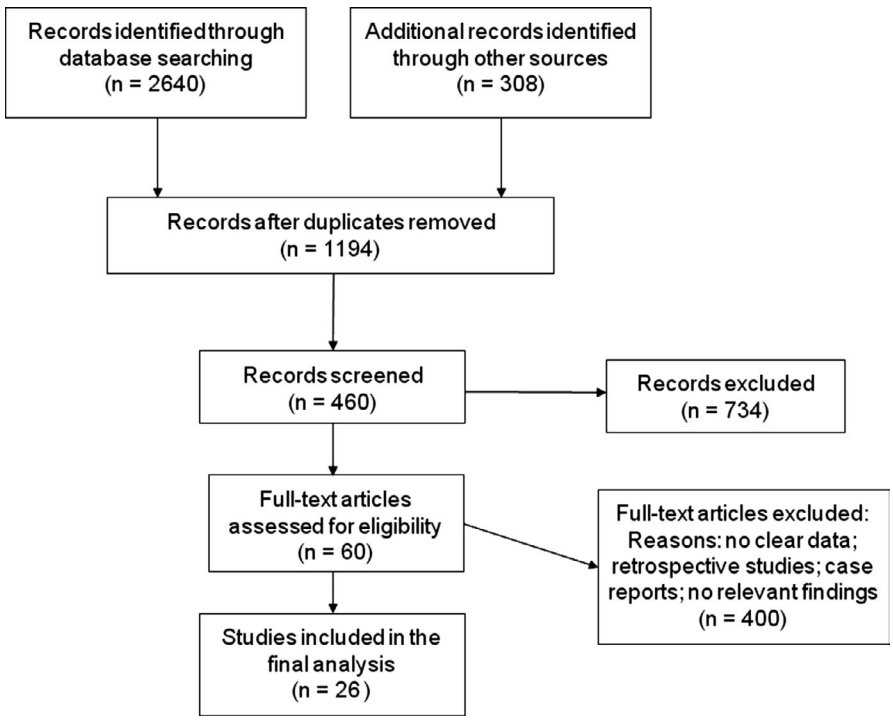

FIGURE 1 Flow diagram of search methods

2.2 | Biosimilars

The past few decades has seen an increase in the importance of biosimilar drugs, thanks to improved technologies with sustainable biotherapeutics.[19] There are currently five filgrastim biosimilars available on the European market. The first was approved in 2009 for the same indications as the comparator following comparability studies between the biosimilar and its reference product.[20] Physiochemical tests revealed identical primary, secondary and tertiary molecular structures. The biosimilars showed an in vitro biological similarity to the comparator in murine myelogenous leukaemia cells stimulated by G-CSFs. Data from several cancer trials reported a comparable pharmacodynamic and pharmacokinetic profile with similar safety and efficacy between the biosimilars and the reference product. [21-27] These drugs also play a key role in reducing costs, thus contributing to the financial sustainability of treatment programmes.[19]

2.3 | Efficacy studies, including comparative studies and relevant case reports

Filgrastim indications are currently as follows:

1. Reduce infections and FN incidence in patients with solid tumours undergoing chemotherapy at high risk of causing severe FN;
2. Decrease time to neutrophil recovery and duration of fever in patients undergoing treatment for acute myeloid leukaemia, especially in patients aged ≥65 years undergoing curative chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab) for diffuse aggressive lymphoma, and with comorbidities;
3. Reduce the duration of neutropenia and neutropenia-related complications, such as FN, in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT);
4. Mobilise autologous haematopoietic cells in the peripheral blood to achieve leukapheresis, alone or in combination with plerixafor;
5. Decrease the incidence and duration of clinical complications of neutropenia (eg. fever, infections, oropharyngeal ulcers) in patients with symptomatic congenital neutropenia, cyclic neutropenia or idiopathic neutropenia;
6. Improve survival in patients exposed to myelosuppressive doses of radiation (Haematopoietic Syndrome of Acute Radiation Syndrome)[3];
7. The use of CSFs in paediatric patients is almost always guided by clinical protocols. As in adults, their use is reasonable for the PP of paediatric patients with a high likelihood of FN. Similarly, the use of CSFs for secondary prophylaxis or for therapy should be limited to high-risk patients;
8. For paediatric indications in which dose-intense chemotherapy is known to have a survival benefit, such as Ewing's sarcoma, CSFs should be used to enable the administration of these regimens.[5]

The study that led to the approval of G-CSFs was that of Crawford et al, published in The New England Journal of Medicine in 1991.[4] In their randomised double-blind phase III trial, 211 patients with small-cell lung cancer treated with cyclophosphamide, doxorubicin and etoposide were randomised to receive filgrastim or placebo. The FN rate was 77% in the placebo group and 40% in the G-CSF group ($P < .001$). A reduction of 50% in the duration of intravenous antibiotic treatment, length of hospitalisation and incidence of infections was seen in the G-CSF group with respect to the placebo group.[4] The authors also concluded that patients with FN at the first treatment cycle were at high risk for subsequent FN events and that prophylactic G-CSFs should be considered for patients receiving moderately to highly myelosuppressive chemotherapy regimens.[28]

Other studies have been carried out on the same topic. Hartmann et al performed a randomised, double-blind, placebo-controlled trial on G-CSFs in severe neutropenic afebrile patients to evaluate the duration of neutropenia, hospitalisation rate, length of hospitalisation, duration of parenteral antibiotic treatment and number of culture-positive infections. The entire population (138 patients) was randomised to receive G-CSF (n = 71) or placebo (n = 67). The use of G-CSFs reduced the median duration of severe neutropenia (2 days) with respect to placebo (4 days). However, no significant differences were seen in the hospitalisation rate, number of days spent in hospital, duration of treatment with parenteral antibiotics and number of culture-positive infections.[29]

Several studies have been performed to evaluate the safety and efficacy of filgrastim compared with placebo. In two studies on acute lymphoblastic leukaemia, patients were randomised to receive filgrastim or placebo after intensive remission-induction chemotherapy.[30,31] In the study by Larson et al,[28] G-CSFs significantly shortened the duration of neutropenia and length of hospitalisation with respect to the control group (median 16 vs 32 days [$P < .001$] and 22 vs 28 days [$P = .02$], respectively. No benefit in overall survival (OS) or progression-free survival was seen.[30] In the work by Pui et al,[31] the use of G-CSFs resulted in a shorter median duration of hospitalisation compared with control (6 days vs 10 days, respectively [$P = .011$]) and fewer documented infections (12 and 27, respectively [$P = .009$]). [31] In randomised trials on non-Hodgkin's lymphoma, patients receiving G-CSFs showed a lower rate of FN and a higher dose intensity than those not given growth factors. Maintaining the full chemotherapy dose did not correlate with a better outcome in any of the studies. [32-34]

Fosså et al evaluated the routine use of filgrastim in patients with malignant germ cell tumours undergoing combination chemotherapy.[35] The growth factor significantly improved adherence to the treatment schedule but did not correlate substantially with failure-free or OS. However, its use was associated with a clinically significant reduction of toxic deaths in the experimental intensified-chemotherapy arm.[35]

In another randomised trial, 130 patients with small-cell lung cancer received filgrastim or placebo after combining chemotherapy with cyclophosphamide, doxorubicin and etoposide.[36] The FN rate was 53% for the 64 placebo patients and 26% for the 65

receiving filgrastim (one patient was not evaluable in the latter group) ($P < .002$). There was a significant reduction in the need for parenteral antibiotics in the G-CSF group (58%) compared with placebo (37%) ($P < .02$) and also in the incidence of infection-related hospitalisation (39% vs 58%, respectively). At least one dose modification in the chemotherapy cycles was needed in 29% of filgrastim patients compared with 61% of those in the placebo group ($P < .001$).[36]

Del Giglio et al studied the efficacy of G-CSFs in reducing the duration of severe neutropenia in patients with breast cancer undergoing treatment with docetaxel/doxorubicin. In the 136 patients receiving G-CSFs, severe neutropenia lasted a median of 1.1 days compared with 3.9 days in the 72 placebo patients.[37] Papaldo et al evaluated the correlation between the use of G-CSFs, maintenance of dose intensity and clinical outcome in terms of disease-free (DFS) and OS. Among the 506 breast cancer patients treated with epirubicin and cyclophosphamide (EC), 129 were assigned to receive EC + G-CSFs. Although the latter had an important positive clinical impact on haematologic toxicity, no differences were seen in dose-intensity, DFS or OS between groups.[38]

In a recent meta-analysis, Dale et al assessed the efficacy of G-CSFs in terms of FN incidence or G3-4 neutropenia, duration of neutropenia, dose intensity of chemotherapy, incidence of infections, use of antibiotics, hospitalisation and OS.[39] The authors reported a reduction in the incidence of FN and in the number of G3-4 neutropenia events, with a decreased duration of neutropenia in favour of patients treated with filgrastim. The use of G-CSFs led to a decrease, albeit not significant, in the incidence of infections, use of antibiotic therapy and hospitalisation.[39] In all of the above studies, patients receiving filgrastim showed better maintenance of the planned dose and better compliance with administration timing. However, there was no clear evidence of a benefit in OS.

An interesting area is the use of G-CSF prophylaxis in elderly patients. A French prospective trial analysed the use of filgrastim in this population (age ≥ 70 years), the authors reporting that filgrastim was usually prescribed as the PP and that chemotherapy delays and dose reductions were similar to those observed for their younger counterparts.[40]

2.4 | Safety and tolerability

The most frequent AE in patients receiving filgrastim is bone pain (cumulative relative risk of 2.61), observed in around a quarter of cases, and which appears to be dose-dependent. In clinical trials evaluating daily filgrastim therapy in patients with severe chronic neutropenia, mild to moderate bone pain was reported in 33% of patients, together with generalised musculoskeletal pain in those receiving fixed-dose filgrastim.[41]

Erythema, swelling or pruritus is occasionally observed at the site of injection. Subcutaneous injection or infusion of filgrastim may result in minor bruising, inflammation or bleeding, and continuous intravenous (IV) infusion sometimes causes inflammation at the site of administration. Adverse local effects generally persist for a day or two and can be minimised by frequently changing the site of administration. Anaphylactic and allergic reactions have occasionally been reported in patients receiving IV filgrastim and are characterised by systemic symptoms involving two or more of the following: skin (rash, urticaria, facial oedema) and cardiovascular (hypotension, tachycardia) and respiratory (wheezing, dyspnoea) systems.[42]

Cutaneous necrotic vasculitis has also been observed infrequently in patients undergoing treatment with filgrastim, and at least two cases of leukocytoclastic vasculitis of the lower extremities have been reported. Cutaneous vasculitis tends to affect patients with severe chronic neutropenia following long-term use of filgrastim and is linked to the increased neutrophil count. In a controlled clinical trial of adults with small-cell lung carcinoma and chemotherapy-induced neutropenia, the incidence of rash was 6% in the filgrastim patients and 9% in the placebo group.[43] Moderate erythema nodosum, possibly related to the use of filgrastim, has been reported in a bone marrow transplantation patient, but a causal relationship is unclear.[14]

Adult respiratory distress syndrome has been registered in septic neutropenic patients undergoing filgrastim treatment and may be the result of neutrophil-derived lung inflammation.[3] Splenomegaly has occasionally been reported, mainly in patients with congenital or cyclic neutropenia on long-term treatment with the drug. Some cases of splenic rupture, including a few fatalities, have also been reported.[44] In patients with sickle cell disease receiving filgrastim, rare cases of sickle cell crisis have been registered.[45] Some patients have developed filgrastim-binding antibodies, but no specific studies on the nature or specificity of these antibodies have been conducted to date. Although it has been hypothesised that filgrastim antibodies may cross-react with endogenous G-CSFs, producing immune-mediated neutropenia, data are insufficient to draw definitive conclusions.[46]

Laboratory abnormalities such as increased serum concentrations of uric acid, alkaline phosphatase and leukocyte alkaline phosphatase have been observed in up to 60% of patients receiving chemotherapy and filgrastim. Such increases are transient and are probably related to the body's response to the G-CSF.[47] The manufacturers have declared that filgrastim is contraindicated in patients who are hypersensitive to the drug, *Escherichia coli*-derived proteins or other components of the drug formulation.[3]

2.5 | Patient-focused perspectives such as quality of life and patient satisfaction/acceptability, adherence and uptake

Data on patient-oriented perspectives are still lacking in clinical trials, indicating the need for a greater focus on outcomes that have a potential impact on quality of life (QoL). QoL frequently deteriorates in cancer populations and is normally evaluated during chemotherapy.[48] Fatigue is the most frequent symptom correlated with QoL and is reported in 70%-100% of patients. [29,49,50] There are very few data on QoL relating to satisfaction in patients treated with G-CSFs, possibly because of the significant variability

in filgrastim administration in clinical practice. In a 2002 study by Lee et al, a QoL analysis in patients with non-Hodgkin's lymphoma undergoing CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy and G-CSFs revealed that, although physical well-being scores declined as treatment progressed, emotional well-being scores actually improved.[51] In a study on a non-cancer population, Van Agthoven et al investigated the impact of filgrastim on QoL and treatment costs in patients with chronic sinusitis compared with placebo. Results showed that QoL was better, albeit not significantly, in the treatment group compared with the placebo group.[52]

Uyl-de Groot et al evaluated the correlation between QoL and G-CSF treatment in 134 patients with haematological malignancies or solid tumours who experienced antineoplastic treatment-induced FN. Patients were randomised to receive subcutaneous G-CSF 5 μg/kg/day or placebo in conjunction with antibiotic therapy, QoL scores showing significant differences in favour of the placebo group.[53] Nilsson-Ehle et al assessed QoL in myelodysplastic syndrome patients treated with darbepoetin alfa ± filgrastim or erythrocyte transfusions. All of the function scores included apart from that relating to cognitive function were higher at the end of the study than at the start and were significant for physical functioning (P = .046), role functioning (P = .018) and social functioning (P = .034).[54] However, dedicated clinical trials are lacking and more data on patient perspectives, including QoL, during filgrastim treatment are clearly needed.

3 | CONCLUSIONS

The present systematic review analysed the latest literature data on the clinical role of filgrastim for the treatment of severe neutropenia. Information on dose, timing and duration was provided in the majority of clinical trials focusing on chemotherapy-induced neutropenia, haematological malignancies and severe chronic neutropenia, but varied widely across studies. The overall common benefit from treatment with filgrastim was a decreased incidence and duration of chemotherapy-induced neutropenia, defined as the outcome of FN or fever incidence and/or duration, grade 3/4 neutropenia incidence and/or duration and time to absolute neutrophil recovery.[55]

A recent meta-analysis of nine randomised clinical trials including 2197 patients (filgrastim, n= 1130; placebo or no treatment, n = 1067) showed that the use of filgrastim led to a decrease in FN incidence (relative risk [RR] 0.63, 95% CI 0.53-0.75),[39] a result further confirmed in two observational studies.[56,57] A meta-analysis of five randomised clinical trials and one non-randomised clinical trial with a total of 1409 patients (filgrastim, n = 714; placebo or no treatment, n = 695) reported a decreased incidence in grade 3/4 neutropenia with filgrastim (RR 0.50, 95% CI 0.37-0.68).[39]

No differences in OS were observed in prospective trials and meta-analyses, suggesting that the use of filgrastim is not associated with a detrimental effect on long-term outcome in cancer populations. Moreover, in a pivotal randomised clinical trial, filgrastim significantly reduced the severity and duration of neutropenia, with a >6-fold increase in absolute neutrophil recovery compared with control.[38] It also led to a substantial reduction in the incidence of infections and antibiotic use in patients with severe chronic neutropenia.[38]

Patient-, disease- and treatment-related factors should be taken into account when deciding whether to use G-CSFs, and treatment should not be denied to a patient solely on the basis of the risk of treatment-related FN.[5] Filgrastim must be administered as per international clinical recommendations to obtain the maximum benefit. In clinical practice, patients receive short courses of daily G-CSFs which may, however, reduce the level of FN protection obtained. Some models have been proposed to optimise G-CSF administration. Although pegfilgrastim, a PEGylated form of the growth factor, increases patient compliance, filgrastim appears to be more ductile, enabling its administration to be individually tailored to patients.[18]

The most common toxicity correlated with filgrastim is bone pain, but pulmonary and skin toxicity and splenomegaly are also frequent. All of these AEs appear to be related to the clinical effect of filgrastim and to the increase in the neutrophil count.

Biological medicines, which are subject to strict regulatory processes, are considered to be highly similar to their reference products. This could potentially restrict the use of G-CSFs in some patients because of higher healthcare costs. Although the use of filgrastim biosimilars has increased, more prospective data are needed to confirm that the biosimilars are equally as effective as the comparator. However, not with standing differences in hospitalisation costs between countries, the use of filgrastim to prevent chemotherapy-induced FN appears to be cost-effective. Further clinical trials are needed to address various issues such as filgrastim timing and dose. Another interesting area is the use of G-CSFs in combination with recently developed antiblastic agents. In particular, several trials are currently evaluating the efficacy of immune-checkpoint inhibitors, chemotherapy and G-CSFs.[58,59] Further research is needed to verify whether filgrastim can also be used to improve immunotherapy efficacy.[60]

In conclusion, the results from the present review support previous findings on the efficacy of filgrastim and its acceptable spectrum of side effects.

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DISCLOSURE

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

A.B, F.R and T.I conceived the study and drafted the article. L.M, L.G, V.F, B.R, ADV and G.M worked on data acquisition. S.C, N,R and SDB was responsible of analysis and interpretations of the different

clinical trials. C.L, C.S, G.M and C.C contributed to the manuscript drafting. All the authors critically reviewed and approved the final version.

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