EXPERT REVIEWS

Lipegfilgrastim for the prophylaxis and treatment of chemotherapy-induced neutropenia

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Chemotherapy is frequently associated with hematologic toxicity. Neutropenia with or without fever is a relevant cause of morbidity, mortality and costs, compromising treatment administration and clinical outcomes. The development of granulocyte colony-stimulating factors has had a positive impact on the clinician's approach to neutropenia. Such agents, currently used for primary and secondary prophylaxis of chemotherapy-induced neutropenia and febrile neutropenia (FN), are effective in limiting hematologic toxicities and consequently allow the administration of intensive dose-dense regimens. Several biosimilar products of filgrastim have been developed over the years, showing effects similar to the originator drug. Until now, pegfilgrastim has been the only available long-acting factor, requiring just a single administration per chemotherapy cycle. The recent approval of the novel granulocyte colony-stimulating factors, lipegfilgrastim, offers interesting therapeutic alternatives. In fact, similar to pegfilgrastim, it has been demonstrated to reduce the duration of neutropenia and the occurrence of FN during chemotherapy safely.

KEYWORDS: chemotherapy induced-neutropenia • GlycoPEGylation • granulocyte colony stimulating factor • lipegfilgrastim • primary prophylaxis

Chemotherapy-induced neutropenia & febrile neutropenia

Neutropenia is one of the most serious and potentially fatal consequences of cytotoxic cancer therapy [1]. This event, very common in pre-engraftment phase of hematopoietic cell transplantation and during induction therapy for acute leukemia, is frequently observed also in patients receiving standard-dose chemotherapy for solid neoplasms, leading to several clinical sequela, including infectious complications [2]. Neutropenia is generally classified according to its severity. The Common Toxicity Criteria of the National Cancer Institute is the most used scale for grading cytopenia associated with chemotherapy. It distinguishes four grades of neutropenia, where 1500–2000 cells/mm^3 is grade 1, 1000–1500 cells/mm^3 is grade 2, 500–1000 cells/mm^3 is grade 3 and <500 cells/mm^3 represents grade 4; profound neutropenia is defined as an absolute neutrophil count <100 cells/mm^3. The risk of severe infection rises when the neutrophil count decreases below 500 cell/mm^3 [3]. Neutrophils are the main defensive strategy that contrasts infections, representing the first cellular component of the inflammatory cascade and an important part of innate immunity. Neutropenia limits the inflammatory response to infections, allowing bacterial spreading. Because neutropenia reduces the signs and the symptoms of infection, fever often represents the only sign of infection. On the basis of these evidences, we found that patients with fever and neutropenia (febrile neutropenia [FN]) need immediate and effective treatments because of the risk of death related to the rapid dissemination of the infection [4].

FN definition varies widely. One of the most commonly used definition identifies it as the occurrence of fever (>38.2°C for >1 h) associated with grade 3 or 4 neutropenia [5]. Neutropenia and FN, both are responsible

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Table 1. Common chemotherapy regimens associated with febrile neutropenia.

Tumor type	Chemotherapy regimen	Febrile neutropenia risk (%)	Ref.
Breast cancer	TAC (Docetaxel/doxorubicin/cyclophosphamide)	25	[78–80]
	Paclitaxel→doxorubicin/cyclophosphamide	40	
	Dose dense FEC	71	
Non-small cell lung cancer	Docetaxel/carboplatin	26	[9,10,49]
	Cetuximab/vinorelbine/cisplatin	16	
	Bevacizumab/carboplatin/paclitaxel	5	
Non-Hodgkin lymphoma	Rituximab/CHOP-21	10–20	[81]
Urothelial cancer	MVAC (methotrexate/vinblastine/cisplatin/doxorubicin)	14	[82]
Sarcoma	AIM (doxorubicin/ifosfamide/mesna)	31–56	[83]
Gastric cancer	DCF (docetaxel/cisplatin/5-fluorouracil)	29	[84]

for morbidity and mortality in patients with cancer, impose several therapeutic measures, including hospitalization, blood cultures and the administration of broad-spectrum antibacterials, which result in high healthcare costs and a negative impact on patient's quality of life [6]. Therefore, limiting or preventing the occurrence of chemotherapy-induced neutropenia (CIN) and its clinical complications is crucial.

Risk factors for CIN

All patients undergoing chemotherapy are at risk of developing CIN and FN, but some factors related to patient-specific characteristics or to the administered treatment particularly increase the risk of developing hematologic toxicities. They may be distinguished as regimen-specific risk factors and patient-specific risk factors.

Regimen-specific risk factors

Specific chemotherapy regimen used is one of the main risk factors of neutropenia, and it is demonstrated that the association of different antineoplastic drugs leads to a higher incidence of myelotoxicity (Table 1). There is a great amount of literature on different chemotherapy combinations and their association with FN risk, but the statements are sometimes contradictory. Fiegl *et al*. reviewed thoroughly this field and offered an extensive list of chemotherapy schemes and their corresponding FN risk [7]. In general, regimens with an overall risk of FN of ≥20% include an anthracycline plus a taxane (frequently used for the treatment of breast cancer), cyclophosphamide, doxorubicin, vincristine, prednisone (cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]-like regimens used for non-Hodgkin's lymphoma [NHL]) and the docetaxel, cisplatin and 5-fluorouracil (DCF/TPF) regimen (used for gastric and head and neck cancer) [8]. Some new regimens, which associate standard chemotherapy drugs to targeted agents (i.e., the addition of cetuximab and bevacizumab in non-small-cell lung carcinoma [NSCLC]), have conferred survival advantages. Although generally well tolerated, such new combination therapies may considerably increase myelosuppression. In particular, the addition of cetuximab to vinorelbine and cisplatin significantly boosts the incidence of grade 3–4 neutropenia and the risk of grade 3–4 sepsis (up to 2%) [9]. Patients treated with bevacizumab and chemotherapy also showed a higher risk of FN when compared with those receiving chemotherapy alone [10,11].

The high intensity (by increasing the frequency and/or the total dose) of a chemotherapy regimen represents an additional important factor for developing neutropenia. It has been clearly demonstrated that the possibility of shortening the time interval between chemotherapy cycles from the conventional 3 weeks to 2 weeks (dose densification) maximizes tumor cell death and decreases cells' regrowth between cycles [12]. Moreover, the completion of chemotherapy in a shorter period of time may allow patients to resume their work and their habitual life sooner. Recent studies with anthracycline/taxane regimens in breast cancer [13], CHOP)-like regimens in aggressive lymphomas [14] and doxorubicin/cyclophosphamide/etoposide (ACE) chemotherapy in small-cell lung cancer (SCLC) showed that dose densification significantly improves response and survival rates [15]. Conversely, dose reductions and delays in chemotherapy resulted in poorer outcomes in several neoplasms, including breast cancer, colorectal cancer, NSCLC and NHL [16–18], probably because of a higher rate of disease recurrence. CIN and FN are the most common dose-limiting toxicities, emerging while administering antineoplastic drugs [19]. They have an impact on the possibility of delivering full doses and maintaining the proper timing for each cycle. Hence, it becomes evident the importance of adopting prophylactic measures for CIN and FN [20].

The risk of neutropenia is strongly related to the phase of therapy. It is well supported by several studies, which showed that the greatest risk of developing CIN or FN is in the earliest cycles. In fact, in elderly patients with aggressive NHL treated with CHOP, the greatest number of toxic deaths, mostly CIN-related, occurred in the first cycle [21,22]. In addition, in two different clinical trials, patients with advanced breast cancer treated with docetaxel and doxorubicin with granulocyte colony stimulating factors (G-CSF) support, developed FN mostly during the first cycle [23]. However, this observation does not still support the limited use of G-CSF prophylaxis for the first cycles only. In fact, an important prospective randomized clinical trial that has been recently published clearly demonstrates

the need for a continued use of primary G-CSF prophylaxis during all chemotherapy cycles in patients with early breast cancer undergoing chemotherapy at high risk for FN [24].

Patient-specific risk factors

Along with factors related to the chosen treatment, patient's characteristics are significant predictors of neutropenic complications. Elderly patients usually carry a limited bone marrow reserve and medical comorbidities, such as hepatic and renal impairment, which increase the risk of treatment-related complications [25,26]. European Organisation for Research and Treatment of Cancer (EORTC) guidelines confirm that older age (>65 years) is the patient-related main risk factor most frequently associated with FN [8]. Other risk factors for CIN and FN include advanced stage of disease, previous episodes of CIN or FN, lack of G-CSF use and no antibiotic prophylaxis [27]. In addition, different capacity to metastasize to the bone related to the specific tumor type must be taken into consideration because of the consequent potentially compromised medullary reserve. As a matter of fact, patients with hematological malignancies have greater risk of CIN/FN than those with solid tumors. Finally, poor performance and nutritional status, comorbidities including renal or heart disease, low blood cell count at the baseline and female sex (probably because most of the studies were conducted in patients with breast cancer receiving doxorubicin/docetaxel) have a negative impact on the incidence of CIN and FN [28,29].

G-CSFs

Historically, the principal strategies for avoiding and minimizing the risk of CIN and FN consisted of reducing dose intensity and total dose of chemotherapy [30]. The discovery, in the 1980s, that a recombinant human granulocyte colony-stimulating factor (rh-GCSF), namely filgrastim, could increase the production of neutrophils was revolutionary for its clinical implications [31]. The introduction of granulocyte colony-stimulating factors (G-CSFs) had a significant impact on the management of hematological toxicities associated with cancer therapy. In fact, G-CSFs stimulate the production of mature and functional neutrophils and have been shown to reduce the incidence of FN when used as prophylaxis after chemotherapy [32]. Three G-CSFs are currently in use: filgrastim, pegfilgrastim and lenograstim. Filgrastim and lenograstim (a glycosylated recombinant G-CSF) are administered as a series of daily injections, whereas pegfilgrastim as a single injection per chemotherapy cycle [33]. Daily subcutaneous doses of G-CSFs, such as filgrastim and lenograstim, are able to reduce the incidence, duration and severity of CIN, the incidence of FN and the risk of infection in patients undergoing chemotherapy [34–37]. They are also able to reduce the need for drug dose reduction and delays, allowing dose intensification and the adoption of aggressive treatments, including the use of dose-dense regimens [35,38].

The pegylation process is involved in the development of a new molecule, pegfilgrastim, characterized by a different pharmacokinetic profile when compared with daily G-CSFs. Pegfilgrastim is made up of the covalent attachment of a 20-kDa polyethylene glycol (PEG) molecule to the N-terminal methionine residue of filgrastim [39,40]. Pegylation leads to a limited renal clearance so that the neutrophil receptor-mediated system becomes the principal mechanism of excretion. This peculiar self-regulated feature determines a high serum concentration during neutropenia, allowing the administration of a single dose of pegfilgrastim per cycle of chemotherapy [40].

Several biosimilar filgrastim molecules are approved in Europe: XMO2 (Tevagrastim®, Ratiograstim® and Biograstim®), EP2006 (Zarzio® and Filgrastim Hexal®) and Hospira filgrastim (Nivestim®) [41,42]. Lipegfilgrastim, an alternative glycol-pegylated G-CSF, is approved as a biosimilar for pegfilgrastim in the UK and by the EMA and it is marketed as Lonquex® [43]. It showed similar efficacy and safety when compared with pegfilgrastim [44].

Biosimilars are biological molecules comparable in structure and activities with the original drug, used and approved for the treatment of the same diseases. The recent introduction of these compounds has expanded the available choices [45].

G-CSFs indications for the use in primary prophylaxis

G-CSFs may be administered as primary prophylaxis (in each chemotherapy cycle starting from first cycle or as secondary prophylaxis (in all remaining cycles after a neutropenic event, such as FN or prolonged severe neutropenia) [46,47]. Guidelines published by the National Comprehensive Cancer Network (NCCN) [48] recommend the routine prophylactic use of CSFs in patients in whom the risk of developing FN or neutropenic events is 20% or higher. Updated guidelines from the EORTC [8], the American Society of Clinical Oncology [27,47] and the NCCN [48] also provide the same recommendations. These guidelines specifically recommend against the routine administration of G-CSFs for primary prophylaxis in previously untreated adult patients receiving regimens with a low probability (<10%) of occurrence of CIN and FN. When this risk is 10–20%, patient additional risk factors must be considered [8,49]. Key characteristics associated with an increased risk include age >65 years, pre-existing neutropenia or extensive bone marrow involvement, advanced stage of disease, poor performance or nutritional status, renal or hepatic comorbidities [28]. Similar to NCCN guidelines, previous chemotherapy/radiation treatment, recent surgery, evidence of infection or open wounds must be carefully considered when evaluating a patient candidate to receive treatment with G-CSFs [48].

G-CSFs indications for the use in secondary prophylaxis

Secondary prophylaxis consists of the administration of G-CSFs in subsequent chemotherapy cycles after neutropenic fever has occurred in a prior cycle. There is a 50–60% risk of FN in subsequent cycles in patients who experienced an episode of fever associated with neutropenia [50,51]. Secondary prophylaxis also includes the use of G-CSFs to shorten the recovery time from neutropenia after a previous cycle of

chemotherapy. Although no prospective studies of secondary CSF prophylaxis have been reported till date, major guidelines from international societies, such as American Society of Clinical Oncology [27,47] and EORTC [8], state that the use of G-CSFs in secondary prophylaxis must be limited to those patients who developed a neutropenic complication during a prior cycle of treatment (in which primary prophylaxis was not administered) if reducing dose intensity can compromise treatment outcome [8,47,48]. This issue is particularly relevant in the curative setting (adjuvant therapy or treatments for potentially curable tumors, such as testicular cancer or lymphoma). Conversely, dose reduction or delay remains an appropriate strategy in palliative setting.

Main GCSFs in use

Filgrastim

Filgrastim is a product of recombinant DNA technology. In fact, the gene for human G-CSF is inserted into the genetic structure of *Escherichia coli* modified to express the human G-CSF gene [52,53]. It stimulates the production, maturation and activation of neutrophils, their release from the bone marrow and it accelerates their recovery, decreasing the duration of the neutropenic phase. Its action is similar to the product of the endogenous G-CSF gene, promoted by its binding to a specific cell-surface receptor. Moreover, filgrastim stimulates the chemotaxis of neutrophils in response to chemoattractants [54]. First studies with filgrastim began in 1980s; Phase I trials evidenced that this G-CSF produced a rapid transient leukopenia followed by a phase of a consistent increase in circulating neutrophils [55]. Following studies showed its efficacy in allowing patients to receive the planned full dose of chemotherapy. Filgrastim was approved by the US FDA, based on Phase III studies involving patients with SCLC treated with cyclophosphamide, doxorubicin and etoposide, a regimen associated with a high risk of CIN and FN [56]. Patients were randomly assigned to receive either filgrastim or placebo. Over all cycles, the incidence of FN was 76% in the placebo group versus 40% in the filgrastim group ($p < 0.001$), and the median duration of grade 4 neutropenia was 6 days in the placebo group versus 3 days in the filgrastim group [20]. Besides reducing the duration and severity of CIN and the cumulative incidence of FN, filgrastim was shown to be able to limit the occurrence of infections, FN-related intravenous antibacterial use and hospitalization, compared with placebo. Patients in filgrastim arm needed dose reductions with significant less incidence than those treated with placebo. In 1991, filgrastim was registered in the USA for its first indication, namely prophylaxis of FN in patients with nonmyeloid malignancies treated with myelotoxic chemotherapy and subsequently approved in many countries to reduce the duration and severity of myelosuppression after bone marrow transplantation, for the treatment of severe chronic neutropenia, aplastic anemia, myelodisplastic syndromes and for mobilizing hematopoietic progenitor cell in transplanted patients [31]. When used for primary and secondary prophylaxis, the recommended dose of filgrastim is 5 μg/kg per day. Its delivery is usually begun 24 to 72 h after the end of treatment, continued with twice weekly control of blood cell counts until the ANC is 5000 to 10,000 per mm^3. Premature discontinuation of G-CSF, before the nadir of white blood cell count has been obtained, may be unsafe and must be avoided [57].

Lenograstim

Lenograstim is a glycosylated recombinant human G-CSF. In randomized multicenter trials in patients with solid tumors or hematologic malignancies, lenograstim prophylaxis compared with placebo only was associated with a significant reduction of CIN duration, hospitalization for infections and the use of iv. antibacterial therapy. This drug was approved by FDA in 1993 and represents an important therapeutic option for CIN, for acceleration of neutrophils recovery after hematopoietic stem cell transplantation and for peripheral blood stem cell mobilization [58].

Pegfilgrastim

Pegfilgrastim is obtained by adding a PEG molecule to filgrastim. The consequent increase of its molecular size reduces renal clearance, supporting neutrophil-mediated elimination. This particular clearance mechanism explains the longer half-life of pegfilgrastim when compared with filgrastim within the body. As a result, only a single dose of pegfilgrastim is required per cycle of chemotherapy rather than a daily filgrastim/lenograstim administration [59]. Two Phase III studies supported the approval of pegfilgrastim by FDA, in 2002 [60,61]. These trials involved patients with metastatic breast cancer receiving doxorubicin and docetaxel every 3 weeks, a regimen associated with a high risk of CIN and FN, without G-CSFs support. Such trials compared the efficacy of pegfilgrastim and filgrastim in reducing the incidence and duration of grade 4 neutropenia and time to neutrophil recovery. Mean duration of grade 4 neutropenia in cycle 1 was 1.8 days in the pegfilgrastim group and 1.6 days in the filgrastim group (difference not significant). A trend toward a lower incidence of FN was noted across all cycles in the pegfilgrastim group when compared with the filgrastim group. Pegfilgrastim resulted comparable in efficacy with filgrastim also in patients with lymphoma, decreasing the duration of severe neutropenia and the depth of ANC nadir [62]. In a further Phase III study, pegfilgrastim showed clinical benefit when used in primary prophylaxis after a moderately myelosuppressive treatment [63]. Compared with placebo, it significantly reduced the incidence of FN, FN-related hospitalization and the use of iv antibacterials. Several trials in breast cancer and NHL also demonstrated pegfilgrastim efficacy in allowing administration of full-planned chemotherapy dose and delivery of dose-dense chemotherapy [64,65]. Interestingly, pegfilgrastim prophylaxis is particularly useful in elderly patients receiving chemotherapy for breast, ovarian, lung cancer and NHL, facilitating the maintenance of full doses [66]. In 2002, pegfilgrastim was registered in the USA and Australia for the prevention of FN in patients with nonmyeloid tumors treated

with chemotherapy. At the same time, this drug received approval in the EU with the indication to limit the duration of neutropenia and to decrease the occurrence of FN in patients treated with myelosuppressive chemotherapy for malignancies. The recommended dose of pegfilgrastim (6 mg in adults, 100 μg/kg in children) is given 24 h after chemotherapy, with at least 14 days of interval before the administration of the next planned cycle [20].

G-CSFs: choice of formulation

Several studies have been designed to evaluate different G-CSFs in terms of efficacy and safety. In particular, filgrastim and pegfilgrastim treatment were compared in many trials [23,60,61,67,68]. A meta-analysis of five studies with a total of 617 patients receiving myelosuppressive therapy was performed to analyze relative efficacies of pegfilgrastim and filgrastim [69]. Such study concluded that one dose of pegfilgrastim is significantly more effective at limiting the incidence of FN than a median of 10–14 days of filgrastim. Pegfilgrastim as well reduced the rate of grade 4 neutropenia when compared with filgrastim. However, these results were largely criticized. Specifically, the original trials were not designed to evidence superiority of one agent over the other in terms of limiting the incidence of FN. Moreover, most of the trials included in the meta-analysis were very heterogeneous because of differences in cancer histology, chemotherapy regimen administered and trial design. On the basis of these considerations, we conclude that the results of this meta-analysis should be considered very cautiously and do not allow to draw definitive and clear conclusions. A further meta-analysis conducted by Lyman *et al*. compared the efficacy of filgrastim and lenograstim with regards to FN, CIN and FN-related endpoints [70]. It included eight studies of prophylactic G-CSF administered before the occurrence of FN in patients with solid tumors or malignant lymphomas receiving myelosuppressive chemotherapy. Findings demonstrated that filgrastim and lenograstim are comparable in reducing the risk of FN and infections associated with chemotherapy treatments. An additional recent review confirmed the similar efficacy of both agents [58].

The principal biosimilars of filgrastim currently in use are XMO2, EP2006 and Nivestim. A meta-analysis of three clinical studies involving patients with lung and breast cancer and NHL compared the impact on FN incidence of G-CSF biosimilar XMO2 with filgrastim [71]. Such analysis established the noninferiority of XMO2 when compared with filgrastim. Likewise, a recent study in 170 patients treated with four cycles of doxorubicin and docetaxel evaluated the efficacy and safety of the filgrastim biosimilar EP2006 [72]. Good results in preventing severe neutropenia were achieved with this new drug, which showed a sufficient comparability with its originator filgrastim. An additional filgrastim biosimilar developed by Hospira (Hospira filgrastim, Nivestim) was approved in 2010. A study that compared physiochemical characteristics of these two drugs evidenced that, in terms of stability, Hospira filgrastim has a longer time of resistance out of refrigerator. As far as efficacy and safety are concerned, randomized trials demonstrated that Nivestim is comparable with the original filgrastim [73].

Lipegfilgrastim: chemical structure and rationale for its development

Lipegfilgrastim is a glycol-PEGylated recombinant methionyl form of human G-CSF, marketed as Lonquex®, approved as a biosimilar for pegfilgrastim in the UK and by the EMA in November 2013 [43]. It is indicated to reduce the duration of CIN and decrease the incidence of FN in adult patients undergoing a cytotoxic chemotherapy for neoplasia (excepted for chronic myeloid leukemia and myelodysplastic syndromes). The development of lipegfilgrastim introduces an effective alternative long-acting G-CSF option to pegfilgrastim, the only long-acting molecule available to date. The addition of PEG to the basic structure of filgrastim allows to improve the chemical activity of the drug, by increasing the solubility and the half-life of the molecule, leading to less frequent administrations and to a better patient compliance [74]. The developing process of lipegfilgrastim redefined the PEGylation process. Lipegfilgrastim was created using a highly site-specific glycoPEGylation technology for direct PEGylation. This new method permits the selective addition of PEG to a previously enzymatically attached glycan moiety instead of directly to the amino acid. The product of glycoPEgylation derives by the conjugation of a single 20-kDa PEG to the natural O-glycosylation site of G-CSF expressed in *E. coli*. The standard pegylation technology used for pegfilgrastim (conjugation of a 20-kDa PEG to the N terminal of *E. coli* G-CSF) creates an heterogeneous product with multiple isoforms requiring further chemical purification, which is not needed for the production of lipegfilgrastim. Furthermore, lipegfilgrastim shows a longer half-life compared with pegfilgrastim *in vitro*, producing the same effects in increasing leukocytes production and recruitment [75].

A randomized double-blind, active controlled trial was performed to identify the optimal dose of lipegfilgrastim compared with pegfilgrastim in 202 patients with breast cancer receiving four cycles of doxorubicin and docetaxel [76]. The primary endpoint was the duration of severe neutropenia (DSN) in cycle 1. The optimal individuated dose of lipegfilgrastim was of 6 mg once per cycle administered subcutaneously 24 h after the completion of treatment. The duration of severe neutropenia observed in cycle 1 resulted 0.8 days in the lipegfilgrastim 6 mg group and 0.9 days in pegfilgrastim 6 mg group, showing a favorable although not clinically meaningful trend for lipegfilgrastim in preventing and limiting CIN.

Efficacy of lipegfilgrastim in preventing CIN & FN: results of Phase III trials

Efficacy of lipegfilgrastim in reducing the duration and incidence of CIN and FN was tested in a recent pivotal study [44]. Primary objective of this randomized, multicenter, double-blind Phase III trial was the demonstration of the noninferiority of lipegfilgrastim compared with pegfilgrastim regarding the duration of severe neutropenia (grade 4) during the first cycle of

therapy in high-risk patients with stage II, III or IV breast cancer (measured in days). The study evaluated the safety and efficacy of a planned dose of lipegfilgrastim versus pegfilgrastim in patients undergoing a myelosuppressive chemotherapy, which combined doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2, repeated every 3 weeks for a maximum of 4 cycles. Eligible patients, randomized in a 1:1 ratio, received once for cycle fixed-dose subcutaneously of either lipegfilgrastim 6 mg or pegfilgrastim 6 mg. Two hundred eighteen patients were screened to participate in the trial, and 202 ultimately were randomized and received at least one dose of the drug. No dose omissions or reductions were reported in lipegfilgrastim set versus eight observed in the pegfilgrastim group. Incidence of FN during all cycles of treatment was a secondary endpoint together with the duration of severe neutropenia in cycles 2–4, incidence and duration of severe and very severe neutropenia (ANC <100/ml) during all cycles. The ANC nadir time and time to recovery (return of ANC to $\geq 2 \times 10^9$/l), the incidence of iv antibiotics administration, hospitalization and quality of life were also carefully evaluated. The study met its primary endpoint: the duration of severe neutropenia was similar in both treatment arms: 0.7 ± 0.9 days in patients treated with lipegfilgrastim versus 0.8 ± 0.9 days in pegfilgrastim group. Lipegfilgrastim resulted noninferior to pegfilgrastim ($p = 0.126$). No statistically significant difference in the incidence of FN among the 2 arms was registered. The duration of severe neutropenia in cycles 2–4 was also comparable. Noteworthy, in each cycle 2–4, more than 75% of patients treated in each group did not experience severe neutropenia. As far as the overall incidence of severe neutropenia during all cycles is concerned, there was no significant difference between the two treatments, with the highest number of cases encountered in the first cycle of chemotherapy (43.6% in lipegfilgrastim group versus 51.1% in pegfilgrastim cohort). Occurrence of very severe neutropenia in all cycles was low (6.4% for lipegfilgrastim versus 11.7% for pegfilgrastim, $p = 0.2066$) and similar in both groups. Depth of ANC nadir was again similar in both cohorts. Interestingly, patients in lipegfilgrastim cohort obtained an overall mean faster time of 1.5 days to ANC recovery in cycle 1 compared with those treated with pegfilgrastim (5.9 vs 7.4 days), maintaining this trend up to cycle 3 and showing similar results during the fourth cycle. Only one patient in the experimental arm required hospitalization because of FN and infection when compared with two patients in pegfilgrastim group. Patients receiving pegfilgrastim stayed in hospital, respectively, for 6 and 5 days, whereas lipegfilgrastim patient for just 1 day. The results collected in this trial clearly affirm the noninferiority of lipegfilgrastim when compared with pegfilgrastim; in fact, the occurrence and the duration of severe neutropenia in patients treated with lipegfilgrastim were similar to those obtained by pegfilgrastim. The comparison between the two different groups showed efficacy of lipegfilgrastim also for secondary endpoints. When some differences between the two treatments were noticed, lipegfilgrastim showed better results concerning antineutropenic activity when compared with pegfilgrastim. Moreover, lipegfilgrastim was associated with a comparable safety profile: the most frequent adverse events were bone-pain–related symptoms (bone pain reported in 13.9% of lipegfilgrastim patients versus 9.9% of pegfilgrastim patients; myalgia 8.9 vs 5.9%; arthralgia 5.0 vs 2.0%), and the difference between the two arms was not statistically significant. None of the symptoms reported were severe or led to the discontinuation of study participation.

An additional double-blind, randomized, Phase III trial, only published in abstract form, was recently undertaken in patients with cancer treated with cisplatin/etoposide (regimen usually associated with a FN risk <20%) chemotherapy for stage IIIb/IV NSCLC [77]. This study evaluated the incidence of FN (primary endpoint) during the first cycle of treatment comparing the effects of 6 mg lipegfilgrastim (250 patients) with placebo (125 patients). The number of patients who were >65 years of age in either group was comparable (n = 53 [21.2%] and n = 30 [24.0%], respectively). No patient in the lipegfilgrastim arm (0/53) and 13.3% patients in the placebo cohort (4/30) presented FN during cycle 1 ($p = 0.064$). Incidence, severity or type of adverse events experienced within treatment groups by age group were similar.

Both trials suggest that a single dose of lipegfilgrastim has comparable efficacy with pegfilgrastim in preventing the development of severe neutropenia in patients receiving myelotoxic chemotherapy. Moreover, when compared with pegfilgrastim, this novel agent showed a favorable trend in its capacity to limit the duration of neutropenia, allowing a faster recovery from hematologic toxicity. Finally, tolerability and safety of the product made it well accepted by treated patients. These promising results need to be confirmed in further large prospective randomized trials.

Conclusions

Neutropenia and FN represent the most severe hematologic complications of cytotoxic chemotherapy. These events, associated with the high risk of systemic infections, other morbidities and mortality, are responsible for high health costs related to hospitalization and determine a negative impact on patient's quality of life. The introduction of G-CSFs completely changed the oncology practice, allowing the administration of more aggressive and effective chemotherapy regimens and treatment of a wider range of patients. The recent introduction of novel G-CSFs molecules and biosimilar products expanded the available treatment options. Lipegfilgrastim represents an effective alternative to pegfilgrastim in preventing and limiting the duration and occurrence of CIN and FN. The advanced technology of glycoPEGylation applied for its design created an efficient long-acting molecule which, compared with pegfilgrastim, showed similar results in contrasting hematologic toxicity during chemotherapy treatments, with a good safety profile. The development and approval for clinical use of this new G-CSFs are crucial, representing the only alternative to pegfilgrastim entering the market to date. The design of new G-CSFs is a compelling necessity, to enable the improvement of patient's

quality of life, cost savings for healthcare system and to counteract the myelotoxic effects of chemotherapy effectively.

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Key issues

- Cytotoxic chemotherapy often leads to severe hematologic adverse events, with neutropenia and febrile neutropenia as the most serious consequences of myelosuppression. Neutropenic complications require several medical measures, including hospitalization and iv. antibiotics use, which negatively affect patient's quality of life, compromise treatment administration and, as a consequence, clinical outcome.
- The discovery of granulocyte colony-stimulating factors (G-CSFs) as means to increase the production and number of circulating neutrophils represented a revolution for its clinical implication. Since their introduction in medical practice, filgrastim and pegfilgrastim showed a good safety profile and a high effectiveness in preventing and limiting hematologic toxicity.
- On the basis of their clinical action, we used G-CSFs for primary and secondary prophylaxis of chemotherapy-induced neutropenia and febrile neutropenia (FN) and they proved to be very helpful in facilitating the delivery of dose-dense and dose-intense regimens, contributing to improve clinical outcomes.
- Pegfilgrastim represented for years the only long-acting GCSF; pegylation mechanism, with which it is developed, determines a slower drug clearance, which in turn increase concentration of the molecule during the period of neutropenia and allows the administration of a single dose of pegfilgrastim per chemotherapy-cycle.
- Lipegfilgrastim, a new glycoPegylated G-CSF, was approved by EMA in 2013 for chemotherapy-induced neutropenia and FN prophylaxis. The innovative technique of glycopegylation used for its design allowed to obtain a therapeutic product with an extended half-life, providing an alternative long-acting G-CSF option to pegfilgrastim.
- Lipegfilgrastim resulted comparable with pegfilgrastim in terms of safety and clinical efficacy in limiting the occurrence and duration of FN. Its introduction has expanded the choices available for clinicians, contributing to achieve a cost-saving for healthcare system and improvement of patient's quality of life.

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