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ORIGINAL ARTICLE

A comparative effectiveness study of lipegfilgrastim in multiple myeloma patients after high dose melphalan and autologous stem cell transplant

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Abstract

G-CSF administration after high-dose chemotherapy and autologous stem cell transplantation (ASCT) has been shown to expedite neutrophil recovery. Several studies comparing filgrastim and pegfilgrastim in the post-ASCT setting concluded that the two are at least equally effective. Lipegfilgrastim (LIP) is a new long-acting, once-per-cycle G-CSF. This multicentric, prospective study aimed to describe the use of LIP in multiple myeloma patients receiving high-dose melphalan and autologous stem cell transplantation (ASCT) and compare LIP with historic controls of patients who received short-acting agent (filgrastim [FIL]). Overall, 125 patients with a median age of 60 years received G-CSF after ASCT (80 patients LIP on day 1 post-ASCT and 45 patients FIL on day 5 post-ASCT). The median duration of grade 4 neutropenia (absolute neutrophil count [ANC] $< 0.5 \times 10$ [9]/L) was 5 days in both LIP and FIL groups, whereas the median number of days to reach ANC $\geq 0.5 \times 10$ [9]/L was 10% lower in the LIP than in the FIL group (10 vs 11 days), respectively. Male sex was significantly associated with a faster ANC $\geq 0.5 \times 10$ [9] L response ($p = 0.015$). The incidence of FN was significantly lower in the LIP than in the FIL group (29% vs 49%, respectively, $p = 0.024$). The days to discharge after ASCT infusion were greater in patients with FN ($p < 0.001$). The study indicates that LIP had a shorter time to ANC recovery and is more effective than FIL for the prevention of FN in the ASCT setting.

Keywords G-CSF · Lipegfilgrastim · Multiple myeloma · High dose melphalan · Autologous stem cell transplant · Filgrastim

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Introduction

The treatment landscape for multiple myeloma (MM) has changed following the introduction of novel agents, including immunomodulatory drugs (IMiDS), proteasome inhibitors (PIs), and monoclonal antibodies (MoAb) [1]. The inclusion of new drugs in the treatment platform has improved overall response rates, quality of responses, progression, and overall survival outcomes [2]. Despite the impressive improvements of recent years, high-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) is still considered a standard of care in eligible patients [3–6], and MM remains the main indication for ASCT worldwide [7, 8]. ASCT may be single or tandem (a planned second course of HDC within 6 months of the first). The advantage of a strategy that routinely incorporates a tandem ASCT remains an open question. The EMN02/HO95 trial explored the results of tandem versus single ASCT in newly diagnosed MM patients [9]. Tandem ASCT improved the depth of the response by 25%, with an approximately 30% reduction in the risk of death and progression. Conversely, the StaMINA trial failed to show superiority of tandem versus single ASCT in the era of novel agents [10].

Current ongoing studies are investigating the incorporation of moAbs in the ASCT platform. Moreau et al. showed that the addition of daratumumab to a PI and an IMiD regimen before and after ASCT improved the stringent complete response rate in patients with newly diagnosed MM [11].

Granulocyte-colony stimulating factor (G-CSF) is commonly administered after ASCT, as supportive care. G-CSF administration has been shown to expedite neutrophil recovery in prospective randomized trials [12–16]. Two of the most widely used G-CSFs available are short-acting filgrastim (FIL) [17] and long-acting pegfilgrastim (PEG) [18]. International guidelines recommend the use of short-acting FIL following ASCT, at a dose of 5 μg/kg, subcutaneously or intravenously, once-daily beginning day +5 to +7 post-transplant until recovery of absolute neutrophil count (ANC) [19]. Long-acting PEG is administered once, and previous studies suggest that a single dose of PEG is at least equally effective, and in some instances superior, to a 10- to 14-day daily course of FIL [20–26].

Lipegfilgrastim (LIP) is a long-acting, once-per-cycle G-CSF that received European Union (EU) marketing approval for the indication "Reduction in the duration of neutropenia and the incidence of FN in adult patients treated with cytotoxic chemotherapy for malignancy (except for chronic myeloid leukemia and myelodysplastic syndromes)" [27]. There is no data describing experience with the use of LIP after ASCT in MM patients.

This comparative effectiveness, multicentric, prospective study describes the use of LIP in patients receiving HDC and ASCT to assess the relative benefits of the drug and similarly to compare LIP with historic controls of MM patients who received short-acting agent (FIL) after HDC. Outcomes of interest were neutropenia-related efficacy and safety.

Patients and methods

Setting and design

This was a single-arm, prospective phase II study. MM patients were recruited from seven hematological centers in the South of Italy (four in Calabria, two in Sicily, and one in Basilicata Region, respectively). All patients were referred to the Stem Cell Transplantation Unit of the Grande-Ospedale-Metropolitano-Bianchi-Melacrino Morelli (GOM-BMM), Reggio Calabria (Italy) for peripheral blood stem cell collection and ASCT. The study was approved by the local institutional review board and was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent before inclusion.

Patients

Inclusion criteria were as follows: transplant-eligible patients, aged 18–65 years, with de novo MM who achieved a favorable response after induction therapy (International Myeloma Working Group criteria); International Staging System (ISS) stage 1–3; and World Health Organization (WHO) performance status 0–3. A WHO performance of three was allowed only if it was caused by MM rather than a comorbid condition. Exclusion criteria were as follows: New York Heart Association class II to IV heart failure, abnormal pulmonary-function findings, systematic amyloid light-chain amyloidosis, non-secretory MM, Waldenstrom macroglobulinemia or IgM MM, and history of active malignancy during the past 5 years except basal cell carcinoma or stage 0 cervical cancer. Laboratory exclusion criteria were creatinine clearance ≤ 15 mL/min, ANC ≤ 1.0 × 10 [9]/L, and platelet count ≤ 75 × 10 [9]/L. Patients who had a refractory disease (progression response) to induction chemotherapy were also excluded.

Treatment

All patients received a bortezomib-based induction therapy. High-dose CY (2–4 g/m [2]) plus G-CSF was used to mobilize peripheral blood stem cells. The minimum target dose of CD34+ cells to safely support two HDC was 2.5 × 10 [6]/kg. Between January 2017 and March 2019, a total of 80 consecutive patients received high-dose melphalan (HDM) (200 mg/m [2]) as a conditioning regimen before ASCT. After ASCT, patients received a single injection of LIP dosed at 6 mg

subcutaneously, 24 h after the conclusion of the stem cell infusion. These MM patients were compared with a historical control group of 45 consecutive patients treated at the same center in the years 2015 and 2016 that received FIL 5 μg/kg day, starting on day +5 until neutrophil engraftment. During the aplastic phase, all patients received oral prophylaxis with levofloxacin at 500 mg/day from day 0 until neutrophil recovery and with acyclovir at 800 mg twice-daily from day +3 post-ASCT until approximately day +90. *Pneumocystis jiroveci* prophylaxis with trimethoprim/sulfamethoxazole (1 double-strength tablet 2 or 3 times weekly) was started after hematological recovery and was continued for 3 months. Cryotherapy with ice chips will be used for the prevention of HDM-induced oral mucositis. Patients started keeping ice chips in their mouths approximately 30 min before the HDM conditioning and for about 6 h afterwards. Red blood cell and platelet transfusions were administered to maintain hemoglobin levels ≥ 8 mg/dL and platelet counts ≥ 10 × 10 [9]/L or in case of symptomatic anemia and/or minimal mucocutaneous hemorrhagic syndrome. Patients received intravenous hydration and electrolyte support.

Neutropenic fever (NF) was defined as ANC < 0.5 × 10 [9]/L and temperature ≥ 38.2 °C on at least 2 consecutive occasions or a persistent temperature ≥ 38.0 °C for at least an hour, in the absence of any documented noninfectious cause, such as transfusion reactions or administration of cytotoxic drugs. Neutropenia was defined as ANC < 0.5 × 10 [9]/L or ANC of 1 × 10 [9]/L and a predicted decline to < 0.5 × 10 [9]/L over the subsequent 48 h. When NF was observed, blood and catheter-drawn cultures were ordered and empiric antibiotic therapy was promptly started (intravenous ceftriaxone).

Efficacy and safety measurements

The primary endpoint of the study was the duration of grade 4 neutropenia (ANC < 0.5 × 10 [9]/L), which was defined as the number of days to achieve an ANC ≥ 0.5 × 10 [9]/L (first of at least three consecutive days). Secondary endpoints were as follows: incidence of febrile neutropenia (FN), duration of FN, incidence of documented infections (clinically or microbiologically documented infection with/without bacteremia according to European Organization for Research and Treatment of Cancer guidelines (EORTC v5.0)) [28]; days with ANC < 0.1, < 0.5 and < 1 × 10 [9]/L; platelet engraftment (defined as platelet count ≥ 20 × 10 [9]/L, without a platelet transfusion in the preceding 7 days); and days to discharge after stem cell infusion. Blood samples for complete blood counts were collected before chemotherapy administration and daily during the aplastic phase until hospital discharge.

The safety endpoint of the study was the incidence of adverse events related to study medication.

Statistical analysis

Data were expressed as median and interquartile range (IQR) and percentages; comparisons between groups were performed by Mann-Whitney test or chi-squared test, as appropriate. Covariates to be introduced into multiple models and associated with growth factor treatment (LIP vs FIL) and with FN (yes/no) were identified by comparative analyses.

To assess the relationship between variables and time to ANC recovery and time to discharge after stem cell infusion, both univariate (Kaplan-Meier analysis) and multivariate survival models, including potential confounders, were constructed. To maximize the precision of effect estimates, both semi-parametric (Cox) and parametric (Weibull) survival models were fitted for both primary and secondary endpoints. The appropriateness of such models was assessed through the Akaike information criterion (AIC) (the lower the AIC, the more appropriate the model) [29]. The suitability of the Weibull model was evaluated by the standard analytical approach (i.e., by plotting the log of the negative log of the estimated survivor function [L-(LS)] against log time). When the model is appropriate, a straight line between the L-(LS) versus log time should be observed. Beyond the model adequacy, such a graphical approach also allows to identify a potential effect modification by time at a given point, indicating the need to calculate two hazard ratios (HR), before and after that point in time. The proportionality assumption was tested through Schoenfeld residuals. The parameters of the Weibull model were positive for both the incidence of ANC by study arms and time to discharge by presence/absence of FN (18.8, 95% confidence intervals [CI] 16.4–21.6 and 6.4, 95% CI 5.6–7.3, respectively), indicating that such a model was more suitable than the exponential model to investigate the relationship between prognostic factors and these two study outcomes. In Weibull models, data were expressed as HR, 95% CI, and *p* values. The correlates of FN, including treatment, were identified by univariate logistic regression analysis and after that, they were jointly introduced into the same multiple logistic regression model. In logistic models, data were expressed as odds ratio (OR), 95% CI, and p values. All multivariate analyses were adjusted by sex and age, irrespectively of their association (significant/not significant) with the outcome.

Results

Demographic and baseline characteristics of patients

Overall, 125 patients (67 males) with a median age of 60 years received G-CSF after ASCT (80 patients received LIP on day 1 post-ASCT and 45 patients FIL 5 μg/kg, starting on day 5 post-ASCT). Table 1 shows

Table 1 Patient characteristics according to treatment

	Lipegfilgrastim		Filgrastim		Total		
	%	Median (IQR)	%	Median (IQR)	%	Median (IQR)	*P* value
Age at transplant (years)		60 (54–65)		57 (51–62)		60 (53–63)	0.173
Sex (males)	58.8		44.4		53.6		0.12
Disease status at transplant							
CR/nCR	65.0		55.6		61.6		0.174
PR	31.3		44.4		36.0		
SD/PROG	3.8		0.0		2.4		
No. CD34+ infused (10^6/kg)		4.35 (3.8–5.1)		4.8 (3.8–5.2)		4.5 (3.8–5.2)	0.431
Number of G-CSF injections		1 (1–1)		9 (9–10)		1 (1–9)	
Efficacy/safety measurements							
Days with ANC < 0.1×10^9/L		3 (2–4)		3 (3–4)		3 (3–4)	0.88
Days with ANC < 0.5×10^9/L		5 (4–5)		5 (4–6)		5 (4–5)	0.30
Days with ANC < 1×10^9/L		5 (4–6)		6 (5–7)		5 (5–6)	0.06
Days to ANC ≥ 0.5×10^9 L		10 (9–10)		11 (11–12)		10 (10–11)	< 0.001
Incidence of febrile neutropenia	29		49		36.0		0.024
Among patients with fever							
Days with fever (≥ 38.2 °C)		3 (2–4)		3 (2–5)		3 (2–4)	0.67
Fever origin							
Microbiologically/clinically documented	27.4		19.1		23.3		0.41
FUO	72.6		80.9		76.7		
Mucositis							
Yes (WHO 0–1)	68.8		75.6		71.2		0.42
Yes (WHO 2–3)	31.3		24.4		28.8		
Diarrhea							
Yes (WHO 0–1)	85.0		75.6		81.6		0.19
Yes (WHO 2–3)	15.0		24.4		18.4		
Hematological recovery after transplant							
Red blood cell transfusions							
No	80.0		77.8		79.2		0.77
Yes	20.0		22.2		20.8		
Among patients with red blood cell transfusions		1(1–2)		2 (1–2)		1 (1–2)	0.78
Platelet transfusions							
No	43.8		51.1		46.4		0.43
Yes	56.3		48.9		53.6		
Among patients with platelet transfusions		2 (1–2)		2 (1–2)		2 (1–2)	0.59
Number of platelet transfusions		1 (0–2)		0 (0–2)		1 (0–2)	
Days to reach platelet count ≥ 20 × 10 [9]/L		13 (12–14)		13 (12–14)		13 (12–14)	0.75
Days to discharge (after stem cell infusion)		16 (15–19)		16 (15–18)		16 (15–18)	0.98

ANC absolute neutrophil count, *CR/nCR* complete or near complete remission, *FUO* fever of unknown origin, *IQR* interquartile range, *PR* partial remission, *PROG* progressive disease, *SD* stable disease

the basal patient characteristics at transplant, efficacy/safety measurements, and hematological recovery after ASCT for the whole study sample as well as for subjects divided according to treatment type. The median number of CD34+ cells infused did not differ between the two groups, and the two arms were well matched for baseline demographic and clinical characteristics.

Study drug administration

Patients treated with LIP received a single dose of 6 mg on day 1 after transplantation. The median number of subcutaneous injections administered to patients treated with FIL was 9 with an average cost per patient until engraftment of 293 ± 21.5 euro (€) vs 613 € of patients treated with LIP.

Transfusions

The number of transfusions did not differ between the two study arms (see Table 1). Eighty percent of patients treated with LIP and 78% with FIL did not receive packed red blood cell transfusions, 13% and 11% had 1 and 8 transfusions, while and 11% had 2 or 3 (median 0 for both groups), respectively.

Duration of grade 4 neutropenia and duration of febrile neutropenia engraftment

The median duration of grade 4 neutropenia (ANC < 0.5 × 10 [9]/L) was 5 days in both LIP and FIL groups (Table 1), whereas the median number of days to reach ANC ≥ 0.5 × 10 [9]/L was 10% lower in the LIP than in the FIL group (10 days, IQR 9–10 vs 11 days, IQR 11–12), respectively. In keeping with this observation, Kaplan-Meier analysis confirmed that the type of treatment was strongly and significantly associated with days to reach the target ANC (Fig.1). Indeed, days to reach ANC ≥ 0.5 × 10 [9]/L (*x*-axis) were fewer for the LIP (black line) than for FIL-treated patients (dotted line) throughout most of the observation period except from day 12 onwards. Although such an effect modification by time (see Supplementary Figure 3) would suggest deriving two HRs, before and after 12 days, due to the small number of patients still at risk from day 12 onwards (5 treated with LIP and 12 with FIL, all reaching the ANC ≥ 0.5 × 10 [9]/L), the analysis was obviously restricted to the time period ≤ 11 days.

In Table 2, the results of the multivariate Weibull model adjusted by age and sex are reported. The HR of ANC ≥ 0.5 × 10 [9]/L was 3.5 times higher in patients treated with LIP than in those treated with FIL (HR 3.50, 95% CI 2.28–5.38, $p < 0.001$), indicating that the response was faster in LIP treated patients than in those treated with FIL. In the same Weibull model, male sex was also significantly related to a faster achievement of an ANC ≥ 0.5 × 10 [9]/L response (HR 1.59, 95% CI 1.10–2.30, $p = 0.015$), whereas age (> 60 years) failed to reach statistical significance by a small margin (HR 1.42, 95% CI 0.98–2.05, $P = 0.06$).

Febrile neutropenia and duration of febrile neutropenia

FN developed in 36% of patients. The incidence of FN was significantly lower ($p = 0.024$) in the LIP than in the FIL group (29% vs 49%, respectively). However, among patients with fever, no differences emerged including days with fever (Table 1). The incidence of documented infections (clinically or microbiologically documented infection with/without bacteremia) was similar between the two groups.

Patients experiencing FN were less frequently males and treated with LIP as compared to those not having this complication (Table 3). Accordingly, males and patients treated with LIP had an unadjusted odds ratio for FN that was 58% lower when compared to that of females and patients on treatment with FIL (Table 4). Of note, these associations, with the exclusion of sex ($p = 0.057$), held in a multivariate logistic regression model simultaneously including sex, treatment type, and age (Table 4).

The days to discharge after ASCT was significantly higher in patients with FN (Table 3; Fig.2) (Log-Rank test, $p < 0.001$) and in females (Log-Rank test, $p = 0.003$) than in those without FN and in males, respectively.

Given the fact that the Weibull model was adequate and that no effect modification by time was observed (indeed, only one straight line could be drawn, see Supplementary Figure 4), such a model was fitted over the whole study period (Table 5). We found that male sex and the absence of FR were strongly associated with faster times to discharge after stem cell infusion (Table 6).

Other toxicities

No significant differences were found in the frequency of mucositis and diarrhea. No deaths occurred in this study. No toxicity could be specifically attributed to LIP or FIL injection. Most adverse events were attributable to complications arising from myelosuppressive chemotherapy or MM disease. The only occurring adverse event considered cytokine-related was mild to moderate bone pain. The overall incidence of bone pain was 10% in LIP patients and 12% in FIL patients. In general, bone pain required no medication or was controlled with non-narcotic analgesia.

Discussion

Severe neutropenia (SN) is a clinical condition characterized by an ANC < 0.5 × 10 [9]/L and occurs in all patients who undergo HDC and ASCT [30]. SN with fever (FN) is a major toxicity of HDC that often requires prolonged hospitalization and broad-spectrum antibiotic use [31] and compromises clinical outcome [32]. Additionally, FN is associated with substantial economic consequences related to hospitalization and loss of employment [33]. Correlations have been reported between changes in neutrophil counts and quality of life, as measured by physical functioning, vitality, and mental health [34].

A primary treatment strategy to reduce the risk of SN and FN is the prophylactic use of G-CSF. International guidelines [19, 35] suggest that G-CSF be used as primary prophylaxis after chemotherapy when the risk of FN is > 20%, as occurs in all patients after HDC and ASCT. Prophylactic use of G-CSFs is associated with a reduction in the incidence, severity, and

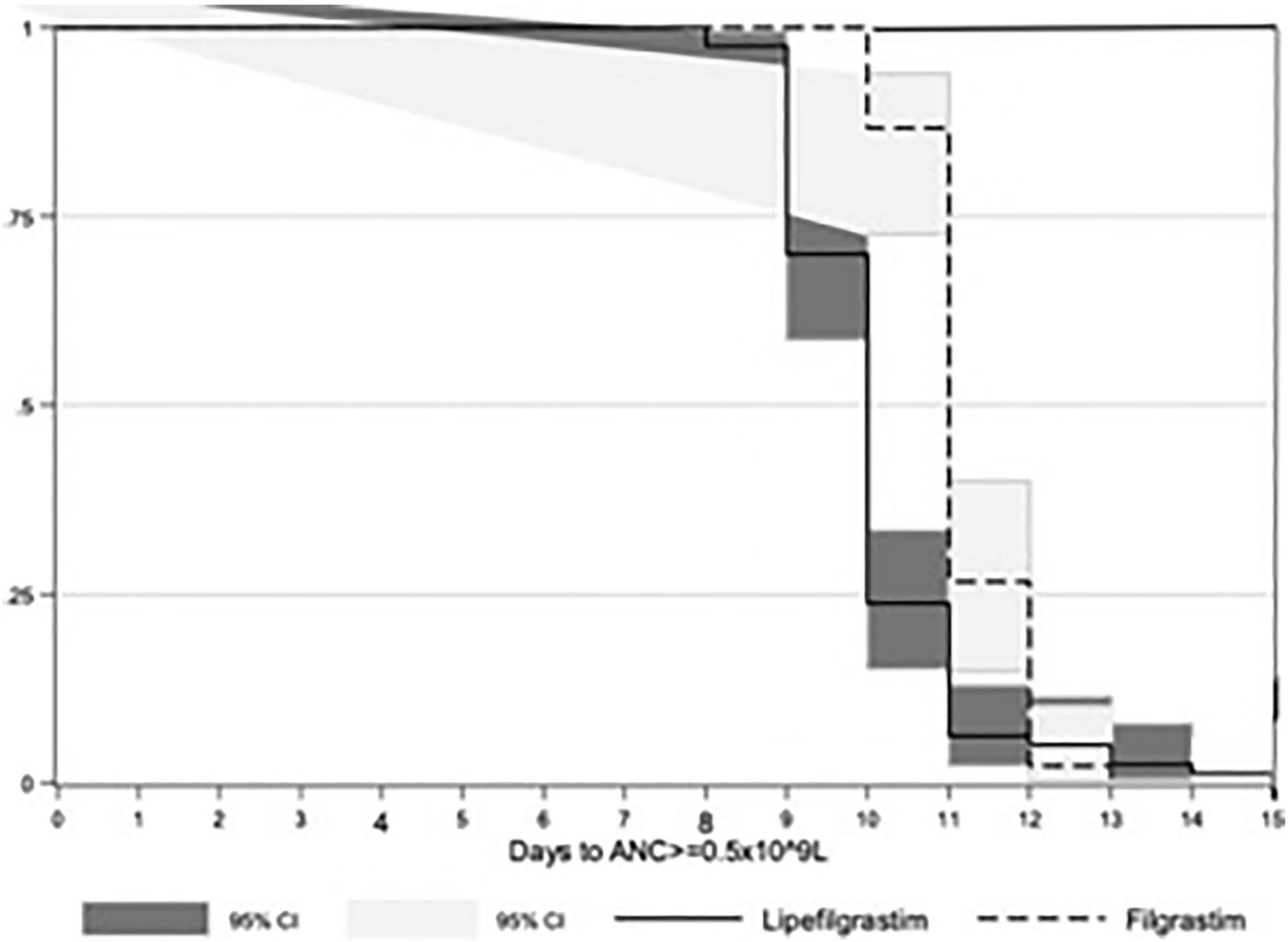

Figure 1 Kaplan-Meier survival functions on day to ANC≥0.5×10^9/L by treatment

duration of SN and FN; a reduction in FN-related hospitalizations; and lower mortality rates due to infection [36–38].

Short-acting FIL and long-acting PEG are widely used after ASCT. FIL is administered subcutaneously or intravenously once daily following its HDC-induced nadir until ANC recovery. Long-acting PEG is administered once, approximately 24 h after stem cell infusion. FIL administration after ASCT has been shown to expedite neutrophil recovery in prospective randomized trials [12–16, 20–23]. However, results have been inconclusive regarding the impact of FIL on the duration of post-ASCT hospital stay, infections, and survival. Several studies comparing FIL and PEG in the post-ASCT setting concluded that the two are at least equally effective [20–26, 39].

Table 2 Multivariate Weibull analysis on days to ANC ≥ 0.5 × 10^9 L

	Weibull (AIC 328.96)	
	HR (95% CI)	*P* value
Lipegfilgrastim vs filgrastim (≤ 11 days)	3.5 (2.28–5.38)	< 0.001
Males vs females	1.59 (1.10–2.30)	0.015
Age (< 60 vs ≥ 60)	1.42 (0.98–2.05)	0.06

ANC absolute neutrophil count, *AIC* Akaike information criterion

LIP is a long-acting, once-per-cycle G-CSF, produced by the conjugation of a single 20-kDa PEG to the natural O-glycosylation site of G-CSF (threonine 134), using a novel glycosylation technology. Because recombinant G-CSF is produced in *Escherichia coli*, the glycosylation site is empty. The addition of the O-glycan is catalyzed by a truncated *N*-acetylgalactosaminyltransferase isoform 2 enzyme fused with maltose-binding protein at the threonine residue site. A 20-kDa PEG-sialic acid derivative is enzymatically transferred to the O-glycan with a sialyltransferase. In contrast, PEG is a recombinant methionyl human G-CSF with a methoxy-polyethylene glycol propionaldehyde 20-kDa PEG covalently conjugated to its N-terminus. The novel pegylation process used in LIP synthesis produces different pharmacokinetic and pharmacodynamic profiles than PEG. LIP represents the first long-acting biosimilar FIL to reach the market in Europe. Phase III trials of chemotherapy-naïve patients with breast cancer reported that LIP was non-inferior to PEG concerning the direction of SN, and the incidence and duration of FN-

Table 3 Patient characteristics according to febrile neutropenia

	Without febrile neutropenia ($n = 80$)		With febrile neutropenia ($n = 45$)		Total ($n = 125$)		P value
	%	Median (IQR)	%	Median (IQR)	%	Median (IQR)	
Sex (males)	61.3%		40.0%		53.6%		0.022
Age at transplant (years)		58 (52–63)		60 (53–64)		60 (53–63)	
CD34+ infused (10^6/kg)		4.45 (3.85–5.3)		4.8 (3.8–5.2)		4.5 (3.8–5.2)	
Lipegfilgrastim treatment	71.3%		51.1%		64.0%		0.024
Hematological recovery after stem cell infusion							
Days to ANC $\geq 0.5 \times 10^9$ L		10 (10–11)		11 (10–11)		10 (10–11)	
Days to discharge		15 (14–18)		18 (16–22)		17 (15–18)	< 0.001

IQR interquartile range

related dose reductions, hospitalizations, and antibiotic use were similar to those of PEG [40, 41]. The safety profile of LIP was also similar to that of PEG, and bone pain-related symptoms were similar in patients receiving LIP or PEG [42]. No experience regarding the use of LIP has ever been reported in the setting of ASCT for MM patients.

Our objective was to assess the impact of LIP on the clinical outcome of patients with MM who received HDM at a dose of 200 mg/m [2]. In this homogenous patient group, we observed that LIP is associated with a 3.5 times faster engraftment compared with FIL, regardless of age and sex. Female sex and FIL are associated with a greater risk of FN, and, again, FN delayed discharge after stem cell infusion. NF was associated with delayed discharge regardless of age and sex. The risk of increased evidence of SN and FN in women has been described in several studies using conventional chemotherapy regimens [43, 44]. The reason for this increased susceptibility of the female sex is unknown, but from our study, we show it also occurs after HDM and ASCT.

In our series, no delay in platelet count recovery was observed with the fixed dose of LIP, and the supposed better control of hematopoiesis following FIL administration [45] appears not to be superior concerning blood transfusions. The non-inferiority of LIP about this critical issue is, therefore, another important finding of our analysis. Bone pain emerges as the main cytokine-related adverse event, while there is no evidence of any difference between the two growth factors.

Wanneson et al. [23] reported their experience in a population of patients undergoing ASCT for either MM or lymphoma, comparing patients treated with PEG to a matched cohort of patients who received standard-of-care G-CSF. Patients with MM reported faster neutrophil recovery kinetics without improvement in duration of hospital stay or intravenous antibiotic use. This was in contrast to patients having ASCT for lymphoma who experienced benefits in terms of neutrophil engraftment and duration of neutropenia as well as intravenous antibiotics and hospitalization, showing that patients undergoing ASCT for different indications (myeloma vs lymphoma) may experience different advantages from post-ASCT G-CSF administration. We are currently testing LIP in lymphoma patients after ASCT to evaluate this hypothesis.

Recently, a meta-analysis was carried to assess the relative benefits of available long-acting agents (LIP versus PEG) and similarly compare LIP to the short-acting agent (FIL), in a total of 5769 patients receiving conventional chemotherapy [46]. Outcomes of interest were neutropenia-related efficacy and safety. Compared with PEG or FIL, LIP had a statistically significantly lower ANC recovery time; however, differences in duration of SN and bone pain were not significant.

The efficacy of LIP could be explained based on the pharmacokinetic properties associated with the drug. In the pivotal study by Bondarenko et al. [40], AUC parameters were almost 50% higher for LIP compared with PEG and the activity of a 6-mg LIP dose would be expected to be greater than that of

Table 4 Univariate and multivariate logistic regression analysis of febrile neutropenia

	Univariate analyses		Multivariate analysis*	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex (male vs female)	0.42 (0.20–0.89)	0.024	0.47 (0.22–1.02)	0.057
Growth factor (lipegfilgrastim vs filgrastim)	0.42 (0.20–0.90)	0.026	0.44 (0.20–0.96)	0.040

OR odds ratio, *CI* confidence interval

*Adjusted by age (below/above the median value)

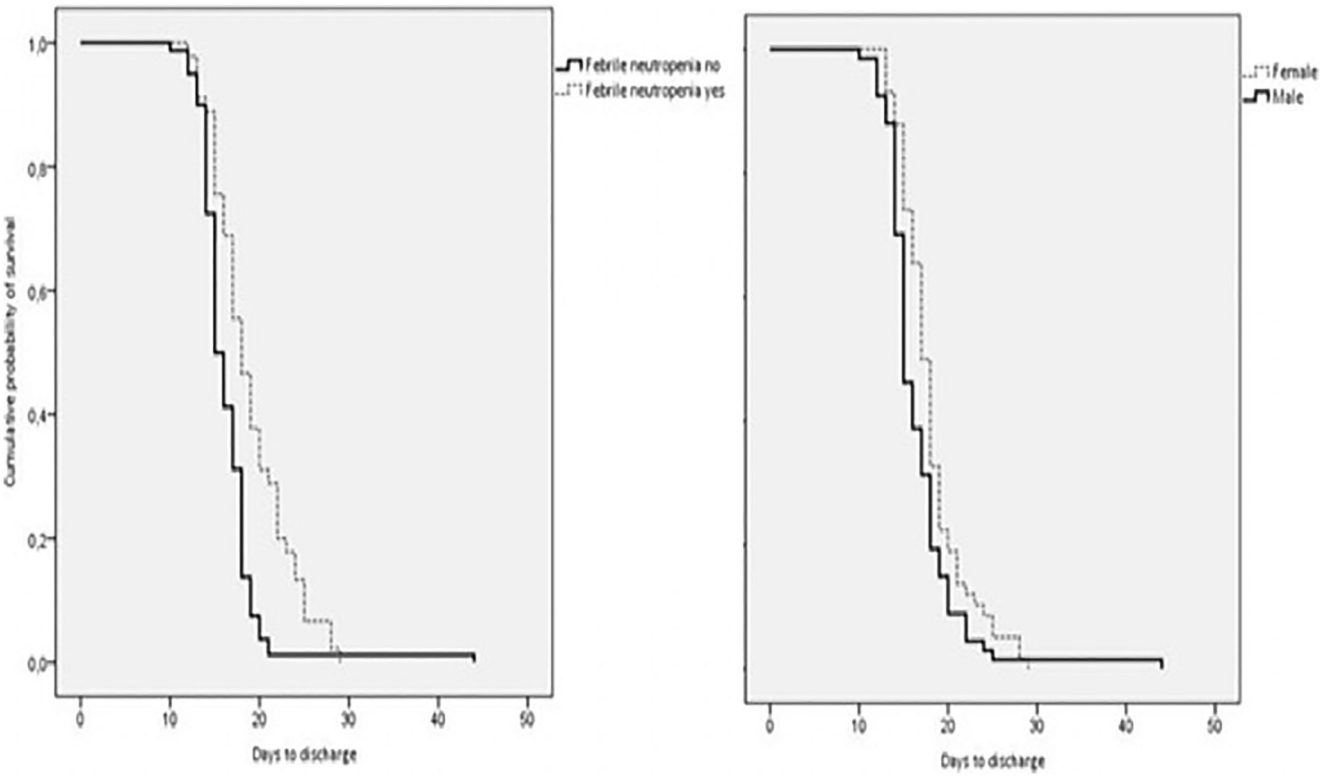

Figure 2 Kaplan-Meier survival functions on days to discharge after stem cell infusion by febrile neutropenia(left)and sex(right)

PEG 6 mg. It is also plausible that if long-acting G-CSF and FIL start on different days, the protective effect on the risk of FN is overestimated [22]. On the other hand, non-randomized controlled trials tend to underestimate the protective effect of long-acting G-CSF on duration of FN and delayed use of FIL tend to moderate the effect of drugs on FN [22].

FIL was previously considered as a cost-effective option compared with placebo after ASCT, mainly because of lower charges for room and supportive therapy after infusion [13, 24]. In our trial, the marginal cost per patient treated was estimated in euro (€) for LIP vs FIL support. Current healthcare costs include the daily cost for LIP and FIL treatment. Drug costs were obtained from the Pharmacy Unit of GOM-BMM of Reggio Calabria (Italy). Considering only this aspect, treatment with LIP has a higher cost per individual patient. However, we believe that it is tempting to assume that faster ANC recovery following HDC and ASCT will result in enhanced patient outcomes with fewer infections, less antibiotic usage, and faster discharge from hospital, with all of the cost savings that would naturally follow from such outcomes. Cost analysis among published trials showed a cost reduction that was mainly reflected in the decreased length of hospitalization, reduced need for chest radiographies, and computed tomography scans and the 34.2% savings in the cost of antibiotics [24, 47]. Our study did not aim to perform a cost-benefit analysis, although it is unlikely that, at current drug costs, an overall cost saving would probably have been observed.

The use of LIP avoids the need for multiple injections, making treatment more convenient for patients, thereby improving their quality of life. Several authors have investigated the feasibility of performing ASCT in patients with MM on an outpatient basis [48–50]. A potential advantage of the routine

Table 5 Multivariate Weibull analysis of days to discharge

	Weibull (AIC 67.38)	
	HR (CI 95%)	*P* value
Febrile neutropenia (no vs yes)	4.22 (2.69–6.63)	< 0.001
Male vs female	1.81 (1.24–2.63)	0.002

AIC Akaike information criterion, *CI* confidence interval, *HR* hazard ratio
*Model is adjusted also by median age

Table 6 Multivariate Weibull analysis on days to discharge after stem cell infusion

	Weibull (AIC 67.38)	
	HR (95%CI)	*P* value
Febrile neutropenia (no vs yes)	4.22 (2.69–6.63)	< 0.001
Male vs female	1.81 (1.24–2.63)	0.002

AIC Akaike information criterion, *HR* hazard ratio, *CI* confidence interval
*Model is adjusted also by median age

use of LIP is that a single dose of LIP may make the delivery of outpatient ASCT more feasible, reducing the risk of readmission for FN.

The main limitation of this study is that we used a series of historical controls and not a pair-matched control group. Thus, bias due to some unmeasured confounders cannot be excluded. Furthermore, although we found a benefit of LIP in terms of FN and this latter impacted upon the duration of hospitalization, we did not observe a direct benefit of LIP on this outcome variable. The lack of a significant association could depend on the fact that this study was not sufficiently powered to address this hypothesis.

In conclusion, our study provides the first evidence in support of LIP efficacy over FIL for the prevention of SN in the ASCT setting. Further, we show that patients treated with LIP had a shorter time to ANC recovery. While LIP is the first long-acting FIL biosimilar to reach the market, additional long-acting biosimilars, some with unique modifications to increase half-life, have been very recently become available to the European market. More head-to-head clinical studies and real-world data analyses are suggested to validate the comparative findings.

Compliance with ethical standards The study was approved by the local institutional review board and was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent before inclusion.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent It was obtained from all patients for being included in the study.

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