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ORIGINAL ARTICLE

Comparison of peripheral blood stem cell mobilization with filgrastim versus pegfilgrastim in lymphoma patients – single center experience

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Summary

Purpose: *The purpose of this study was to evaluate mobilization outcomes with biosimilar pegfilgrastim versus filgrastim in association with chemotherapy as a mobilization strategy for lymphoma patients.*

Methods: *In the current study we included 32 lymphoma patients that received mobilization therapy and PBSC harvesting at the Bone Marrow Transplantation Department of Fundeni Clinical Institute, Bucharest, Romania between January and December 2019.*

Results: *Pegfilgrastim had beneficial effect when compared to filgrastim in reducing grade IV neutropenia both in the univariate and multivariate logistic models. Additionally, similar efficacy, as mobilization rate, after both filgrastim and pegfilgrastim was observed and no differences were noted between the two groups considering the need for platelet or red blood cell support.*

Conclusion: *The use of biosimilar pegfilgrastim is a viable alternative to filgrastim in PBSC mobilization for lymphoma patients.*

Key words: *filgrastim, pegfilgrastim, biosimilar, mobilization, apheresis*

Introduction

Autologous hematopoietic stem cell transplantation (ASCT) is used as a standard therapeutic procedure in several clinical situations. These situations include eligible lymphoma patients after first-line chemotherapy failure, patients with relapsed/refractory disease or as a consolidation after the first remission in mantle cell lymphoma patients [1]. In 2018, more than 8700 ASCT were performed for lymphoma patients according to the European Society of Blood and Marrow Transplantation Group (EBMT) activity survey. In almost all cases, peripheral blood stem cells (PBSC) were used [2]. Under normal conditions, the number of the circulating cells needed for this procedure is very low. Because of this, interventions are needed in order to "mobilize" hematopoietic stem cells into peripheral blood in sufficient numbers to allow a sufficient number to be harvested by leukapheresis and, thus sustain hematopoietic reconstitution after transplantation [3]. There is a demon-

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strated correlation between the number of PBSC harvested and infused and post-ASCT outcome with the minimum recommended PBSC dose being 2-2.5×10^6 CD34+ cells/kg. Studies have shown that using a number of PBSC below this threshold leads to delayed neutrophil and platelet recovery, increased red blood cells transfusion requirements and permanent loss of engraftment [4-10]. On the other hand, PBSC doses over 3-5×10^6 CD34+ cells/kg are associated with improvement in neutrophil and platelet recovery [4,5,10].

In the current clinical practice, there are three types of approved approaches used for mobilization. These are represented by: myeloid growth factors like granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF); chemotherapy followed by growth factor administration and the combination of G-CSF with the CXCR4 antagonist plerixafor [3,4,11]. Thus, it can be observed that a myeloid growth factor is present in all mobilization approaches and can be considered as an essential step in this procedure.

The administration of growth factors reduces the neutropenic period following chemotherapy and thus the infection risk. Even more, they also stimulate mobilization by inducing cleavage of adhesion molecules by bone marrow proteases [3,12,13]. Filgrastim is the G-CSF widely used as standard and recommended in evidence-based guidelines for PBSC mobilization [14,15]. Given the short half-life of G-CSF of approximately 4 h, it requires a multi-injection administration regimen of 5-15 μg/kg/day starting at 1-6 days after chemotherapy which continues until leukapheresis is performed. This negatively impacts convenience and comfort for patients and staff [3,14-16]. Pegfilgrastim is a pegylated formulation G-CSF which has a reduced renal clearance and enzymatic degradation resulting in a longer plasmatic half-life of 33 h. Thus, after a single dose of 6 mg therapeutic serum levels of G-CSF are maintained over a period of 14 days [3,14,16-19].

Considering these pharmacokinetic properties, pegfilgrastim has been evaluated as an alternative to non-pegylated G-CSF for the mobilization of PBSCs for ASCT by multiple experimental studies and comparative clinical studies. The analysis of several aspects such as apheresis efficiency, CD34+ cell yield, neutrophil recovery, pegfilgrastim dosage have led to conflicting results [3,20-27].

Given the controversial data in the literature, we conducted a prospective analysis to evaluate mobilization outcomes with pegfilgrastim versus filgrastim in association with chemotherapy as a mobilization strategy for lymphoma patients.

Methods

This was a prospective, comparative, interventional and open-label study.

Patients

In the current study we included lymphoma patients that received mobilization therapy and PBSC harvesting at the Bone Marrow Transplantation Department of Fundeni Clinical Institute, Bucharest, Romania, between January and December 2019.

The study was performed in accordance with the declaration of Helsinki and was approved by the Ethics Committee of Fundeni Clinical Institute (55623/21/12/2018; 21887/02.05.2019). Blinding was not performed, with patients being able to choose either pegfilgrastim or filgrastim.

PBSC mobilization and processing

Mobilization regimens used in our study were IGEV (Ifosfamide 2000 mg/mp days 1-4; Gemcitabin 800 mg/m^2 day 1 and day 4; Vinorelbin 20 mg/m^2 day 1; Dexamentazone 40 mg/day days 1-4), or DHAP (Cisplatin 100 mg/mp day 1; Cytarabine 2 g/m^2 BID day 2; Dexametazone 40 mg/day, days 1-4).

Pegfilgrastim (PelgrazR-Accord Healthcare's) was given as a single dose of 6 mg on day 5, while filgrastim (AccofilR-Accord Healthcare's or ZarzioR-Sandoz GmbH) was given at 10-15 mg/kg/day from day 5 onward until stem cell harvesting.

The PBSC count was started at a white blood cell (WBC) count in peripheral blood of>0.4×10^6/L. The PBSC count was determined using a Navios Flow Cytometer from Beckman Coulter system, Navios Cytometer 1.2 soft according to the International Society of Hematotherapy and Graft Engineering guidelines [28]. Apheresis was started at PBSC count of>2×10^6/L in the peripheral blood. Harvesting was performed using Cobe Spectra or Optia Spectra apheresis equipment. Apheresis was continued until the collection of a minimum target of >2×10^6 CD34+ cells/kg of body weight.

After harvest, PBSCs were cryopreserved in liquid nitrogen at -196°C or electric freezer at -80°C for a maximum of 6 months. Viability check of PBSC was performed using 7AAD (7-Aminoactinomycin D) staining.

Study definitions

We collected the following data from our patients: gender, age, weight, diagnosis, stage, disease status, mobilization failure, days from stimulation to harvest, peak of absolute CD34+ cells, percent of CD34+ cells in harvest, total blood volume processed, WBC in peripheral blood at apheresis, WBC in apheresis, CD34+ cells in harvest, days between chemotherapy and harvest, number of prior treatment cycles, use of radiotherapy, occurrence of grade IV neutropenia, duration of grade IV neutropenia, occurrence of febrile neutropenia, need for red blood cell (RBC) support, need for platelet support and the use of plerixafor.

The study endpoints were the following: apheresis efficiency, CD34+ cell yield, grade IV neutropenia oc-

currence, febrile neutropenia occurrence, need for red blood cell transfusion, need for platelet transfusion, use of plerixafor.

Disease status was defined as complete remission (CR) if the tumor lesions were not observable and the patient did not present lymphoma-associated symptomatology. Partial remission (PR) was defined as the reduction of the lesions with at least 50%. Progressive disease (PD) was defined if any of the following was present: appearance of any new lesion of >1.5 cm in longest diameter, an increase of at least 50% from nadir in the sum of the products of the longest perpendicular diameters of any previously involved lymph nodes or at least a 50% increase in the longest diameter of any single previously identified node >1 cm in its long axis.

Staging defined in accordance with the Ann Arbor criteria [29] was performed at diagnosis.

Grade IV neutropenia was defined as an absolute neutrophil count under 500/mm^3 according to CTCAE criteria.

Statistics

Data analysis was performed using R 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were presented as absolute value (percent). Contingency tables were analyzed using Fisher's test. Shapiro-Wilk test and histogram visualization were used to determine the normality of the distribution. The sample size was also taken into consideration when assessing normality of the distribution. Non-normally distributed variables were presented as median (quartile 1, quartile 3). Mann-Whitney-Wilcoxon test was used when assessing the differences between two non-normally distributed groups. The univariate logistic model was used to determine the variables that significantly influenced an endpoint. Variables that presented a p value under 0.1 in the univariate logistic model were used in the multivariate logistic model. A p value under 0.05 was considered statistically significant. A p value between 0.05 and 0.1 was considered to have a tendency for statistical significance.

Results

We enrolled 32 patients from the above-mentioned center, diagnosed with lymphoma, aged 18-65 years. One transferred patient that did not have enough information was removed from the cohort. Thus, in the present study we included 31 patients. No infections were observed in this cohort. In all patients that were successfully stimulated one leukapheresis was needed. The initial characteristics of these patients are presented in Table 1. The main difference between the two groups considering these variables was represented by the fact that patients receiving filgrastim also had a higher number of therapy cycles in their history. Added to this, although only with a tendency for statistical significance, patients receiving filgrastim had a lower weight compared to those receiving pegfilgrastim.

The differences in mobilization and harvest results between the two groups are presented in Table 2. We observed that patients that received filgrastim had a higher WBC count in the peripheral

Table 1. General characteristics of the cohort and differences between filgrastim and pegfilgrastim

Variable	*Overall (n=31)* *n (%)*	*Filgrastim (n=20)* *n (%)*	*Pegfilgrastim (n=11)* *n (%)*	*p value*
Male gender	14 (45.2)	8 (40.0)	6 (54.5)	0.478
Age (years)	41 (28, 52)	40 (31, 50)	42 (33, 48)	0.772
Weight (kg)	69 (63, 78)	68 (65,73)	77 (69,83)	0.057
Diagnosis				0.631
B-NHL	12 (38.7)	9 (45.0)	3 (27.3)	
T-NHL	6 (19.4)	3 (15.0)	5 (45.5)	
HL	13 (41.9)	8 (40.0)	3 (27.3)	
Stage				0.928
1	1 (3.2)	1 (5.0)	0 (0)	
2	8 (25.8)	5 (25.0)	3 (27.3)	
3	11 (35.5)	6 (30.0)	5 (45.5)	
4	11 (35.5)	8 (40.0)	3 (27.3)	
Disease status				0.607
CR	11 (35.5)	6 (30.0)	5 (45.5)	
PR	18 (58.06)	12 (60.0)	0 (0)	
PD	2 (6.5)	2 (10.0)	6 (54.5)	
Prior treatment	9 (7,11)	10 (8, 11)	6 (2, 8)	<0.01
Previous RT	9 (29)	7 (35.0)	2 (18.2)	0.429

RT: radiotherapy

Table 2. Mobilization and harvest results and differences between filgrastim and pegfilgrastim

Variable	*Overall (n=31)*	*Filgrastim (n=20)*	*Pegfilgrastim (n=11)*	*p value*
Mobilization failure, n (%)	3 (9.7)	2 (10.0)	1 (9.1)	1
Stimulation to harvest (days)	7 (6, 8)	8 (6, 8)	7 (6, 8)	0.767
Peak of absolute CD34+ cells (IL)	69.5 (35.0, 107.0)	72.0 (38.0, 113.0)	43 (28.8, 95.0)	0.615
Percent of CD34+ in harvest	2.1 (0.9, 2.8)	1.9 (1.1, 2.4)	2.5 (0.8, 2.9)	0.533
Total blood volume processed (mL)	13.941 (11.301, 15.445)	12.914 (11.217, 15.132)	15.203 (12.290, 16.815)	0.172
WBC in peripheral blood at aphersis (/mmc)	10.27 (7.18, 18.98)	15.65 (9.37, 21.46)	8.18 (5.17, 9.36)	0.040
WBC in apheresis (/mmc)	126.06 (76.33, 168.98)	128.53 (91.49, 169.22)	122.35 (59.60, 140.60)	0.348
CD34+ cells harvest (10^6/kg)	7.01 (4.62, 9.69)	7.74 (4.85, 9.77)	5.95 (3.67, 9.06)	0.429
Time between chemotherapy and harvest (days)	11 (10, 12)	12 (10, 12)	11 (10, 11)	0.085
Grade IV neutropenia, n (%)	21 (67.7)	18 (90.0)	3 (27.3)	<0.001
Grade IV neutropenia duration (days)	1 (0, 1)	1 (1, 1)	0 (0, 0)	<0.001
Febrile neutropenia, n (%)	8 (25.8)	6 (30.0)	2 (18.2)	0.676
RBC support, n (%)	4 (12.9)	3 (15.0)	1 (9.1)	1
Platelet support, n (%)	11 (35.5)	9 (45.0)	2 (18.2)	0.241
Plerixafor, n (%)	2 (6.5)	2 (10.0)	0 (0)	0.527

WBC: white blood cells, RBC: red blood cells.

Table 3. Univariate logistic model having as the dependent variable the occurrence of grade IV neutropenia

Variable	*OR*	*95% Lower CI*	*95% Upper CI*	*p value*
Male gender	0.410	0.081	1.878	0.257
Age (years)	0.994	0.937	1.051	0.820
Weight (kg)	0.956	0.888	1.019	0.182
Pegfilgrastim	0.042	0.004	0.253	<0.01
Stimulation failure	NA	NA	NA	NA
Stimulation to harvest (days)	1.892	1.016	4.451	0.086
Peak of absolute CD34+ cells (IL)	0.999	0.984	1.014	0.863
Percent of CD34+ in harvest	0.851	0.475	1.500	0.562
Total blood volume processed (mL)	1.000	1.000	1.000	0.837
WBC in peripheral blood at aphersis (/mmc)	1.097	0.989	1.258	0.120
WBC in apheresis (/mmc)	1.004	0.995	1.018	0.451
CD34+ cells harvest (10^6/kg)	0.942	0.788	1.117	0.484
Diagnosis				
HL vs B-NHL	1.125	0.203	6.281	0.258
T-NHLvs B-NHL	1.000	0.127	9.529	1
Stage 3-4	1.071	0.184	5.455	0.935
Disease status CR	0.208	0.0378	1.006	0.057
Time between chemotherapy and harvest (days)	2.472	1.166	7.277	0.049
Prior treatment	1.220	0.967	1.584	0.105
Previous RT	0.933	0.183	5.440	0.935

HL: Hodgkin Lymphoma, B-NHL: B-nonHodgkin Lymphoma, T-NHL: T-nonHodgkin Lymphoma, RT: radiotherapy.

Table 4. Multivariate logistic model for assessing the independent influence of Pegfil-grastim in reducing the occurrence of grade IV neutropenia. Color coding of the bars was used to specify the groups for which a multivariate logistic model was used

Variable	*OR*	*95% Lower CI*	*95% Upper CI*	*p value*
Stimulation to harvest (days)	3.113	1.221	19.603	0.085
Pegfilgrastim	0.009	0.000	0.125	<0.01
Disease status CR	0.131	0.006	1.126	0.095
Pegfilgrastim	0.031	0.001	0.238	<0.01
Time between chemotherapy and harvest (days)	3.257	1.251	20.090	0.094
Pegfilgrastim	0.011	0.000	0.146	<0.01

HL: Hodgkin Lymphoma, B-NHL: B-nonHodgkin Lymphoma, T-NHL: T-nonHodgkin Lymphoma, RT: radiotherapy.

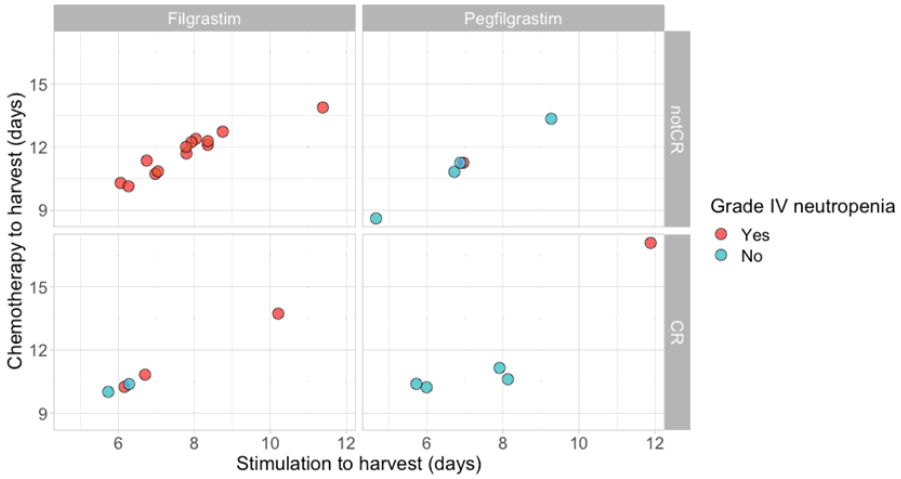

Figure 1. Representations of the interrelations between stimulation to harvest (days), chemotherapy to harvest (days), CR status, agent used and the occurrence of grade IV neutropenia.

blood at apheresis, but also had a higher occurrence of grade IV neutropenia.

Because of the differences between the two groups considering the occurrence of grade IV neutropenia we used a univariate logistic model to determine the variables that were associated with grade IV neutropenia (Table 3). Through this we observed that the occurrence of grade IV neutropenia was statistically significant associated with filgrastim use when compared to pegfilgrastim use and with a higher number of days between chemotherapy and harvest. We also observed that there was a tendency for statistical significance for the associations between grade IV neutropenia and a higher number of days between stimulation to harvest and a non-CR disease status.

We further adjusted the association between pegfilgrastim and a low occurrence of grade IV neutropenia with the variables that had at least a tendency for statistical significance ($p<0.1$) when associated with grade IV neutropenia. Because of the relatively small cohort, we adjusted pegfilgrastim with the selected variables in a "one-by-one" manner (Table 4). We observed that pegfilgrastim maintained its effect when adjusted with either one of the selected variables (days between stimulation to harvest, disease status or days between chemotherapy and harvest).

To better observe the variables assessed in Table 3 we presented them in Figure 1.

Discussion

In the present study we assessed the effect of pegfilgrastim in comparison to filgrastim when assessing mobilization and harvest results and when evaluating complications that these patients can present. Herein, we observed the beneficial effect that pegfilgrastim has when compared to filgrastim in reducing grade IV neutropenia both in the univariate and multivariate logistic models.

Multiple studies compared pegfilgrastim to filgrastim for PBSC mobilization in ASCT patients with controversial results. Generally, pegfilgrastim is considered a viable and safe alternative to filgrastim in the chemomobilization of lymphoma patients. Nonetheless, there are very few data about biosimilar pegfilgrastim in mobilization of PBSC and the reported results of pegfilgrastim mobilization lack reproducibility, being heterogeneous in the literature. With this being said, there are several studies showing the beneficial effects of pegfilgrastim use regarding apheresis including earlier apheresis [30], reduction in the required apheresis procedures [26,30-32]. Interestingly, most study groups did not see differences regarding parameters related to WBC counts, red blood cells and platelets, with pegfilgrastim presenting similar results regarding recovery time and the need for red blood cell or platelet support [26,30,31]. We also observed that the need for red blood cell or platelet support was not different between the two groups but revealed the association between the use of pegfilgrastim and a lower incidence of grade IV neutropenia. The lack of reproducibility between studies could be explained by differences regarding the general characteristics of the patient population, the used chemotherapy regimen for mobilization, schedule of growth factor administration and pegfilgrastim dose with different studies using 6, 12 or 18 mg/day [14,26,30-32].

In a metaanalysis, Kim et al included 8 studies which had quantitative data and observed that, in the case of lymphoma patients, filgrastim

was better than pegfilgrastim regarding the total CD34+ cell collection count, while there was no difference for multiple myeloma patients between the two approaches [14]. We did not observe any difference between the two approaches regarding the total CD34+ cell collection count, but we observed a higher number of WBC in the peripheral blood associated with the use of filgrastim. In their metaanalysis, Kim et al did not assess the occurrence of grade IV neutropenia but did not see differences regarding the day of WBC recovery between the two approaches [14]. Nonetheless, Kim et al concluded that pegfilgrastim is a viable option for mobilization and could be especially useful if an earlier apheresis starts. In our study, we observed a tendency for statistical significance for pegfilgrastim to have a shorter time between chemotherapy and harvest compared to filgrastim, but the difference between the two medians was of only one day so we do not consider this finding clinically relevant.

The main strength of the current study is represented by the fact that it adds to a heterogeneous field of research, helping to better guide the clinical choice between pegfilgrastim and filgrastim in the case of lymphoma patients undergoing ASCT. More than this, this was a prospective study, thus being able to remove some of the bias that retrospective studies generally have.

The main limitation of this study is represented by the low number of the patients included, which might give an uncertainty to the results presented with larger multicentric studies being needed to validate our and other's studies regarding the differences between pegfilgrastim and filgrastim. Nonetheless, considering the important reduction of grade IV neutropenia associated with pegfilgrastim compared with filgrastim and the stability of this association in the multivariate model we consider that the results presented here could be reproducible in larger studies conducted in a similar manner. Added to this, it must be mentioned that, although we included a rather small number of patients, the present study is still comparable from a cohort standpoint to other studies on the same issue. Another limitation of this study is the fact that it was not blinded. Nonetheless, the deviation from randomness was represented by the patient's preference between pegfilgrastim or filgrastim. Thus, although a double-blind study would have been preferred, we consider that the non-clinically oriented subjective choice of the patient should not biased the study in an exaggerated manner. More than this, grade IV neutropenia was neither influenced by the number of cycles of therapy, nor by the weight of the patients, showing that the effect on grade IV neutropenia in the current study was due to the effect of pegfilgrastim and not due to bias.

Conclusions

Thus, in the present study, we observed that biosimilar pegfilgrastim offers the same PBSC mobilization rate as filgrastim. Furthermore, pegfilgrastim is associated with a lower occurrence of grade IV neutropenia, even when considering the multivariate model. Even though some of the results from other studies, like a better platelet recovery, we consider that the reduction in the occurrence of grade IV neutropenia can constitute an important argument for the use of pegfilgrastim as a viable alternative to filgrastim.

Author contributions

Conceptualization A.T. Formal analysis, A.C. (Andrei Colita) and S.P. Investigation L.L., L.S., C.C.., S.P., C.S. Methodology, A.T. and A.C. (Andrei Colita). Resources L.L., L.S., C.C.., S.P., C.S. Supervision, A.T. Validation C.T. and A.C. (Anca Colita); Visualization A.C. (Andrei Colita), L.L., L.S., C.C.., S.P., C.S., C.T, A.C. (Anca Colita). Writing-original draft, A.C. (Andrei Colita), S.P. Writing-review & editing, A.C. (Andrei Colita), C.T., A.T. and A.C. (Anca Colita). All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of Fundeni Clinical Institute (55623/21/12/2018), (21887/02.05.2019).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Conflict of interests

The authors declare no conflict of interests.

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