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ORIGINAL ARTICLE

Kinetics of peg-filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell transplantation

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Peg-filgrastim is a form of G-CSF with a sustained duration of action due to self-limited clearance. We administered 6 mg peg-filgrastim to 18 autograft recipients on day +1 after transplantation for hematologic malignancies. Plasma samples were collected at baseline and during transplantation. Hematopoietic recovery and clinical outcomes were compared to the historical data of 54 patients not receiving G-CSF. Patients receiving peg-filgrastim achieved a serum level of 115 000 pg/ml on day +2, 24 h after drug administration. Drug level maintained a plateau until day +8 and, after day +10, declined concomitantly with myeloid recovery. Patients experienced prompt neutrophil recovery: days +9 and +10 to 500 and 1000 neutrophils per microliter, and 4 days with an absolute neutrophil count <100 cells per microliter. Duration of antibiotic therapy was significantly shortened, but we did not observe significant differences in other end points. In conclusion, peg-filgrastim was well tolerated and efficacious, and hastened myeloid recovery.
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Introduction

G-CSF is used to accelerate hematopoietic recovery following ABMT[1–4] or peripheral blood stem cell transplantation (aPBSCT), although there is no consensus about its optimal use.[5–10] While G-CSF promotes ANC recovery, its impact on the length of hospitalization, the use of nonprophylactic antibiotics (NPA), bloodstream infections (BSIs) and the overall cost of the procedure is unclear.[3,11–15] We do not routinely administer G-CSF after unmanipulated aPBSCT, but do use it from day +1 following CD34+ selected aPBSCT.[16]

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Filgrastim requires daily subcutaneous administration since it has a plasma half-life of 3–4 h due to renal- and neutrophil-mediated clearance.[17,18] Peg-filgrastim, a G-CSF form characterized by an increased plasma half-life, has been recently approved for clinical use. It comprises a 20-kd polyethylene glycol molecule linked to the N terminus of the filgrastim molecule resulting in greater physical and thermal stability, the resistance to enzymatic degradation and the decreased renal clearance; therefore, neutrophil-mediated clearance becomes the predominant route of elimination.[19]

The availability of this new G-CSF form prompted us to study its pharmacokinetics profile, and safety and efficacy in patients undergoing aPBSCT for hematologic malignancies.

Materials and methods

Patients

From February 2004 to August 2005, we enrolled 18 patients undergoing aPBSCT: 12 male, 6 female, median age 48 (range 18–62); reason for aPBSCT was multiple myeloma (MM) in 6 patients, non-Hodgkin's lymphoma (NHL) in 8 patients and Hodgkin's disease (HD) in 4 patients. The disease status at transplant was (1) progressive disease (PD) in 3 patients, (2) CR in 5 patients and (3) PR in 10 patients. These patients received a single subcutaneous 6 mg fixed dose of peg-filgrastim on day +1 after stem cells infusion (A group). Characteristics of patients of A group are shown in Table 1. In order to perform a matched-pair analysis, (1:3), these patients were compared to a group of 54 patients extracted from our database of 348 patients submitted to aPBSCT, and without G-CSF administration after transplantation (B group). These patients were matched for sex, age, disease, transplant procedure and conditioning regimen: 36 male, 18 female, median age 46 years (range 20–67); 15 MM, 2 POEMS syndrome, 1 plasma cell leukemia, 24 NHL and 12 HD. Characteristics of patients are shown in Table 1. Informed written consent was obtained from all patients or guardians before study participation. The protocol was approved by the Institutional Review Board at Universita' Cattolica Sacro Cuore.

Table 1 Characteristics of patients

	A Group	*B Group*
No. of patients	18	54
Sex (female/male)	6/12	18/36
Age, years (range)	48 (18–62)	46 (20–67)
Disease	HD 4 NHL 8 MM 6	HD 12 NHL 24 MM 15 POEMS syndrome 2 Plasmacell leukemia 1
Conditioning regimens[a]	HDMel 3 BEAM 4 BuMel 11	HDMel 9 BEAM 12 BuCy 1 BuMel 31 BuTTMel 1
CD34+ cells $\times 10^6$ per kg infused (range)	5.96 (3.38–16.48)	6.0 (1.37–46.6)

Abbreviations: HD = Hodgkin's disease; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; POEMS = polyneuropathy, organomegaly, endocrine disturbances, M-protein and skin changes.
[a]Full details on conditioning regimens are shown in the text.

Methods

Transplant procedure. Different conditioning regimens were used: BuMel (busulfan 4 mg/kg on days −5 to −2, melphalan 90 mg/m^2 on day −1) in 42 patients, BEAM (BCNU 300 mg/m^2 on day −6, aracytin 200 mg/m^2 on days −5 to −2, etoposide 200 mg/m^2 on days −5 to −2, melphalan 140 mg/m^2 on day −1) in 16 patients, HDMel (melphalan 100 mg/m^2 on day −3 and −2) in 12 patients, BUTTMel (busulfan 4 mg/kg on days −8 to −6, Thiotepa 10 mg/kg on day −6, melphalan 140 mg/m^2 on day −2) in 1 patient, BuCy (busulfan 4 mg/kg on days −7 to −4 and cyclophosphamide 60 mg/kg on days −3 and −2) in 1 patient. All patients received G-CSF mobilized and cryopreserved PBSCs. PBSCs were thawed bedside and reinfused on day 0.

Supportive care. Patients were treated in single bed with reverse isolation. Patients were administered prophylactic treatment for *Pneumocystis carinii* pneumonia with trimethoprim-sulfamethoxazole 1 double strength tablet every 12 h until day −1 and later when a stable engraftment was achieved; oral ciprofloxacin (500 mg every 12 h) from day −7 until stable granulocyte recovery; acyclovir (500 mg/m^2) from day −7 to day +100; oral amphotericin B suspension. When fever developed, with body temperature >38°C, NPA therapy was started with amikacin 7.5 mg/kg every 12 h, ceftazidime 2 g every 8 h and vancomycin 15 mg/kg every 12 h or teicoplanin 12 mg/kg every 24 h. Amphotericin B 0.5–1.0 mg/kg every 24 h was added in case of persistence of fever (>72 h). BSIs and catheter-related infections were defined according to Centre for Disease Control.[20]

Packed red cells were transfused when Hb declined to <8.0 g/dl and single-donor platelets were transfused when the platelet count was $<15 \times 10^9$ per liter. All blood products were irradiated with 15 Gy.

G-CSF assay. In patients receiving peg-filgrastim, plasma samples were obtained before high-dose chemotherapy, 24 h after drug administration and then, every 48 h until day +14 after transplant. Blood was collected and serum was separated by centrifugation (15 min at 4000 r.p.m.) shortly after collection, aliquoted and stored at –80°C until used. G-CSF serum level was detected by sensitive and specific immunoassay (Quantikine, R&D Systems, Abingdon, Oxon, UK). This assay does not distinguish peg-filgrastim from filgrastim or endogenous G-CSF.[20] G-CSF levels are expressed as pg/ml.

End points. During this study, Peg-filgrastim serum levels were assayed and correlated to PMN counts to verify neutrophil-mediated clearance. We also evaluated the following clinical outcomes: time to neutrophil recovery, number of days with ANC<100 per microliter, incidence of febrile neutropenia (defined as body temperature >38°C concurrent with an ANC less than 500 per microliter), time to platelets recovery, time to lymphocyte recovery with subsets reconstitution (baseline, day +15, +30 and +60 after transplant), length of hospitalization from hospital admission, duration of NPA use, number of days with fever, incidence of BSI, reticulocyte recovery (>1%), time to untransfused Hb >10 g/dl, number of packed red blood cell unit and single-donor unit infused. CD34+ cells count was evaluated every other day after transplant until the discharge, and bone marrow aspiration was performed on days +14 and +30.

Statistical analysis. Statistical analysis was performed using 'GraphPad Prism' GraphPad Software Inc. (5755 Oberlin Drive, #110, San Diego, CA, USA). Hematopoietic recovery and clinical outcomes of patients receiving peg-filgrastim were compared in a matched-pair analysis 1:3, to the historical data of 54 patients (B group) extracted from our database of 348 patients submitted to aPBSCT not receiving G-CSF. Mann–Whitney *U* test was used to analyze continuous factors. Chi-square test was chosen for the analysis of the categorical factors. Spearman's correlation was used to describe and test the correlation between two continuous factors. The results of hematopoietic recovery were analyzed according to the Kaplan–Meier method. Statistical significance was defined as $P<0.05$.

Results

G-CSF assay

Patients submitted to peg-filgrastim administration achieved a serum level of 115 000 pg/ml on day +2, 24 h after drug administration. Drug level maintained a plateau until day +8 and declined from day +10 concomitantly with myeloid recovery (Figure 1). On day +14, peg-filgrastim serum level was fivefold greater than baseline level. Comparison with our previously published data[16] shows that single peg-filgrastim administration induced a

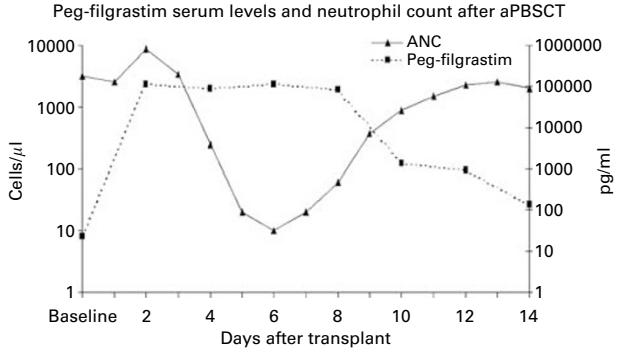

Figure 1 Peg-filgrastim level maintained a plateau until day +8 and since day +10 decreased together with early myeloid recovery.

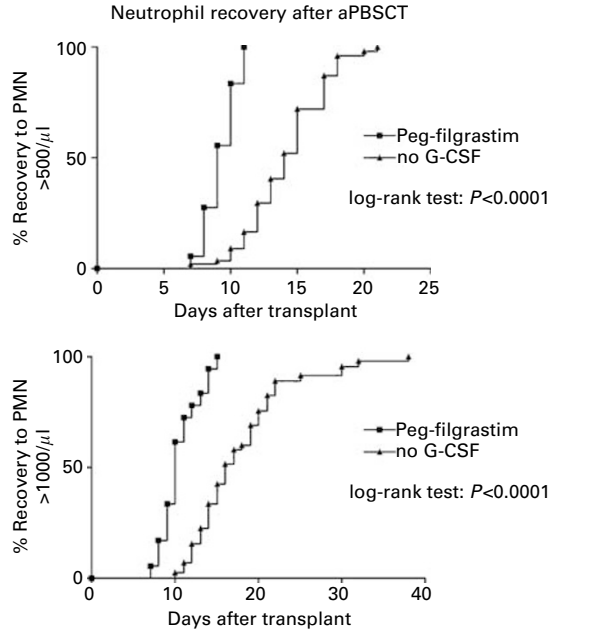

Figure 2 Comparison of myeloid engraftment between A and B groups.

serum level 20-fold greater than level achieved after daily G-CSF administration in the same setting and 200-fold greater than observed after aPBSCT in patients not receiving exogenous drug administration (endogenous G-CSF).

Hematopoietic recovery

Patients of A group received a median of 5.96×10^6 CD34+ cell/kg. Peg-filgrastim was well tolerated and only one patient complained of mild bone pain after administration with spontaneous resolution at 24 h.

All patients engrafted achieving 500 and 1000 PMN per microliter on day +9 and 10 (Figure 2); the number of days with a PMN count <100 per microliter was 4 and incidence of febrile neutropenia was 94%. Platelet recovery at 20, 50 and 100×10^3 platelets per microliter was achieved on day +10, +15 and +25, respectively. Patients of A group achieved an untransfused Hb level >10 g/dl on day +30 and a reticulocytes count >1% on day +12.

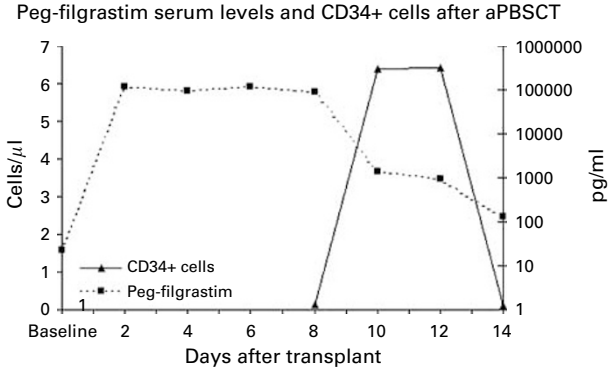

Figure 3 CD34+ cells are detectable after day +8.

Lymphocytes count >500 per microliter was achieved on day +14. Median transfusion requirements were 0 packed red blood cells and 1 unit of platelets. Hospitalization length was 21 days; days of body temperature >38°C were 3.5 and days of nonprophylactic antibiotics were 7. Lymphocytes subset analysis did not show significant differences in immune recovery between A and B groups except for CD 16+ to 56+ subset on day +30 (140 per microliter vs 310 per microliter, $P = 0.009$) and +60 (176 vs 358 per microliter, $P = 0.02$) after transplantation.

CD34+ cells were detectable starting from day +8 after transplantation achieving a peak of 6.4 cells/μl on day +10 (Figure 3). Complete data and comparison with B group are shown in Table 2.

Discussion

The use of G-CSF after autologous SCT has been recently included in the American Society of Clinical Oncology guidelines,[10] and a recent multicenter randomized trial on the use of lenograstim after autologous stem cell transplant documented a significant reduction of microbiologically documented infections until neutrophil recovery and also a significant reduction of both hospitalization and antibiotic requirements.[15] The strong evidence present in this carefully designed study deserves further attention and will probably influence the clinical attitude on the use of G-CSF after autologous SCT although there is still debate on this issue. Furthermore, cost effectiveness analysis of G-CSF in this setting is limited and not conclusive.[21,22]

Pegylated G-CSF has a longer half-life, greater physical and thermal stability, greater resistance to enzymatic degradation, more stable plasma concentration and predominant neutrophil-mediated clearance allowing high drug serum level during severe neutropenia. Previous clinical trials in solid tumors showed that a single 6 mg fixed dose of peg-filgrastim once per cycle led to a lower incidence of chemotherapy-induced febrile neutropenia than daily filgrastim administration.[23–28]

Our study showed that on day +2 (24 h after administration), peg-filgrastim achieved a peak serum level of magnitude comparable with level obtained after drug administration in healthy volunteers.[19] Then, drug level

Table 2 Results

	A group (range)	*B group (range)*	*Statistical analysis*
CD34+ cells $\times 10^6$ per kg infused	5.96 (2.29–16.48)	6.00 (1.37–46.6)	0.78[a]
Days to lymphocytes > 500 per microliter	14 (8–40)	18 (8–35)	0.1[b]
Days to ANC > 500 per microliter	9 (7–11)	14 (7–21)	*<0.0001*[b]
Days to ANC > 1000 per microliter	10 (7–15)	16 (10–38)	*<0.0001*[b]
Days of ANC < 100 per microliter	4 (3–7)	6 (3–13)	*<0.0001*[a]
Days to Plts > 20×10^3 per microliter	10 (8–40)	11 (7–25)	0.59[b]
Days to Plts > 50×10^3 per microliter	15 (11–68)	14 (10–60)	0.34[b]
Days to Plts > 100×10^3 per microliter	25 (13–120)	17 (12–330)	0.87[b]
Days to reticulocytes > 1%	12 (10–30)	14 (10–60)	0.6[b]
Days to Hb > 10 g/dl	30 (10–84)	23 (10–210)	0.28[b]
Days of fever	3.5 (1–10)	5 (0–20)	0.09[a]
Incidence of febrile neutropenia	94%	91%	0.625[c]
Days of non prophylactic antibiotic therapy	7 (3–20)	10 (0–30)	0.01[a]
Bloodstream infections	5/18	12/54	0.63[c]
Number of pRBCu	0 (0–5)	0 (0–6)	0.28[a]
Number of Sdu	1 (0–4)	1 (0–6)	*0.073*[a]
Days of hospitalization	21 (16–30)	24 (17–34)	0.1[b]

Abbreviations: ANC = absolute neutrophil count; Hb = hemoglobin; Plts = platelets; pRBCu = packed red blood cell unit; Sdu = single donor unit.
Results are expressed as median values.
Statistically significant values are in italic.
[a]Analyzed according to the Mann–Whitney *U* test.
[b]Analyzed according to the Kaplan–Meier method.
[c]Analyzed according to the χ^2-test.

kept a plateau until day +8; on day +10 drug level decreased together with early myeloid recovery. Furthermore, G-CSF serum level on day +14 did not return to baseline (Figure 1). There was a statistically significant negative correlation between drug levels and ANCs confirming the self-regulated neutrophil-mediated clearance of peg-filgrastim ($R = -0.89$, $P = 0.033$) also in aPBSCT setting. Peg-filgrastim administration led to a G-CSF peak serum level about 200-fold greater than observed after aPBSCT in patients not receiving exogenous drug administration. Drug level was also about 20-fold greater than level achieved after daily G-CSF administration in the same setting.[16]

All patients achieved a prompt engraftment showing a marked improvement of granulocyte recovery, significantly faster than the matched control group (Figure 2). These data are comparable to those reported by Jagasia *et al*.[29] Differences observed in the infection-related outcomes such as days of fever and length of hospitalization did not reach statistical significance, while length of NPA was significantly shorter in patients receiving peg-filgrastim.

Platelet recovery did not show significant differences, but median time to platelet recovery >50 and $>100 \times 10^3$ per microliter seems to be longer than control group. Erythroid recovery was comparable as was transfusion requirements.

Lymphocyte recovery (ALC > 0.5×10^9 l) was not significantly altered by peg-filgrastim. The analysis of immunological reconstitution showed a significant reduction, on day +30 and +60 after transplant, of CD16+CD56+ lymphocyte subset in patients treated with peg-filgrastim. This difference was due to a reduction of the characteristic natural killer subset overshoot observed consistently after aPBSCT not receiving G-CSF[30] and, although there is no current explanation for this observation, it is worth to be addressed in depth.

Interestingly after peg-filgrastim, circulating CD34+ cells were not detected until day +8 after stem cell infusion. Then CD34+ cell count analysis showed a peak level on day +10, when myeloid recovery started (Figure 3), in agreement with Albo *et al*.[31]

Our results also confirm the neutrophil-mediated clearance of peg-filgrastim posttransplant. Now, studies to assess cost effectiveness of peg-G-CSF are needed.

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