Ann Hematol (2011) 90:89–94
DOI 10.1007/s00277-010-1036-8

ORIGINAL ARTICLE

Pegfilgrastim reduces the length of hospitalization and the time to engraftment in multiple myeloma patients treated with melphalan 200 and auto-SCT compared with filgrastim

Panagiotis Samaras · Marcel Blickenstorfer · Raffaele Daniele Siciliano · Sarah R. Haile · Elefteri M. Buset · Ulf Petrausch · Axel Mischo · Hanspeter Honegger · Urs Schanz · Georg Stussi · Rolf A. Stahel · Alexander Knuth · Frank Stenner-Liewen · Christoph Renner

Received: 15 July 2010 / Accepted: 25 July 2010 / Published online: 13 August 2010

Abstract To reduce the duration of neutropenia after conditioning chemotherapy and autologous peripheral blood stem cell transplantation (APBSCT), granulocyte-colony stimulating factors (G-CSF) are commonly administered. We retrospectively evaluated the impact of pegfilgrastim compared to filgrastim on neutrophil engraftment, hospital stay, and supportive measures in patients with multiple myeloma after conditioning with Melphalan 200 (Mel200) followed by APBSCT. Ninety-two APBSCT after Mel200 treatment were performed in 72 patients between January 2006 and December 2009 at our institution. Patients received either single-dose pegfilgrastim (n=46; 50%), or daily filgrastim (n=46; 50%) after APBSCT (median duration of filgrastim use, 9 days; range, 3–14 days). Duration of neutropenia grade IV was shorter with pegfilgrastim compared with filgrastim (median, 5 days (range, 3–14 days) versus 6 days (range, 3–9 days), p=0.0079). The length of hospitalization differed significantly (pegfilgrastim (median, 14.5 days; range, 11–47 days) versus filgrastim (median, 15.5 days; range, 12–64 days), p=0.024). Pegfilgrastim-treated patients had less red blood cell transfusions (median, 0 transfusions (range, 0–10) versus 0.5 transfusions (range, 0–9), p=0.00065). Pegfilgrastim was associated with reduced cost of the treatment procedure compared with filgrastim (p=0.031). Pegfilgrastim appears to be at least equivalent to filgrastim without additional expenditure in myeloma patients treated with Mel200 and APBSCT.

Keywords APBSCT · Filgrastim · Pegfilgrastim · Engraftment · Mel200

Abbreviations

MM	multiple myeloma
APBSCT	autologous peripheral blood stem cell transplantation
G-CSF	granulocyte-colony stimulating factor
Mel200	high-dose melphalan (200 mg/m^2)

Panagiotis Samaras and Marcel Blickenstorfer contributed equally to this article

Christoph Renner and Frank Stenner-Liewen share senior authorship

P. Samaras · M. Blickenstorfer · E. M. Buset · U. Petrausch · A. Mischo · R. A. Stahel · A. Knuth · F. Stenner-Liewen (✉) · C. Renner
Department of Oncology,
University Hospital Zürich,
Rämistrasse 100,
8091 Zürich, Switzerland
e-mail: frank.stenner@usz.ch

R. D. Siciliano · H. Honegger
Medical Oncology,
Triemli City Hospital,
Zürich, Switzerland

S. R. Haile
Biostatistics Unit,
Institute of Social and Preventive Medicine,
University of Zürich,
Zürich, Switzerland

U. Schanz · G. Stussi
Department of Hematology,
University Hospital Zürich,
Zürich, Switzerland

ANC	absolute neutrophil count
i.v.	intravenous
ICU	intensive care unit

Introduction

Autologous peripheral blood stem cell transplantation (APBSCT) is an established treatment modality for patients with multiple myeloma (MM) [1, 2]. Infectious complications may occur during a period of severe neutropenia that put the patients at risk for morbidity and mortality after high-dose chemotherapy [3–5]. To reduce the time to neutrophil engraftment and eventually the risk for neutropenic fever, many transplantation centers use granulocyte-colony stimulating factors (G-CSF) after APBSCT, although data on their impact on relevant clinical parameters as duration and onset of fever, length of hospital stay, the use of antibiotics, infectious mortality, and ultimately treatment cost are still ambiguous [6–9]. This is also reflected by the differing recommendations of American and European guidelines. The former recommend the use of G-CSF after APBSCT, while the latter classify their use as controversial for this indication [10, 11].

Filgrastim (Neupogen©, Amgen) is the G-CSF most commonly used in this setting. Due to its short half-life, daily injections are necessary until neutrophil recovery has been documented for at least three consecutive days. In the past, our center had reported on the superiority of filgrastim treatment after autologous bone marrow transplantation compared with no administration of filgrastim with respect to neutrophil recovery and duration of neutropenic fever [12].

Pegfilgrastim (Neulasta©, Amgen) is the pegylated form of filgrastim. Due to the long-term formulation it has the advantage over filgrastim of a single application after the ablative chemotherapy, thus improving patient comfort. The efficacy of pegfilgrastim has already been shown in patients treated with conventional doses of chemotherapy by reducing the duration of neutropenia and the need for antibiotic treatment [13–15]. Until now, only a few studies with small or heterogenous patient collectives have been performed which assess the impact of pegfilgrastim in this setting [16–20]. The most relevant limitation of the data available in the literature is that patients with different diseases treated with different conditioning regimens were analyzed together, without taking into account that patient collectives likely differ in terms of chemotherapy associated toxicity and the necessary patient care [21–23].

Here, we report on the efficacy of pegfilgrastim compared with filgrastim in patients with multiple myeloma receiving Melphalan 200 (Mel200) and APBSCT, with special emphasis on treatment cost during the post-transplant period.

Patients and methods

We performed a 'per transplant' analysis of myeloma patients receiving high-dose chemotherapy with Mel200 and subsequent APBSCT during the last 4 years (2006–2009) at our center. The analysis was approved by our local ethical committee.

Patients received either pegfilgrastim or daily filgrastim after APBSCT. From January 2006 to December 2007 patients routinely received filgrastim. Expecting benefits regarding patient comfort and safety, we decided by late 2007 to implement a practice change, accordingly from January 2008 to December 2009 pegfilgrastim was generally administered after APBSCT. No other practice changes within the transplantation program were applied during the whole analysis period. Pegfilgrastim was administered as a single fixed dose of 6 mg subcutaneously at day +1 after stem cell reinfusion. Filgrastim was given at a dose of 5 μg/kg body weight subcutaneously once daily, starting at day +5 after stem cell reinfusion, until the absolute neutrophil count (ANC) was $\geq 0.5 \times 10^9$ cells/L for at least three consecutive days. This analysis includes all patients with multiple myeloma who received Mel200 during this period. Patients treated with APBSCT for other diseases or myeloma patients who received a reduced conditioning chemotherapy (i.e., Mel140) were excluded from this analysis.

The medical records of the patients and our prospectively collected transplantation database were screened for hospital stay, appearance and duration of neutropenic fever, the use of intravenous antibiotics, and the need for red blood cell and platelet transfusions during hospital stay, and then compared between the groups.

Neutropenia was defined as ANC below 0.5 x 10^9 cells/L. Fever was defined as body temperature ≥38.4°C. Every day of fever was considered for analysis when a body temperature over this cut-off was documented in the patient charts. Hospitalization time in this analysis was defined as time from the day of stem cell reinfusion (day 0) to the day of patient's discharge.

Statistical analyses

Statistical methods comparisons of patient characteristics were made using either a Mann–Whitney *U* test, or a Fisher's exact test, as appropriate. Continuous clinical outcomes are presented as median (range), and compared using the Mann–Whitney *U* test, while binary clinical outcomes are presented as a percentage, and compared using Fisher's exact test. Cost analysis is based on the average cost of blood products, average length of stay, and on average cost of filgrastim or pegfilgrastim per patient (compared with the Kruskal–Wallis test).

All analyses were performed in the R programming language [24].

Results

Patient demographics

Between January 2006 and December 2009, a total of 122 APBSCT with subsequent G-CSF support were performed in MM patients at our institution. Ninety-two (75%) APBSCT were performed with Mel200 in 72 patients and were included into this analysis. During this time period, 67 (73%) were first APBSCT, and 25 (27%) were second APBSCT. There was an equal balance between patients receiving either single-dose pegfilgrastim or filgrastim after APBSCT with 46 (50%) cases per treatment group. Filgrastim was applied after APBSCT for a median of 9 days (range, 3–14 days). The patient characteristics were well-balanced between the two groups including the dose of CD34+ stem cells reinfused and the number of APBSCT performed (Table 1).

Efficacy

Neutrophil engraftment was faster with pegfilgrastim than with filgrastim (median 9 days (range, 8–18 days) versus 10 days (range, 8–12 days), p=0.032), and accordingly, the median duration of neutropenia grade 4 was significantly shorter in the former patients (median 5 days (range, 3–14 days) versus 6 days (range, 3–9 days), p=0.0079). No difference between the two groups was observed regarding the duration of thrombocytopenia grade 4 (median, 3.5 days (range, 0–15 days) versus 3 days (range, 0–10 days); p= 0.39). In addition, less red blood cell transfusions were necessary in the pegfilgrastim-treated patients (median, 0 transfusions (range, 0–10 days) versus 0.5 transfusions (range, 0–9 days); p=00065). No significant differences were observed regarding the number of platelet transfusions, the duration of fever, and the duration of intravenous antibiotic treatment between the two groups (Table 2).

Overall, 23 (50%) patients receiving filgrastim needed red blood cell transfusions during their hospital stay compared with eight (17.4%) pegfilgrastim-treated patients (p=0.0018). No significant difference was seen in the number of patients needing intravenous antibiotics or platelet transfusions. Also, no differences were seen regarding the incidence of fever or the need for transfer to the intensive care unit between the two groups (Table 3). Overall, treatment related mortality was 0%.

Cost analysis

Cost analysis was performed using the Swiss drug prices listed for the year 2008. The median cost per patient for filgrastim was 1,979 Swiss francs, compared with 2,077 Swiss francs for pegfilgrastim (p=0.25, Mann–Whitney U test).

An integrated cost analysis including the cost of the G-CSF used, the infused blood products, and the hospital stay

Table 1 Patient characteristics ('per transplant' analysis).

Parameter	Filgrastim (n=46)	Pegfilgrastim (n=46)	p value
Age			
Median, years	56.5	57.9	
Range, years	44–68.7	38–67.7	0.82
Gender			
Male, no. (%)	22 (52)	32 (70)	
Female, no. (%)	24 (48)	14 (30)	0.056
CD34+ cells reinfused			
Median	3.2	3.2	
Range	2.0–7.9	2.0–13.0	0.51
Number of APBSCT			
First APBSCT, no. (%)	31 (67)	36 (78)	
Second APBSCT, no. (%)	15 (33)	10 (22)	0.35
Myeloma type			
IgG, no. (%)	28 (61)	27 (59)	
IgA, no. (%)	7 (15)	9 (19.5)	
IgD, no. (%)	1 (2)	0 (0)	
Bence Jones, no. (%)	8 (17)	9 (19.5)	
Nonsecretory, no. (%)	2 (4)	1 (2)	0.93

Table 2 Clinical outcomes in MM patients treated with Mel200

Parameter	Filgrastim (n=46)	Pegfilgrastim (n=46)	p value
Length of hospital stay			
Median, days	15.5	14.5	
Range, days	12–64	11–47	0.024
Time to Engraftment			
Median, days	10	9	
Range, days	8–12	8–18	0.032
Duration of neutropenia grade 4			
Median, days	6	5	
Range, days	3–9	3–14	0.0079
Duration of thrombocytopenia grade 4			
Median, days	3	3.5	
Range, days	0–10	0–15	0.39
Duration of fever			
Median, days	2	1	
Range, days	0–12	0–19	0.13
Duration of i.v. antibiotic treatment			
Median, days	6	5.5	
Range, days	0–22	0–36	0.12
Red blood cell transfusions			
Median, number	0.5	0	
Range, number	0–9	0–10	0.00065
Platelet transfusions			
Median, number	1	1	
Range, number	0–8	0–10	0.92

Data presented as median (range)

p values from Mann–Whitney U test

i.v. intravenous

revealed that treatment cost were lower with pegfilgrastim than with filgrastim (p=0.031, Mann–Whitney U test) with an additional expenditure of 1,274 Swiss francs per patient (6%) in the filgrastim-treated cohort.

Discussion

Our objective was to assess the impact of pegfilgrastim on the clinical outcome of patients with multiple myeloma who received melphalan in a dose of 200 mg/m^2, since patients with different diseases may differ in terms of demographics, and conditioning regimens may also vary in terms of toxicity [21–23].

In this homogenous patient collective, we observed that pegfilgrastim is able to reduce the duration of grade 4 neutropenia and, accordingly, the time to engraftment when compared with filgrastim.

Furthermore, the length of hospital stay was reduced with pegfilgrastim. This finding may be directly associated with the reduced time to engraftment since our patients are generally discharged when neutrophil recovery has been documented and no additional reasons for inpatient treatment are present. Interestingly, we could not observe a reduction in the incidence of fever and the need for intravenous antibiotics during the hospitalization. Although fever was documented in the majority of patients in both subgroups (72% and 63%,

Table 3 Clinical outcomes (binary) in MM patients treated with Mel200

Parameter	Filgrastim (n=46)	Pegfilgrastim (n=46)	p value
Intravenous antibiotics, no. (%)	41 (89)	37 (80)	0.38
Incidence of fever, no. (%)	33 (72)	29 (63)	0.51
Red blood cell transfusions, no. (%)	23 (50)	8 (74)	0.0018
Platelet transfusions, no. (%)	36 (78)	34 (74)	0.81
Transfer to ICU, no. (%)	3 (7)	2 (4)	1

Data presented in absolute patient numbers and percent

p values from Fisher's exact test

ICU intensive care unit

respectively), the duration of fever was similar and generally short lasting in both groups (median of 2 days with filgrastim and 1 day with pegfilgrastim, respectively), which may also explain the lack of a significant difference in the use of intravenous antibiotics.

Filgrastim was administered for a median of 9 days per case, and therefore absolute treatment cost of the two G-CSF did not differ significantly between the two groups. In contrast, an integrated analysis including the cost of G-CSF applied, the cost of blood products, and the daily cost of inpatient care at our clinic revealed that treatment with pegfilgrastim reduced the overall cost by 6% compared to filgrastim. The main reasons for this finding are probably the faster discharge of patients who received pegfilgrastim and the reduced need for blood products.

The latter observation is of particular interest as it is known that post-transplant use of G-CSF may impair the recovery of other hematopoietic progenitors. Bensinger and colleagues have suggested a steal phenomenon whereas myeloid progenitors may be favored over platelet progenitors by the use of G-CSF resulting in delayed platelet recovery [25]. Further evidence for such a mechanism comes from the use of G-CSF in congenital neutropenia where overstimulation of the neutrophilic compartment with pegfilgrastim has been reported to result in a thrombocytopenia among other adverse effects [26]. In our series, no delay in erythrocyte or thrombocyte recovery was observed with the fixed dose of pegfilgrastim, and the supposed better control of the hematopoiesis by using filgrastim appears not to be superior with regard to blood transfusions. The non-inferiority of pegfilgrastim with regard to this critical issue is therefore another important finding of this analysis.

A few non-randomized retrospective analyses and small prospective studies have reported on this issue, but to our knowledge, this is the largest homogenous patient cohort analyzed so far to address this question [16–20]. Strength of this analysis is that patient care within our autologous transplantation program is highly regularized by standardized operating procedures and relevant clinical patient data is collected prospectively within our transplantation database.

Further, by focussing on one entity and one standardized conditioning regimen any possible bias caused by the heterogeneity of patients and treatment modalities is minimized.

In conclusion, considering the nature of this analysis—retrospective, single-center design, superiority of pegfilgrastim in this setting cannot be claimed, but equivalence of the two G-CSF formulations is highly probable.

Pegfilgrastim appears to be at least comparable to filgrastim regarding the time to neutrophil engraftment, the length of hospital stay, the need for red blood cell transfusions and the treatment cost in MM patients undergoing conditioning with Mel200 followed by APBSCT. No differences between the two G-CSF administered regarding incidence and duration of neutropenic fever, use of intravenous antibiotics, and need for platelet transfusions were detectable. For confirmation of these data, a randomized prospective trial with a sufficient and homogenous patient collective would be preferable. However, in the absence of definitive proof we provide clinicians with promising data regarding safety and equivalence of the application of pegylated G-CSF in autologous transplantation following Mel200 as conditioning regimen.

Acknowledgment We thank Dora Greuter for the excellent technical assistance regarding cell processing and evaluation of the laboratory data of the patients. We also acknowledge Waltraud Naumann's continuous care of our prospective patient data base and the excellent quality management of our transplantation program. Finally, we would like to thank Denise Diener and Anja Augstburger for their help in collecting patient data for the final analysis.

Authorship and Disclosures PS, MB, CR, and FSL designed this analysis, collected and analyzed the data, and wrote the manuscript. SRH performed the statistical analysis. RDS and EMB collected and analyzed the data. UP, AM, RAS, HPH, US, GS, and AK participated in the patients' care, the transplantation program, and in the critical data analysis.

All authors were involved in the revision process and approved the final manuscript. All authors state that they have no conflicts of interest.

References

1. Attal M, Harousseau JL, Stoppa AM et al (1996) A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med 335:91–97
2. Attal M, Harousseau JL, Facon T et al (2003) Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 349:2495–2502
3. Offidani M, Corvatta L, Olivieri A et al (1999) Infectious complications after autologous peripheral blood progenitor cell transplantation followed by G-CSF. Bone Marrow Transplant 24:1079–1087
4. Kolbe K, Domkin D, Derigs HG et al (1997) Infectious complications during neutropenia subsequent to peripheral blood stem cell transplantation. Bone Marrow Transplant 19:143–147
5. Hamalainen S, Kuittinen T, Matinlauri I et al (2009) Severe sepsis in autologous stem cell transplant recipients: microbiological aetiology, risk factors and outcome. Scand J Infect Dis 41:14–20
6. Schmitz N, Ljungman P, Cordonnier C et al (2004) Lenograstim after autologous peripheral blood progenitor cell transplantation: results of a double-blind, randomized trial. Bone Marrow Transplant 34:955–962
7. Klumpp TR, Mangan KF, Goldberg SL et al (1995) Granulocyte colony-stimulating factor accelerates neutrophil engraftment following peripheral-blood stem-cell transplantation: a prospective, randomized trial. J Clin Oncol 13:1323–1327

8. Spitzer G, Adkins DR, Spencer V et al (1994) Randomized study of growth factors post-peripheral-blood stem-cell transplant: neutrophil recovery is improved with modest clinical benefit. J Clin Oncol 12:661–670
9. McQuaker IG, Hunter AE, Pacey S et al (1997) Low-dose filgrastim significantly enhances neutrophil recovery following autologous peripheral-blood stem-cell transplantation in patients with lymphoproliferative disorders: evidence for clinical and economic benefit. J Clin Oncol 15:451–457
10. Smith TJ, Khatcheressian J, Lyman GH et al (2006) 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 24:3187–3205
11. Crawford J, Caserta C, Roila F (2009) Hematopoietic growth factors: ESMO recommendations for the applications. Ann Oncol 20(Suppl 4):162–165
12. Stahel RA, Jost LM, Cerny T et al (1994) Randomized study of recombinant human granulocyte colony-stimulating factor after high-dose chemotherapy and autologous bone marrow transplantation for high-risk lymphoid malignancies. J Clin Oncol 12:1931–1938
13. Green MD, Koelbl H, Baselga J et al (2003) A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol 14:29–35
14. Holmes FA, O'Shaughnessy JA, Vukelja S et al (2002) Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 20:727–731
15. Vogel CL, Wojtukiewicz MZ, Carroll RR et al (2005) First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. J Clin Oncol 23:1178–1184
16. Castagna L, Bramanti S, Levis A et al (2009) Pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. Ann Oncol 21(7):1482–1485
17. Mathew S, Adel N, Rice RD et al (2010) Retrospective comparison of the effects of filgrastim and pegfilgrastim on the pace of engraftment in auto-SCT patients. Bone Marrow Transplant. doi:10.1038/bmt.2009.373
18. Martino M, Pratico G, Messina G et al (2006) Pegfilgrastim compared with filgrastim after high-dose melphalan and autologous hematopoietic peripheral blood stem cell transplantation in multiple myeloma patients. Eur J Haematol 77:410–415
19. Musto P, Scalzulli PR, Terruzzi E et al (2007) Peg-filgrastim versus filgrastim after autologous stem cell tranplantation: case-control study in patients with multiple myeloma and review of the literature. Leuk Res 31:1487–1493
20. Staber PB, Holub R, Linkesch W et al (2005) Fixed-dose single administration of Pegfilgrastim vs daily Filgrastim in patients with haematological malignancies undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 35:889–893
21. Puig N, de la Rubia J, Remigia MJ et al (2006) Morbidity and transplant-related mortality of CBV and BEAM preparative regimens for patients with lymphoid malignancies undergoing autologous stem-cell transplantation. Leuk Lymphoma 47:1488–1494
22. Jo JC, Kang BW, Jang G et al (2008) BEAC or BEAM high-dose chemotherapy followed by autologous stem cell transplantation in non-Hodgkin's lymphoma patients: comparative analysis of efficacy and toxicity. Ann Hematol 87:43–48
23. Zaucha R, Gooley T, Holmberg L et al (2008) High-dose chemotherapy with BEAM or Busulphan/Melphalan and Thiotepa followed by hematopoietic cell transplantation in malignant lymphoma. Leuk Lymphoma 49:1899–1906
24. R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org. 2009.
25. Bensinger WI, Longin K, Appelbaum F et al (1994) Peripheral blood stem cells (PBSCs) collected after recombinant granulocyte colony stimulating factor (rhG-CSF): an analysis of factors correlating with the tempo of engraftment after transplantation. Br J Haematol 87:825–831
26. Beaupain B, Leblanc T, Reman O et al (2009) Is pegfilgrastim safe and effective in congenital neutropenia? An analysis of the French severe chronic neutropenia registry. Pediatr Blood Cancer 53:1068–1073