The effect of lipegfilgrastim on hematopoietic reconstitution and supportive treatment after megachemotherapy with autologous peripheral blood stem cell transplantation in patients with lymphoproliferative malignancies

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ABSTRACT

Megachemotherapy with autologous peripheral blood stem cell transplantation (auto-PBSCT) is a standard treatment option in patients below 70 years of age with multiple myeloma (MM) as well as with relapsed and refractory lymphomas. Recombinant granulocyte colony-stimulating factors (G-CSF) are commonly used to accelerate bone marrow recovery after chemotherapy and reduce the duration of severe neutropenia. Lipegfilgrastim is a glicopegylated G-CSF with prolonged action registered for adult patients with malignant neoplasms in order to reduce the duration of neutropenia and the incidence of febrile neutropenia (FN). So far, there is not enough data to confirm the effectiveness and safety of this drug in patients with hematological malignancies including those undergoing auto-PBSCT. The aim of this study was to determine the effect of lipegfilgrastim on hematopoietic regeneration and supportive care after auto-PBSCT in patients with lymphoproliferative malignancies. The study population consisted of 30 patients (12 female and 18 male; median age: 50 years ± 13), including 13 patients with MM, 5 with Hodgkin's lymphoma (HL) and 12 with non-Hodgkin's lymphoma (nHL). The median number of transplanted CD34+ cells was 3.96 ± 1.56 × 10^6/kg of body mass. On day +1 after auto-PBSCT, the patients received lipegfilgrastim in a single 6 mg subcutaneous injection. The control group consisted of 32 patients (13 female and 19 male; median age: 50 years ± 6.4), including 13 with MM, 8 with HL and 11 with nHL, who received subcutaneous filgrastim in a dose of 5 μg/kg/day from day +1 after transplantation and continued to an absolute neutrophil count (ANC) > 1.5 × 10^9/L. There was no significant difference in the time of regeneration ANC > 0.5 × 10^9/L which was 10.65 ± 1.00 vs. 11.51 ± 2.29 days respectively in the study and control group. Similar observations were noted regarding the duration of febrile neutropenia (2.16 ± 2.22 vs. 1.70 ± 4.17 days; p = 0.998), regeneration of platelets (PLT) > 20 × 10^9/L (12.41 ± 2.41 vs. 13.82 ± 4.48 days; p = 0.233) and demand for transfusion of red blood cells (0.76 ± 1.07 vs. 1.33 ± 2.33 units; p = 0.414) and platelets (11.5 ± 6.9 vs. 19.2 ± 17.7 units; p = 0.08). Different results were observed for the length of hospitalization, which was significantly shorter in the lipegfilgrastim group (16.14 ± 14 vs. 24.46 ± 6.79 days; p = 0.000). Lipegfilgrastim is as effective as filgrastim with regards to the regeneration of the hematopoietic system, duration of febrile neutropenia, demand for transfusion of blood products and significantly reduces hospitalization in patients with lymphoproliferative malignancies after auto-PBSCT.

KEY WORDS: lymphoproliferative malignancies, auto-PBSCT, G-CSF

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INTRODUCTION

Megachemotherapy with autologous peripheral blood stem cell transplantation is a standard procedure in patients with diagnosis of MM and refractory or relapsed lymphomas [1–4]. Auto-PBSCT is a relatively safe procedure with the early transplant mortality rate (up to 100 days) of no more than 10%. It is directly related to the patient's age, therefore the procedure is usually performed on patients < 65–70 years old. The most common adverse event of this treatment is life-threatening infections caused by severe neutropenia [5, 6], which require broad spectrum antibiotics, additional microbiological testing and typically extended hospitalization. These complications worsen the patient's quality of life and also increase the total cost of treatment. To accelerate bone marrow recovery and reduce the duration of severe neutropenia after chemotherapy, granulocyte colony-stimulating factors are recommended independently of the number of transplanted CD34+ cells [7–10]. The commonly used factors include filgrastim with biosimilar forms or lenograstim, which – due to its short half-life – requires daily application. Pegylated long-acting forms of filgrastim allow for a single injection to suffice for the entire period of aplasia. One of them is pegfilgrastim. Its efficacy and safety in patients undergoing auto-PBSCT has been confirmed in many randomized studies [11–15]. Lipegfilgrastim is a long-acting glicopegylated G-CSF which was registered in the European Union at the end of 2013. This drug is a covalent combination of filgrastim and one of the methoxypolyethylene glycol (PEG) molecules through a carbohydrate bond consisting of glycine, N-acetylneuraminate and N-acetylgalactosamine. It binds to the human G-CSF receptor in a similar manner as filgrastim and pegfilgrastim; however, it is characterized by a longer half-life (32–62 h) than filgrastim due to a decreased renal clearance [16]. It is registered for use in order to shorten neutropenia and decreased frequency of febrile neutropenia in adult patients treated with chemotherapy for malignant neoplasms, excluding chronic myelogenous leukemia and myelodysplastic syndromes. It has been shown that the optimal dose of lipegfilgrastim is 6 mg, which is "no worse" compared to the same dose of pegfilgrastim in terms of shortening the duration of severe neutropenia [17]. So far, there is not enough data evaluating the efficacy and safety of this drug in patients with haematological malignancies. Below we present effects of lipegfilgrastim administration on hematopoietic reconstitution and supportive care in patients with lymphoproliferative diseases after auto-PBSCT.

MATERIAL AND METHODS

The study consisted of 30 patients hospitalized at the Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation in Wrocław Medical University (12 female and 18 male; median age 50 ± 13 years), including 13 patients with multiple myeloma (MM), 5 with Hodgkin's lymphoma (HL) and 12 with non-Hodgkin's lymphoma (nHL). The study was approved by decisions of the local ethics committee at Wrocław Medical University. The patients with MM were conditioned with melfalan 140/200 mg/m^2, while patients with HL and nHL received megachemotherapy BEAM (BCNU 300 mg/m^2 d.-7; etoposide 200 mg/m^2 and cytarabine 400 mg/m^2 d.-6, -5, -4, -3; melphalan 120–140 mg/m^2 d.-2) or CBV (cyclophosphamide 60 mg/kg d.-3, -2; BCNU 400 mg/m^2 d.-3; etoposide 800 mg/m^2 d.-3, -2). The median number of infused CD34+ cells was 3.96 ± 1.56 × 10^6/kg of body mass. On day +1 after auto-PBSCT, the patients received a single 6 mg subcutaneous injection of lipegfilgrastim. The control arm consisted of a historical group of 32 patients (13 female and 19 male; median age 50 ± 6.4 years), including 13 patients with MM, 8 with HL and 11 with nHL, who underwent megachemotherapy according to the same protocol as the study group. The median number of transplanted CD34+ cells was 3.78 ± 1.22 × 10^6/kg of body mass. Patients received 5 μg/kg/24 h subcutaneous filgrastim from day + 1 after transplantation until absolute neutrophil count (ANC) reached > 1.5 × 10^9/L. The clinical characteristic of both groups is presented in table 1. In the statistical analysis, the following parameters were considered: time of regeneration ANC > 0.5 × 10^9/L, PLT > 20 × 10^9/L, number of blood products transfusions, duration of febrile neutropenia and hospitalization from the day of transplant (day 0). All patients received typical anti-infective prophylaxis: ciprofloxacin 500 mg every 12 h p.o., acyclovir 800 mg 1 × 1 p.o., co-trimoxazole 960 mg p.o. twice a week, fluconazole 100 mg 1 × 1 p.o. Red blood cells and platelet concentrates were transfused when hemoglobin or platelet level fell below 8 g/dl and 20 × 10^9/L respectively. The program STATISTICA 10.0 was used to perform the statistical analysis.

RESULTS

The median duration of filgrastim therapy in the control group was 12.5 ± 2.3 days while the median consumption of filgrastim vials ā 300 μg was 19. There were no significant differences in the median time to ANC > 0.5 × 10^9/L engraftment, which in the study and control group was 10.65 ± 1.00 vs. 11.51 ± 2.29 days respectively (p = 0.244). A negative correlation between the number of transplanted CD34+ cells and the median time to ANC > 0.5 × 10^9/L was observed in the patients receiving lipegfilgrastim (Spearman's rank correlation coefficient = -0.401; p = 0.03). The median time to PLT > 20 × 10^9/L regeneration in lipegfilgrastim and filgrastim group was 12.41 ± 2.41 vs. 13.82

TABLE 1.

Clinical characteristics of both study groups.

	Lipegfilgrastim, n = 30	Filgrastim, n = 32
Sex (F/M)	12/18	13/19
Age, years (x ± SD)	50 ± 13	50 ± 6.4
Diagnosis: MM	**13**	**13**
CR	0	10
VGPR	5	1
PR	7	2
PD	1	0
HL	**5**	**8**
CR	3	4
PR	2	4
nHL	**12**	**11**
CR	5	7
PR	6	4
PD	1	0
Chemotherapy: melfalan 140/200 mg/m²	13	13
BEAM	16	19
CBV	1	0
Time from diagnosis to transplant (months)	21.4 ± 24.9	14.9 ± 9.6
Number of transplanted CD34+ cells (x ± SD) × 10^6/kg	3.96 ± 1.56	3.78 ± 1.22

F – female; M – male; x – median; SD – standard deviation; MM – multiple myeloma; HL – Hodgkin's lymphoma; nHL – non-Hodgkin's lymphoma; CR – complete remission; PR – partial remission; VGPR – very good partial remission; PD – progression of disease.

± 4.48 days (p = 0.233). We also observed that the median units of platelet transfusions was lower in the study group compared to the control arm and this difference had borderline significance (11.53 ± 6.94 vs. 19.20 ± 17.76; p = 0.08) (fig. 1).

No statistical differences in the number of red blood cells transfusions were found in either cohort, which was 0.76 ± 1.07 vs. 1.33 ± 2.33 units in the study and control group respectively. There was also no difference in the median duration of febrile neutropenia (2.16 ± 2.22 vs. 1.70 ± 4.17 days; p = 0.998). Both lipegfilgrastim and filgrastim were well tolerated. The main adverse event observed after administration was bone pain, however in the grade ≤ 2 according to CTCAE v4. We noted one death in the study group on day + 6 after transplantation. The cause of death was septic shock due to *Klebsiella pneumoniae* urinary tract infection. Finally, patients who received lipegfilgrastim had significantly shorter hospital stay in comparison to the control group (16.14 ± 2.95 vs. 24.46 ± 6.79 days; p = 0.0001) (fig. 2). The summary of all results is shown in table 2.

FIGURE 1.

Platelet transfusions in both study groups.

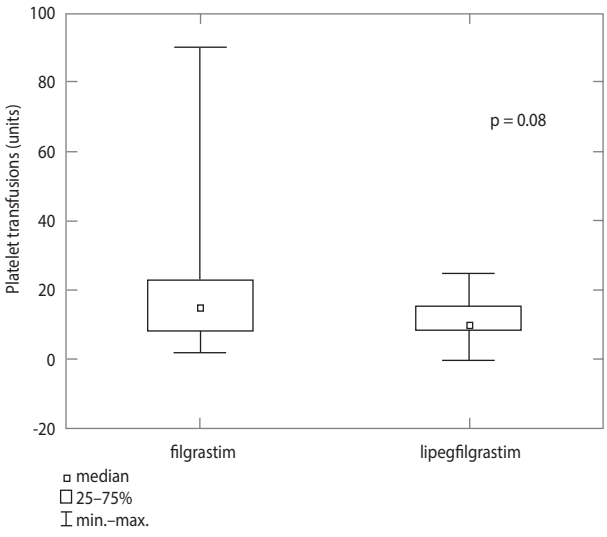
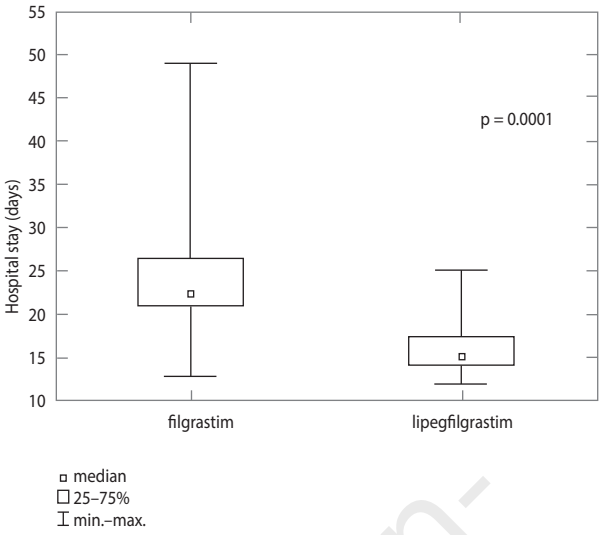


FIGURE 2.
Duration of hospitalization in both study groups.



patients with solid tumors [17, 26–28]. Moreover, we find no studies comparing the use of lipegfilgrastim and short-acting G-CSFs in patients after chemotherapy. In data presented by Volovat et al., lipegfilgrastim significantly reduced the frequency and duration of severe neutropenia compared to placebo in patients with non-small cell lung cancer receiving myelosuppressive chemotherapy [26]. In the phase III randomized trial which compared the efficacy and safety of lipegfilgrastim versus pegfilgrastim in chemotherapy-naïve breast cancer patients receiving doxorubicin/docetaxel chemotherapy, no significant difference was observed in the duration of severe neutropenia from cycle 1 to 4 [27]. Our single-center study is one of the first that evaluates bone marrow recovery and supportive treatment in patients with lymphoproliferative malignancies after auto-PBSCT. The obtained results were related to the historical control groups treated with filgrastim, whose clinical characteristics as well as the number of transplanted CD34+ cells were comparable to the study group. There were no significant differences in the duration of severe neutropenia, incidence of febrile neutropenia, platelets regeneration and the transfusion of blood products. In contrast, lipegfilgrastim-treated patients had significantly shorter length of hospital stay. Use of pegfilgrastim not lipegfilgrastim in patients with lymphoproliferative malignancies after auto-PBSCT has been described in many publications. In some of them, no significant difference was reported for the duration of granulocyte regeneration, hospitalization or supportive treatment between pegfilgrastim and filgrastim [14, 19–21]. However, Samaras et al. proved that pegfilgrastim significantly reduced the duration of severe neutropenia and the hospital stay in patients with MM [25]. In one of the meta-analysis, pegfilgrastim vs. filgrastim reduced the duration

TABLE 2.
Summary of all evaluated parameters in both study groups.

	Filgrastim, n = 32		Lipegfilgrastim, n = 30		
	x ± SD	min.–max.	x ± SD	min.–max.	p-value
ANC > 0.5 × 10^9/L (days)	11.51 ± 2.29	8.0–18.0	10.65 ± 1.00	9.0–13.0	0.244
PLT > 20 × 10^9/L (days)	13.82 ± 4.48	8.0–31.0	12.41 ± 2.41	9.0–19.0	0.233
Red blood cells transfusion (units)	1.33 ± 2.33	0.00–12.0	0.76 ± 1.07	0.0–3.0	0.414
Platelet transfusion (units)	19.20 ± 17.76	2.0–90.0	11.53 ± 6.95	0.0–25.0	0.08
Febrile neutropenia (days)	1.70 ± 4.17	0.0–21.0	2.16 ± 2.22	0.0–7.0	0.998
Hospitalization (days)	24.46 ± 6.79	13.0–49.0	16.14 ± 2.95	12.0–25.0	**0.000**

x – median; SD – standard deviation; min.– minimum; max. – maximum; ANC – absolute neutrophil count; PLT – platelets.

DISCUSSION

The introduction of G-CSF in the late 1980s has changed the practice of performing SCT (stem cells transplantation) and of pre-engraftment supportive care. This is particularly important for auto-PBSCT, where the use of G-CSF accelerated myeloid regeneration, reduced the infection complications in aplasia period as well as the length of hospitalization [18]. In clinical practice, long-acting forms of filgrastim seem to be preferred especially due to the easier method of administration and potential savings according to some studies [14]. Efficacy of pegfilgrastim compared to filgrastim in patients after auto-PBSCT was evaluated in many retrospective and prospective randomized studies or with historical control groups [14, 18–25]. In contrast, efficacy and safety of lipegfilgrastim have been assessed only in a few studies mainly focused on

of severe neutropenia and febrile neutropenia but had no effect on the risk of FN or length of stay [11]. Therefore, long-acting pegfilgrastim seems to be as effective as filgrastim and these drugs can be used as alternatives in patients post auto-PBSCT. We also observed that lipegfilgrastim is equally effective as filgrastim in the ANC regeneration and it seems to be comparable in the duration of febrile neutropenia and transfusion of blood concentrates. There was only one difference, namely in the duration of hospitalization, which was significantly shorter in patients receiving lipegfilgrastim. Our analysis revealed that the median number of platelet transfusions was lower in the study group compared to the control arm. This difference was borderline significant, thus it could be one of the explanations for the shorter hospital stay in these patients.

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