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Research Article

A Combination of Pegfilgrastim and Filgrastim has No Benefit compared to Filgrastim alone for autologous Stem Cell Mobilization

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Abstract

Background: Autologous stem cell transplantation is an established therapy for various hematological malignancies. A precondition is the efficient and save mobilization of blood stem cells, which is achieved by treatment with granulocyte-colony stimulating factors. Previously, it has been demonstrated that the pegylated form of filgrastim, pegfilgrastim, is comparable to filgrastim in the efficiency of stem cell mobilization. Here, we examine, whether a combination of pegfilgrastim and filgrastim exerts a benefit compared to filgrastim alone in safety and efficiency of autologous stem cell mobilization.

Patients and methods: We retrospectively analyzed the data of 131 patients undergoing stem cell mobilization for autologous stem cell transplantation. The patients received filgrastim (n = 66) or pegfilgrastim and filgrastim (n = 65) for stem cell mobilization.

Results: Infection rate, fever of unknown origin and stem cell harvest were similar in both groups. After autologous stem cell transplantation, time to neutrophil recovery was equal in both groups.

Conclusion: Combination of filgrastim and pegfilgrastim is not superior in efficiency and safety of blood stem mobilization in unselected patients.

INTRODUCTION

Autologous stem cell transplantation (ASCT) improves the prognosis of various hematological malignancies, and tandem or multiple ASCT have become recognized treatment options [1]. Especially if two or more ASCT are planned, the efficient mobilization of autologous peripheral blood stem cells is mandatory. Stem cell mobilization is usually enabled by a conditioning chemotherapy regimen and subsequent stem cell growth stimulation with granulocyte colony-stimulating factor (G-CSF). The most widely used G-CSF preparation is filgrastim, a non-glycosylated recombinant human G-CSF. The half-life of filgrastim is four hours, requiring at least daily applications [2].

Pegfilgrastim is a pegylated form of filgrastim and contains a 20-kd polyethylene glycol molecule linked to the N terminus causing a greater physical and thermal stability, resistance to enzymatic degradation by masking of proteolytic cleavage sites and a decreased renal clearance [3, 4]. Thus, pegfilgrastim clearance is mainly dependent on binding to G-CSF receptors on neutrophils, subsequent cellular uptake, intracellular degrading and cleavage by neutrophil elastase [5]. During neutropenia, this mechanism is quickly saturated and a single injection of pegfilgrastim at a dose of 6 mg is sufficient to maintain high plasma concentrations for over 14 days [6].

Of late, pegfilgrastim is increasingly used for stem cell

mobilization. The continuous stimulation might result in a better mobilization effect compared to the pulsatile stimulation evoked by filgrastim: After pegfilgrastim treatment, the median $CD34^+$ cell count is higher on day 4 [7], and in some studies, pegfilgrastim is slightly superior to filgrastim regarding the time to white blood cell recovery and to the first apheresis procedure [8-10] and the median number of $CD34^+$ cells collected at first apheresis [11]. However, data comparing mobilization therapies using filgrastim or pegfilgrastim are sparse and mobilization regimens combining the two agents have scarcely been studied to date. We here examined, whether the addition of filgrastim to pegfilgrastim may help to provide a more sustained $CD34^+$ mobilization and thereby a more efficient stem cell harvest.

PATIENTS AND METHODS

Patients

We retrospectively analyzed the data of 131 consecutive patients undergoing peripheral blood stem cell mobilization from 2008 until 2012 at the Clinic and Policlinic IV, Ludwig-Maximilians-Universität München, Munich. Patients suffered mainly from multiple myeloma and non-Hodgkin´s lymphoma, but also patients with Hodgkin´s disease, acute myeloid leukemia, sarcoma and neuroblastoma were included.

Mobilization therapy and G-CSF treatment

Patients received mobilizing cytostatic chemotherapy according to standard practice. Mobilization chemotherapies comprised cyclophosphamide (3.0 g/m^2), IEV (ifosfamid, epirubicin, vepesid), bortezomib/dexamethasone or other chemotherapy regimens as indicated in Table 1. In patients not receiving pegfilgrastim, filgrastim was started on day 5 (5 µg/kg/d) and continued until the last day of leukapheresis. Pegfilgrastim at a dose of 6 mg was injected subcutaneously on day 5. Filgrastim (5 µg/kg/d) [12] was started in patients having received pegfilgrastim two days before the anticipated onset of the leukapheresis (day 10) and was continued until the end of the leukapheresis. After the end of the chemotherapy or after the administration of pegfilgrastim, respectively, patients were discharged from the hospital. Standardized supportive care included oral ciprofloxacin, oral amphotericin B, and transfusions to maintain a hemoglobin above 80 g/L and platelets above 10000/µl. Piperacillin/tazobactam was started empirically during neutropenia after a single oral temperature > 38.5 °C or when fever > 38.0 °C was present over at least one hour [13].

Table 1: Characteristics of 131 patients undergoing stem cell mobilization.

	Pegfilgrastim and filgrastim (n = 65)	Filgrastim (n = 66)	*p-value*
Male gender	36 (55%)	39 (59%)	0.669
Age at leukapheresis, median (range)	63 (24-74)	64 (25-75)	0.068
Body weight in kg, median (range)	74 (45-117)	75 (44-120)	0.219
Previous chemotherapy cycles before mobilization, median number (range)	4 (0-20)	3 (0-14)	0.417
Previous irradiation before mobilization	20 (30%)	15 (23%)	0.300
Disease			
Multiple Myeloma	35 (54%)	43 (65%)	
Multiple Myeloma and Amyloidosis	2 (3%)	4 (6%)	
Non-Hodgkin Lymphoma	15 (23%)	13 (20%)	
Hodgkin Disease	5 (8%)	3 (4.5%)	
Acute Myeloid Leukaemia	6 (9%)	3 (4.5%)	
Sarcoma or Neuroblastoma	2 (3%)	0 (0%)	
Mobilization chemotherapy regimens			
IEV (ifosfamid, epirubicin, vepesid)	14 (21%)	10 (15%)	
Cyclophosphamid (3 g/m^2)	35 (54%)	24 (36%)	
Bortezomib/dexamethason	0 (0%)	8 (12%)	
Other chemotherapy regimens	13 (20%)	13 (20%)	

Stem cell collection

Patients were readmitted to hospital on day 9 after mobilization chemotherapy. Daily measurements of blood $CD34^+$ cells were initiated after recovery of the leukocyte count to a level of 10^9/L. $CD34^+$ cell count was determined by flow cytometry with a FacsCanto flow cytometer (Becton-Dickinson, San Jose, CA, USA) using TrueCount™ tubes and Procount™ reagents. Apheresis was initiated when the $CD34^+$ count reached ≥ 10 cells/µl. Apheresis was performed using a Cobe Spectra apheresis system (Caridian BCT, CO, USA). For one ASCT, the target yield was 2 × 10^6 $CD34^+$ cells/kg. In all patients, we aimed to collect sufficient stem cells for at least two transplantations (≥ 4 × 10^6/kg). In case of failure to achieve the intended $CD34^+$ target yield, a second mobilization therapy with filgrastim, filgrastim plus pegfilgrastim or filgrastim plus AMD3100 (Plerixafor®) was performed. The apheresis product containing 10% dimethyl sulfoxide was frozen using the computer-controlled device Kryo 560-16, Planer, Sunbury, Middlesex, UK, and stored in the vapor phase of liquid nitrogen at -140°C.

High-dose chemotherapy and ASCT

High-dose chemotherapy was administered according to the malignancies as indicated in Table 4. Myeloma patients received melphalan at a dose of 140 or 200 mg as described previously [14], whereas lymphoma patients mainly received BEAM (carmustine, etoposide cytarabine, melphalan). Of the patient group having received pegfilgrastim combined with filgrastim, 82% underwent at least one ASCT. Of the patient group treated with filgrastim only, 68% were transplanted until data collection. Reasons to refrain from ASCT were progressive disease or death. Following stem cell infusion, G-CSF was applied until the neutrophil count rose above 10^9/L.

Statistical analysis

For statistical analyses we used the SPSS software (IBM Deutschland GmbH, Ehningen, Germany). Clinical characteristics, infection rate and stem cell collection outcomes were compared between the patient group receiving filgrastim plus pegfilgrastim and the patient group receiving filgrastim using the Mann-and-Whitney-U-test. The level of statistical significance was set at 5%.

RESULTS AND DISCUSSION

Patient characteristics

Clinical characteristics of 131 patients included in the

analysis are listed in Table 1. No significant differences were detected in gender, age, body weight, number of chemotherapy cycles and irradiations preceding the conditioning chemotherapy for stem cell mobilization. Filgrastim was applied in patients having received pegfilgrastim two days before the anticipated leukapheresis initiation and was continued until the end of the leukapheresis, resulting in a median filgrastim application time of four days (mean 4.5 ± 2.7 days). Median duration of filgrastim therapy was 10 days in the filgrastim group (mean 10.1 ± 3.1 days).

Infection rate

No significant differences were detected in the infection rate in the patient group receiving pegfilgrastim in combination with filgrastim compared to patients receiving only filgrastim. Proportions of patients with neutropenic fever and the median number of days with fever were similar in both study groups. In the patient group receiving filgrastim only, the number of documented bacterial infections was non-significantly higher than in the patient group receiving pegfilgrastim plus filgrastim (15 vs. 8) (Table 2).

Stem cell harvest and outcome after ASCT

Of 131 patients undergoing stem cell mobilization, 122 achieved the $CD34^+$ target yield after the first mobilization therapy. Nine patients (four patients in the pegfilgrastim plus filgrastim group, five patients in the filgrastim group) failed to collect the intended $CD34^+$ number. Of these poor mobilizers, five underwent a second mobilization with filgrastim stimulation, one with filgrastim plus pegfilgrastim and three with filgrastim and AMD3100. A sufficient stem cell number was finally collected in all patients.

Table 2: Infection rate.

	Pegfilgrastim and filgrastim (n = 65)	Filgrastim (n = 66)	*p-value*
Fever > 38.0°C	14 (22%)	16 (24%)	0.714
Days with fever > 38.0°C, median (range)	2 (1-4)	2 (1-12)	0.559
Infection rate	8 (12%)	13 (20%)	0.251
Fever of unknown origin	7 (11%)	7 (11%)	0.874
Documented infections[a]			
Bacterial	8	15	
Viral	2	1	
Mycotic	0	1	
Infection localizations			
Pneumonia	2	6	
Sepsis	2	3	
Urinary tract	1	2	
Upper respiratory tract	1	0	
Jaw area	0	1	
Herpes genitalis	1	0	
Herpes zoster	0	1	
Haemorrhoidal	1	0	
Perianal abscess	0	1	
Colitis	0	3	
Proctitis	1	0	

[a] given is the number of documented infections in each patient group. Some patients experienced more than one infection

Table 3: Autologous stem cell harvest.

	Pegfilgrastim and filgrastim (n = 65)[a]	Filgrastim (n = 66)[b]	*p-value*
Median leukapheresis number (range)	1 (1-4)	1 (1-3)	0.661
Total amount of harvest $CD34^+$ cells, median number × 10^6/kg (range)	8.8 (1.3-31.5)	6.6 (0.5-50.5)	0.073
$CD34^+$ cells per leukapheresis, median number × 10^6/kg (range)	5.8 (0.7-31.5)	4.4 (0.5-50.5)	0.248

[a] four and [b] five patients, respectively, failed to collect the intended $CD34^+$ yield and underwent a second mobilization therapy

Patients treated with pegfilgrastim and filgrastim collected a total median amount of 8.8 × 10^6 $CD34^+$ cells/kg (range 1.3-31.5) and patients in the filgrastim group had a median $CD34^+$ cell count of 6.6 × 10^6/kg (range 0.5-50.5), which was not significantly different. There was also no significant difference in the $CD34^+$ yield per apheresis session or the number of apheresis cycles required (Table 3). It has been shown previously that the final $CD34^+$ cell yield, the mean number of apheresis sessions and the peak concentration of neutrophils in lymphoproliferative malignancies are not superior after pegfilgrastim as compared to filgrastim treatment [7,10,15,16]. A reason might be that the median $CD34^+$ count 10 days after chemotherapy and the $CD34^+$ peak tend to be lower after pegfilgrastim treatment [9,15,17], which is probably due to the context-sensitive half-live of pegfilgrastim. Once G-CSF receptor-expressing cells are present, pegfilgrastim is cleared from the plasma, resulting in declining levels during neutrophil recovery. A post-nadir absolute neutrophil count of > 10^9/L is a threshold for the clearance to sub-therapeutic levels [18]. Especially in cases of early neutrophil recovery, pegfilgrastim may be cleared before sufficient $CD34^+$ cells are stimulated. A reason for the failure of additional filgrastim to induce a stronger stem cell mobilization after partial recovery of neutrophils in our study may be an accumulation of injected G-CSF and endogenous cytokines, rendering additional G-CSF superfluous. In one previous study, addition of filgrastim to pegfilgrastim was performed in poor mobilizers (mainly heavily pretreated patients), resulting in a sufficient $CD34^+$ yield in some of these patients. However, a control group was not available [19]. Enhancement of stem cell mobilization by cytokines targeting different pathways of stem cell mobilization may be more efficient, since addition of the CXCR-4 antagonist AMD3100 to G-CSF resulted in an increase in mobilization of $CD34^+$ cells in previous studies [20,21].

The amounts of transplanted stem cells were 2.9 and 2.5 × 10^6 $CD34^+$ cells/kg in the pegfilgrastim/filgrastim and the filgrastim group, respectively. However, not only the number of transplanted stem cells is decisive, but also their functionality. Pegfilgrastim-mobilized autologous stem cells may have different biological properties than filgrastim-mobilized cells, including altered cell cycle kinetics and different $CD34^+$ subset composition. The more continuous G-CSF stimulation might lead to the stimulation of less mature hematopoietic progenitor cells [10,22]. However, in line with previous data [23], we found no difference in the time to neutrophil recovery after ASCT in the study group receiving pegfilgrastim plus filgrastim compared to

Table 4: Autologous stem cell transplantation: Conditioning regimes, amount of transplanted stem cells and hematopoietic recovery.

	Pegfilgrastim and filgrastim (n = 65)	Filgrastim (n = 66)	*p-value*
First ASCT/second ASCT			
Number of transplanted patients	54/18	45/30	
Transplanted CD34⁺ cells, median number × 10^6/kg (range)	2.9 (2.0-10.5)/ 3.0 (2.0-10.5)	2.5 (2.0-11.4)/ 2.7 (2.0-11.4)	0.207/ 0.477
Days to neutrophil recovery, median (range)[a]	10 (8-13)/ 10 (8-12)	10 (8-13)/ 10 (9-13)	0.867/0.812
High-dose chemotherapy regimen, n			
Melphalan 140 mg/m²	23 (43 %)/12 (67 %)	27 (60 %)/21 (68 %)	
Melphalan 200 mg/m²	11 (20 %)/6 (33 %)	8 (18 %)/9 (32 %)	
BEAM (carmustine, etoposide, cytarabine, melphalan)	16 (30 %)	8 (18 %)	
Busulfan/Cyclophosphamid	3 (5 %)	1 (2 %)	
other	1 (2 %)	1 (2 %)	

[a] defined as an absolute neutrophil count > 500/µl

patients treated with filgrastim. The median time to neutrophil recovery after transplantation was 10 days in both groups after the first and the second ASCT (Table 4).

CONCLUSIONS

The current study demonstrates that a combination of pegfilgrastim and filgrastim does not result in a higher stem cell yield and thus disproves our hypothesis that the addition of filgrastim in the early phase of leukocyte recovery might help to increase stem cell mobilization. The data suggest that there is currently no rationale to combine pegfilgrastim and filgrastim for autologous stem cell mobilization in unselected patients. The major limitation of the current study is its retrospective design. Furthermore, our study did not allow examination of patient subgroups, such as heavily pretreated patients and patients with poor mobilization or early neutrophil recovery. Whether a combination of filgrastim and pegfilgrastim may be beneficial in such patients needs to be clarified in further studies.

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