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ORIGINAL ARTICLE

Recombinant granulocyte colony-stimulating factor (rG-CSF) in the management of neutropenia induced by anthracyclines and ifosfamide in patients with soft tissue sarcomas (NEUSAR)

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Abstract
Purpose Anthracycline and ifosfamide-based chemotherapy represents a widely used regimen both in early and advanced settings in soft tissue sarcoma (STS). Prophylaxis with granulocyte colony-stimulating factor (G-CSF) reduces the severity of chemotherapy-induced neutropenia. The aim of this study was to assess the efficacy and safety of biosimilar G-CSF in these patients.
Methods Between 2003 and 2013, 67 patients with soft tissue tumors under epirubicin and ifosfamide (EI) treatment receiving biosimilar filgrastim (Zarzio®), originator filgrastim (Granulokine®, Neupogen®), and lenograstim (only originator Myelostim®) as primary prophylaxis for a total of 260 cycles of therapy were retrospectively analyzed. Baseline patient characteristics were summarized in a propensity score (PS).
Results The incidence of febrile neutropenia (FN) was 44.0 % in biosimilar filgrastim, 40.0 % in originator filgrastim, and 45.5 % in the lenograstim groups ($p = 0.935$). All grade and G4 neutropenia were similar in the three groups with the same safety profile. The use of biosimilar filgrastim achieved cost savings of €225.25 over originator filgrastim and €262.00 over lenograstim.
Conclusion Biosimilar G-CSF was effective in preventing FN and in reducing the need for hospitalization in STS patients undergoing EI treatment. It also proved comparable to its reference products from both a clinical and cost-effective standpoint.

Keywords Neutropenia · Biosimilar filgrastim · rG-CSF · Sarcoma · Neutropenia · Anthracycline · Ifosfamide · Epirubicin

Introduction

Soft tissue sarcomas (STS) represent less than 1 % of all malignant tumors, originating from mesenchymal cells all over the body [1, 2]. Combined modality treatment, including surgery, radiotherapy, and chemotherapy, leads to local control in a high proportion of patients, reducing the occurrence of distant metastases [3, 4]. Chemotherapy remains one of the most important therapeutic approaches in metastatic setting.

The potential benefits of more aggressive combinations are burdened by increased toxicities, mainly in the form of dose-limiting myelosuppression. The most frequently used chemotherapy schedules are anthracycline and ifosfamide-based regimens, with 58 % risk of febrile neutropenia (FN) without prophylaxis with granulocyte colony-stimulating factor (G-CSF) [5, 6].

Prophylactic administration of G-CSF after doxorubicin, ifosfamide, and dacarbazine in patients with STS has been shown to improve hematological tolerance to chemotherapy, leading to a significant reduction in the duration of

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neutropenia, neutrophil recovery time, and febrile neutropenia (FN) incidence [7].

Recombinant granulocyte colony-stimulating factors (rG-CSFs) are widely used to treat chemotherapy-induced neutropenia and to mobilize peripheral blood stem cells (PBSC) [8–10]. To our current data, these complex biopharmaceutical products, defined as biosimilars, are comparable but not identical to their originator product [9].

To reduce costs, many pharmaceutical companies have developed biosimilars of G-CSF. Biosimilars of filgrastim are produced differently than originator drugs by the use of different bacterial supports, consisting of unique molecules; this may produce dissimilarities in clinical efficacy and safety [10]. To confirm the value of biosimilar G-CSF, clinical observations and studies are needed.

The aim of this study was to evaluate the comparability of biosimilar and originator products through the analysis of the proportion of patients experiencing FN after receiving epirubicin and ifosfamide (EI) combination both in adjuvant and metastatic settings.

Material and methods

We enrolled in this study STS patients treated with EI regimen and receiving G-CSF, with available information on chemotherapy and G-CSF administration.

G-CSFs were administered as primary prophylaxis in accordance with EORTC clinical guidelines [8] to patients with ≥20 % expected risk of FN, according to chemotherapy regimen. Originator and biosimilar filgrastim were administered at a dose of 30 MU/0.5 ml as daily subcutaneous injections until neutrophil recovery. Lenograstim was administered subcutaneously at a dose of 34 MU daily until neutrophil recovery.

The primary endpoint was to identify the proportion of patients experiencing FN, defined according to CTAE version 4.0 as the proportion of patients experiencing <1000/mm^3 ANC and a single temperature of >38.3 °C or a sustained temperature of ≥38 °C for more than 1 h. The secondary endpoints were cost analysis related to the use of originator vs. biosimilar growth factors and neutropenia characteristics related to the type of growth factor adopted.

In case of FN, patients were hospitalized and empirical antibiotic therapy was initiated according to internal guidelines. Blood cultures were carried out for specific antibiotic therapy. Normal cardiac (left ventricular ejection fraction) and renal function, neutrophil count ≥1500 × 109/l, hemoglobin ≥9 g/dl, and platelets count ≥0,000 were required before the first cycle.

Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 [11]. All adverse events, occurring during the study and due to G-CSF, were recorded, as observed by the investigator or reported by the patient. Blood cell counts were performed starting from day 11.

The study was approved by the Local Ethics Committee (Comitato Etico Area Vasta Romagna e IRST).

Statistical analysis

Frequency tables were performed for categorical variables. Continuous variables were presented using median and range. Group comparisons for categorical variables based on chi-square or Fisher exact test were performed to evaluate the difference in the three G-CSF groups, while the Kruskal-Wallis test was used to compare continuous variables among G-CSF groups.

Propensity score (PS) was defined as the conditional probability of receiving a growth factor, given a set of observed potential confounders. In this way, all the information from a set of potential confounders were summarized into a unique balancing score variable, called PS. PS assures that the distribution of measured baseline covariates expected to be the same in the different groups identified throughout different G-CSFs. Multinomial PS score for each patient was estimated with the TWANG package (R Software) assuming the G-CSF used as a dependent variable, whereas age, sex, body mass index (BMI) and type of setting as pretreatment variables. Balance measure [absolute standardized mean difference (ASMD)] was evaluated to assess if patient characteristics were the same among G-CSF groups [12]. Estimated PSs were included as weights in a logistic model using the R software SURVEY package.

Overall survival (OS) was defined as the time from date of diagnosis to date of death. Event-free patients were censored on date of last follow-up. OS was reported as median value expressed in months, with confidence interval of 95 % (95 % CI). Survival curves were estimated using the product-limit method of Kaplan-Meier and compared by the log-rank statistic test.

$p < 0.05$ was considered statistically significant. Statistical analyses were carried out with R Software (version 3.2.2) and with STATA/MP 10.1 for Windows (Stata Corp LP, USA).

Economic evaluation

We performed a cost-minimization analysis, considering the direct costs met by a healthcare provider as a buyer of any of the three alternative agents. We calculated the actual cumulative cost of alternative treatment with originator filgrastim, biosimilar filgrastim, and lenograstim administered to one patient after one chemotherapy cycle.

Indirect costs were not included, thus costs are equal to acquisition price. We excluded any cost associated with the administration of the treatment or any other expense related to

the management of FN (such as in-patient and out-patient care, clinicians' fees, and costs of associated treatment reductions). Unit dose costs are based on the price paid by public and private hospitals in the Emilia Romagna region (Italy), not on retail drug prices (i.e., prices paid by the general public). Such institutions negotiate a 50 to 90 % discount on official drug prices with the agent supplier. All calculations are in Euros (EUR, €). The unit dose acquisition price inputs used were €11.94 for biosimilar filgrastim, €56.99 for originator filgrastim, and €64.34 for lenograstim.

Results

Patient characteristics

Between 2003 and 2013, 83 patients with STS were treated with EI regimen both in adjuvant and metastatic setting. Information on chemotherapy and G-CSF administration was available for 67 (80.7 %) of these. Age was similar in all the three groups, with a median age of 60 years (range 28–78); 58.2 % of patients were female. Of those receiving G-CSF, 37.3 % underwent biosimilar filgrastim, 29.9 % originator filgrastim, and 32.8 % lenograstim. All patients received a median of 4 cycles (range 1–6) of EI regimen according to the following schedule: epirubicin was administered as a 4-h infusion on day 1 and day 2 q21, at a dose of 60 mg/m^2/day; ifosfamide was administered from day 1 to day 3 q21, at a dose of 3000 mg/m^2/day in a 2-h infusion; uroprotection with mesna, hydration with an electrolyte and glucose solution, and antiemetics were also administered. Of the 67 patients, 34 (50.7 %) were treated in a metastatic setting and 33 (49.3 %) in either a neoadjuvant or adjuvant setting. Patients with metastatic soft tissue tumors received the EI regimen as first-line treatment. Patient characteristics were similar among the three groups (Table 1).

Efficacy

The proportion of patients experiencing at least one FN episode was similar in the three groups (44.0 % for biosimilar filgrastim, 40.0 % for originator filgrastim, and 45.5 % for lenograstim), and no statistically significant difference was observed. Proportions were similar also for patients with at least one event of all-grade neutropenia or G4 neutropenia (in the 260 analyzed cycles of therapy) (Table 2).

Median duration of G-CSF administration was 5 days with both biosimilar filgrastim (range 3–11), originator filgrastim (range 5–8), and lenograstim (range 3–8) starting on day 6 (range 4–16) without any difference in the three groups ($p = 0.229$).

After the first cycle of therapy 48.1 % of patients, 10 (40 %) in the biosimilar group, 5 (20 %) in the originator group and 10 (40 %) in the lenograstim group required a dose reduction due to age, comorbidities, or causes other than myelosuppression. No treatment-related deaths occurred. Thirty-three patients had at least one fever episode after chemotherapy administration, without any difference among groups ($n = 14$, 56.0 % in biosimilar filgrastim, $n = 8$, 40.0 % in originator filgrastim, and $n = 11$, 50.0 % in lenograstim subgroup; $p = 0.564$). Eight patients had more than one febrile episode. The fever rate decreased during treatment cycles: 29.9 % in first cycle, 14.3 % in the second, 11.9 % in the third, and 11.3 % in the fourth and following cycles of therapy. Twenty patients had at least one hospitalization because of fever. No differences were seen among the groups ($n = 7$, 28.0 % in biosimilar, $n = 5$, 25.0 % in originator filgrastim, and $n = 8$, 36.4 % in lenograstim subgroup; $p = 0.701$).

Table 1 Baseline patient characteristics

Variable	Total	Biosimilar filgrastim (%)	Originator filgrastim (%)	Lenograstim (%)	*p*
Overall	67	25	20	22	–
Median age, years (range)	60 (28–78)	58 (32–78)	59 (35–72)	61 (28–75)	0.989
Sex					
Male	28 (41.8)	14 (56.0)	9 (45.0)	5 (22.7)	0.069
Female	39 (58.2)	11 (44.0)	11 (55.0)	17 (77.3)	
Median weight, kg (range)	68 (44–108)	70 (44–105)	65 (46–90)	65 (45–108)	0.197
BMI					
<25.0	36 (53.7)	10 (40.0)	14 (70.0)	12 (54.5)	0.140
≥25.0	31 (46.3)	15 (60.0)	6 (30.0)	10 (45.5)	
Setting					
Neoadjuvant/adjuvant	33 (49.3)	12 (48.0)	8 (40.0)	13 (59.0)	0.484
Advanced	34 (50.7)	13 (52.0)	12 (60.0)	9 (41.0)	

BMI body mass index

Table 2 Incidence of febrile neutropenia, neutropenia, and G4 neutropenia

Variable	Total (%)	Biosimilar filgrastim (%)	Originator filgrastim (%)	Lenograstim (%)	*p*
Overall	67	25	20	22	–
Febrile neutropenia					
≥One event	29 (43.3)	11 (44.0)	8 (40.0)	10 (45.5)	0.935
None	38 (56.7)	14 (56.0)	12 (60.0)	12 (54.5)	
All grade neutropenia					
≥One event	43 (64.2)	17 (68.0)	10 (50.0)	16 (72.7)	0.272
None	24 (35.8)	8 (32.0)	10 (50.0)	6 (27.3)	
G4 neutropenia					
≥One event	36 (53.7)	12 (48.0)	8 (40.0)	16 (72.7)	0.080
None	31 (46.3)	13 (52.0)	12 (60.0)	6 (27.3)	
Sepsis					
≥One event	4 (6.0)	1 (4.0)	0 (0.0)	3 (13.6)	0.193
None	63 (94.0)	24 (96.0)	20 (100.0)	19 (86.4)	

About half of the patients ($n = 34$) had chemotherapy-related thrombocytopenia, 15 (44 %) G1-G2 and 19 (56 %) G3-G4. There were no significant differences between the three groups. Of the entire case series, 25 patients experienced at least one episode of monocytosis, without, however, any significant differences between the three G-CSF groups ($n = 13$, 54.2 % in biosimilar filgrastim; $n = 5$, 27.8 % in originator filgrastim, and $n = 7$, 31.8 % in the lenograstim group).

Antibiotic therapy was administered at least once in 32 patients, without any difference among the groups ($n = 14$, 56.0 % in biosimilar filgrastim, $n = 7$, 35.0 % in originator filgrastim, and $n = 11$, 50.0 % in lenograstim subgroup; $p = 0.362$). As per internal clinical guidelines, single-agent empiric antibiotic therapy with quinolones was used. The incidence of sepsis was low, occurring in one patient in the biosimilar group and in three in the lenograstim group. No deaths related to sepsis or febrile neutropenia were observed.

PS was estimated for each patient, and overlap assumption of PS across the three groups was met. Univariate logistic models were performed, and estimated PS was included as weights. As shown in Table 3, risks of developing FN were not statistically different in each growth factor. The same results were reached when considering all grade neutropenia or G4 neutropenia as outcomes. Odds ratio (OR) in unweighted models were the same as in weighted models. Thus, G-CSF choice was independent from patient characteristics.

In a follow-up period of 59 months (95 % CI: 51.6–78.5), 40 deaths were recorded in 65 evaluable cases, with a median OS of 32 months (95 % CI: 25.7–45.9). No difference was observed among the three groups of G-CSF neither in the whole population ($p = 0.1799$) nor in the metastatic setting ($p = 0.8826$) (Fig. 1a, b).

Side effects were similar in the three groups, the most frequent being bone pain and arthralgia; these occurred in five (20.0 %) patients in the biosimilar filgrastim group, four (20.0 %) in the originator filgrastim group, and four (18.2 %) in the lenograstim group ($p = 0.985$).

Table 3 Univariate logistic models unweighted and weighted by propensity score

	Weighted model			Unweighted model		
Variable	Odds ratio (OR)	*p*	95 % CI	OR	*p*	95 % CI
Model 1—outcome variable: febrile neutropenia						
Originator filgrastim vs. biosimilar filgrastim	0.804	0.748	0.214–3.026	0.848	0.787	0.252–2.799
Lenograstim vs. biosimilar filgrastim	1.007	0.992	0.281–3.608	1.061	0.920	0.332–3.386
Model 2—outcome variable: all grade neutropenia						
Originator filgrastim vs. biosimilar filgrastim	0.516	0.348	0.131–2.031	0.471	0.224	0.135–1.569
Lenograstim vs. biosimilar filgrastim	1.538	0.556	0.369–6.391	1.255	0.724	0.357–4.582
Model 3—outcome variable: G4 neutropenia						
Originator filgrastim vs. biosimilar filgrastim	0.651	0.527	0.173–2.443	0.722	0.591	0.215–2.365
Lenograstim vs. biosimilar filgrastim	2.782	0.150	0.701–11.037	2.889	0.089	0.876–10.368

Cost analysis

The cumulative cost of treatment with biosimilar filgrastim ran from €35.82 on day 3 to €131.34 on day 11, compared to treatment with originator filgrastim, running from €170.97 on day 3 to €626.89 on day 11, and lenograstim, from €193.02 on day 3 to €707.74 on day 11. The cost data over time are reported in Table 4 and Fig. 2. On day 5, the cost savings in absolute

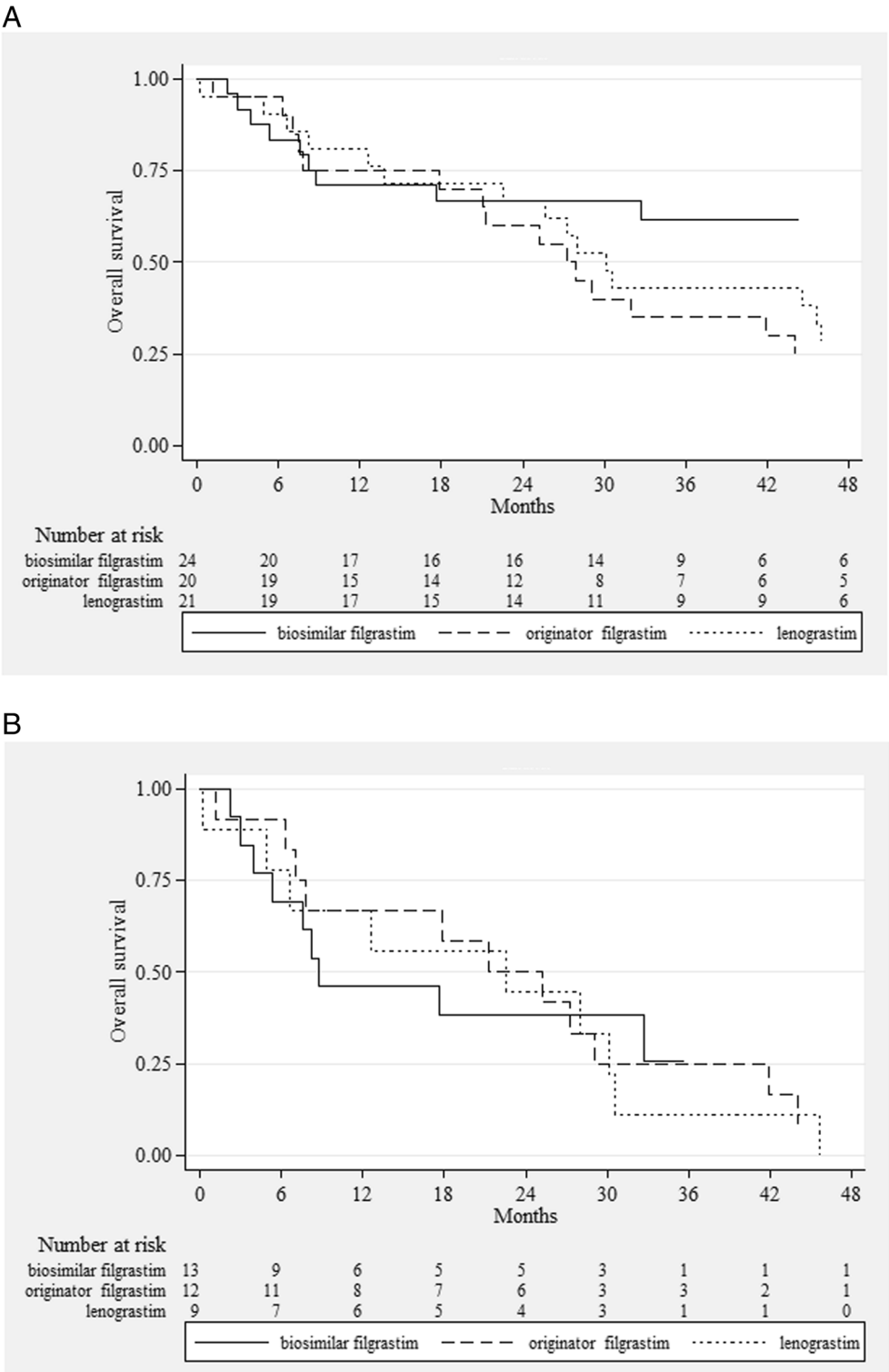

Figure 1 OS according to G-CSF in **a** the whole population ($p = 0.1799$) and **b** the metastatic setting ($p = 0.8826$)

Table 4 Cumulative cost of treatment and cost savings of biosimilar filgrastim over originator filgrastim and lenograstim

Days	3	4	5	6	7	8	9	10	11
Cumulative cost of treatment over 11 days (€)									
Biosimilar filgrastim	35.82	47.76	59.70	71.64	83.58	95.52	107.46	119.40	131.34
Originator filgrastim	170.97	227.96	284.95	341.94	398.93	455.92	512.91	569.90	626.89
Lenograstim	193.02	257.36	321.70	386.04	450.38	514.72	579.06	643.40	707.74
Cumulative savings on day 5 (€)									
Biosimilar filgrastim vs. filgrastim	135.15	180.20	225.25	270.30	315.35	360.40	405.45	450.50	495.55
Biosimilar filgrastim vs. lenograstim	157.20	209.60	262.00	314.40	366.80	419.20	471.60	524.00	576.40

terms associated with treating one patient during one chemotherapy cycle with biosimilar filgrastim was €225.25 over originator filgrastim and €262.00 over lenograstim (Table 4).

Discussion

STS are rare malignancies, and anthracycline and ifosfamide chemotherapy represents one of the most important therapeutic approaches in adjuvant and metastatic settings. The role of chemotherapy is still unclear in the adjuvant setting, although it seems to improve both disease-free survival (DFS) and OS [4, 13]. The potential benefit of more aggressive chemotherapy regimens is limited by increased toxicity: in particular, neutropenia is a major cause of morbidity and mortality. According to the EORTC guidelines, the risk of experiencing FN without G-CSF is over 50 % [8] in STS treatment regimens, including EI.

Several types of G-CSF are currently available for the treatment of neutropenia, including biosimilars, such as biosimilar filgrastim, and the originator products of growth factors, such as originator filgrastim and Lenograstim.

Biosimilars are similar, but not identical, versions of the originator biological drugs whose patents have expired. They were approved in Europe in 2008 by the European Medicines Agency (EMA), even though their clinical use is still controversial [14]. The current use of biosimilars in clinical practice is based on the results of in vitro cell proliferation assay, showing analogies between biosimilar filgrastim and originator filgrastim protein structures, with a comparable binding to the G-CSF receptor biosimilar filgrastim. New recombinant human granulocyte colony-stimulating factors were evaluated in healthy volunteers and neutropenic patients in phase I and III studies, demonstrating their biosimilarity from a pharmacodynamic and pharmacokinetic point of view [15].

Moreover, there are several clinical "real-world" experiences that are leading and have lead to the approval of these agents [16].

EORTC clinical guidelines recommend the use of biosimilar filgrastim and originator filgrastim to prevent chemotherapy-

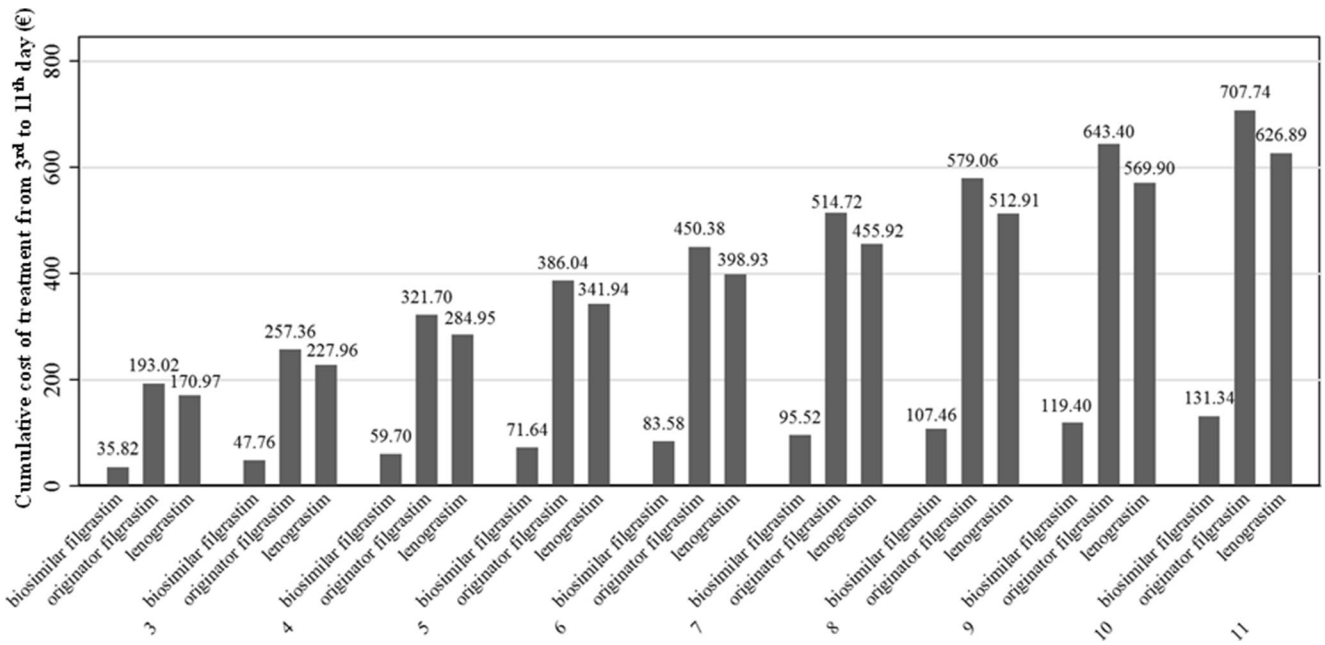

Fig. 2 Cumulative cost of treatment of biosimilar filgrastim with respect to originator filgrastim and lenograstim from 3rd to 11th day of treatment

induced neutropenia, stating that the choice of whichever factor is based on an individual clinical decision [8].

Beyond efficacy, the use of biosimilars represents a potentially significant cost savings to healthcare authorities, essential to monitor levels of expenditure.

Unfortunately, prospective clinical trials are lacking, and no data based on rG-CSFs as prophylaxis in specific high myelotoxic chemotherapeutic regimens are available.

In this retrospective study, the use of prophylactic biosimilar filgrastim compared to originator filgrastim and lenograstim showed no difference in incidence of all-grade neutropenia, FN, and hospitalization in the 260 cycles of therapy analyzed. In addition, the median duration of G-CSF administration was similar in the three groups, with a biosimilar filgrastim cost savings of €225.25/patient over originator filgrastim, and €262.00/patient over lenograstim.

No differences in terms of clinical outcome were seen in patients treated with either biosimilar or originator as prophylaxis for neutropenia induced by EI regimen. Dose reductions needed for reasons other than myelosuppression were similar throughout three groups and did not influence patient outcome or response to the biosimilar. Thirty-three patients had at least one episode of fever, with little difference between the three groups. Single-agent prophylactic fluoroquinolone could be considered for patients when prolonged (>7 days) neutropenia is expected, regardless of the G-CSF used. All-cause costs were roughly the same for filgrastim, biosimilar, and lenograstim.

The interpretation of our results is limited by several sources of bias, mainly the retrospective nature of the study and the considerable length of time over which it was conducted. However, it must be pointed out that the only change in patient management during the study period concerned the type of G-CSF used. Patients were not consecutive due to the lack of information. In addition, no data are available on the impact of neutropenia, morbidity associated, and hospitalization on the economical system and patient's quality of life. Another limitation of the study is the assumption that G-CSF administration by day 6 of a cycle represents primary prophylaxis rather than treatment.

In conclusion, the results of this study indicate that the prophylactic use of biosimilar filgrastim over originator filgrastim and lenograstim in STS patients receiving high myelosuppressive regimen like EI is effective and cost-saving.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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