# Mobilization of peripheral blood stem cells in myeloma with either pegfilgrastim or filgrastim following chemotherapy

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## ABSTRACT

Quality and quantity of mobilized peripheral blood stem cells determine the safety of tandem autologous transplants in myeloma. Using the same mobilization chemotherapy with DT-PACE in two consecutive protocols, robustness of stem cell collection and rapidity of engraftment after transplantation were assessed. We employed either twice a day filgrastim versus two doses of pegfilgrastim. Advantages of pegfilgrastim were: (i) a higher percentage of patients collected $15x10^6$/kg in the first three days ($p<0.001$); (ii) the median number of CD34 cells/kg collected on day 1 was higher ($p=0.004$ ); (iii) the median number of growth factor injections was 2 versus 26 ($p<0.0001$); (iv) post-transplantation neutrophil recovery was faster after first and second transplant ($p<0.001$) and (v) platelet recovery was faster after first transplant (when less stem cells were infused) ($p=0.01$). Pegfilgrastim may be considered the standard of care for stem cell mobilization.

Key words: stem cells, mobilization, myeloma, pegfilgrastim.

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## Introduction

The introduction of peripheral blood stem cells to support high dose chemotherapy has resulted in a significant reduction in duration of cytopenia post-transplantation.[1,2] Consistent rapid platelet recovery ($>50\times10^9$/L) within a narrow time frame (<14 days) is only seen if $>5\times10^6$/kg CD34 cells are infused.[3] The combination of chemotherapy and hematopoietic growth factors significantly increases the CD34 yield compared with growth factors alone.[4] Important factors predicting successful stem cell collection include a platelet count $>200\times10^9$/L pre-mobilization, and 12 months or less of preceding chemotherapy.[4] Filgrastim is commonly used to mobilize peripheral blood stem cells. Pegylation of filgrastim (pegfilgrastim) leads to prolongation of its half-life without loss of activity.[5,6] While filgrastim is also cleared by the kidneys, pegfilgrastim is mainly eliminated via a neutrophil-mediated clearance mechanism. In 2001 and 2003, two studies were designed at our institution for the treatment of myeloma patients who had already received more than one cycle or more than one month of chemotherapy prior to their first visit. The treatment regimens were comparable and employed DT-PACE as mobilization chemotherapy.[7] In the first study patients received twice a day filgrastim, until completion of stem cell collection; in the second study two doses of pegfilgrastim were administered after DT-PACE.

## Design and Methods

### Patients

The eligibility criteria for the two studies were the same. Patients had received more than one cycle or one month of prior chemotherapy. There was no age limitation. Exclusion criteria were as reported before.[8] Between 08/2001 and 08/2003, 96 patients were enrolled in our protocol UARK 2001-12, which was a randomized study comparing high dose melphalan transplants to a hybrid regimen of DT-PACE with a lower dose of melphalan. Patients received a cycle of DT-PACE7 and on day +6 after the start of chemotherapy, filgrastim was started at a dose of 5mcg/kg bid subcutaneously until stem cell collection was completed. Patients then proceeded to tandem transplants and were randomized to either melphalan 200 mg/m$^2$ (patients 70 years or older received a

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dose of melphalan 140 mg/m$^2$), or a combination of DT-PACE/melphalan. In the latter group, dexamethasone was given at a dose of 40 mg/m$^2$ from day -3 until day 0; thalidomide 200 mg from day -3 until day +5; cisplatin 20 mg/m$^2$, adriamycin 20 mg/m$^2$, cyclophosphamide 800 mg/m$^2$, etoposide 80 mg/m$^2$ all as continuous infusions on days -3 and -2 and melphalan 50 mg/m$^2$ on days -3 and -2. Post-transplantation, patients received another cycle of DT-PACE followed by two years of maintenance therapy with dexamethasone and thalidomide. Seven patients were excluded from analysis because they failed to collect any stem cells. Protocol UARK 2003-41 enrolled 140 patients between 5/2004 and 7/2006. After a cycle of DT-PACE, pegfilgrastim 6 mg was given subcutaneously on days +6 and +13. If the WBC count > 100×10$^9$/L by day +13 the second dose of pegfilgrastim was not administered. Patients then proceeded to a first transplant with melphalan 200 mg/m$^2$, except for patients 70 years or older, who received melphalan 140 mg/m$^2$. This was followed by a second transplant with BEAM chemotherapy.[9] After a consolidation cycle with DT-PACE, patients were maintained on thalidomide and dexamethasone similar to UARK 2001-12. Two patients were excluded because they were inadvertently mobilized with filgrastim instead of pegfilgrastim and 3 patients did not collect any stem cells. Both UARK 2001-12 and UARK 2003-41 were approved by the Institutional Review Board of the University of Arkansas Medical Science. All patients signed an informed consent form.

### Peripheral blood stem cell collection

Once the prediction indicated a collection of one million CD34 cells/kg or more, leukapheresis was started. The predictive formula used was: number of liters to process x CD34 cells/mcL x machine collection efficiency divided by patient's weight in kg. All patients had a dialysis type catheter placed. Large volume aphereses (30 L per session) were performed until the goal of 15×10$^6$/kg was reached or until a drop in peripheral CD34 count to <10/mcl was seen.

### Statistical analysis

A Mann-Whitney test was applied to compare median numbers of CD34 cells collected and median number of CD34 cells infused with the first and second transplant in the two studies. Inverse Kaplan Meier plots were generated to compare recovery times for neutrophils and platelets. Differences in recovery time were calculated using the log rank test.

## Results and Discussion

### Patient characteristics

Characteristics of patients enrolled on UARK 2001-12 and UARK 2003-41 are listed in Table 1. No significant differences in characteristics between the two studies were seen.

### Stem cell collection

Whereas the proportions of patients mobilizing total CD34 cells/kg of more than or equal to 15,10 and 5 ×10$^6$ respectively, were similar in the two studies, there were striking differences in favor of pegfilgrastim during the first three days of collection for all 3 subgroups (Figure 1). When limiting the results to the first day of collection, the median numbers of CD34 cells/kg collected were 10.0 for filgrastim and 14.5×10$^6$ for pegfilgrastim respectively ($p$=0.004). The median number of filgrastim injection was 26 (range: 18-62); the median number of pegfilgrastim injections was 2 (range: 1-2) ($p$<0.0001).

### Recovery post-transplantation

There was no difference in number of CD34 cells/kg infused with the first ($p$=0.49) or second transplant ($p$=0.51) between the two studies. Platelet recovery to 50×10$^9$/L or more proceeded faster after the first (when a lower number of CD34 cells were infused; median number: 4.14 and 4.2×10$^6$/kg respectively), but not after the second transplant (when a high number of CD34

**Table 1.** Patient characteristics.

| Patient characteristics | 2001-12 (N=97) | 2003-41 (N=140) |
|---|---|---|
| $\beta_2$ microglobulin (mg/L) | | |
| Mean (Median) | 3.4 (2.6) | 3.3 (2.7) |
| Range (Min-Max) | 1.0-16.5 | 1.2-12.8 |
| LDH (U/L) | | |
| Mean (Median) | 221 (191) | 179 (168) |
| Range (Min-Max) | 89-1583 | 89-485 |
| Creatinine (mg/dL) | | |
| Mean (Median) | 1.1 (1.0) | 1.0 (0.9) |
| Range (Min-Max) | 0.5-3.4 | 0.5-2.9 |
| Albumin (mg/dL) | | |
| Mean (Median) | 4.0 (4.1) | 3.9 (3.9) |
| Range (Min-Max) | 2.6-5.2 | 2.7-5.1 |
| Hemoglobin (g/dL) | | |
| Mean (Median) | 12.0 (12.1) | 11.9 (11.9) |
| Range (Min-Max) | 8.2-16.1 | 7.7-16.0 |
| Platelets (x10$^9$/L) | | |
| Mean (Median) | 241 (234) | 250 (241) |
| Range (Min-Max) | 47-547 | 76-533 |
| Platelet >150 (%) | 84 | 91 |
| Serum M protein | | |
| Mean (Median) | 1.7 (0.8) | 1.8 (1.5) |
| Range (Min-Max) | 0.0-8.0 | 0.0-7.5 |
| Age (Median) | 57 | 62 |
| Range (Min-Max) | 37-75 | 30-76 |
| Age ≥65 (%) | 13 | 34 |
| Abnormal cytogenetics (%) | 31 | 25 |
| Duration of prior therapy (mo.) | | |
| Mean (Median) | 11.5 (5.0) | 12.2 (5.7) |
| Range (Min- Max) | 1-245 | 1-84 |
| >12 months of prior therapy (%) | 19.6 | 29 |

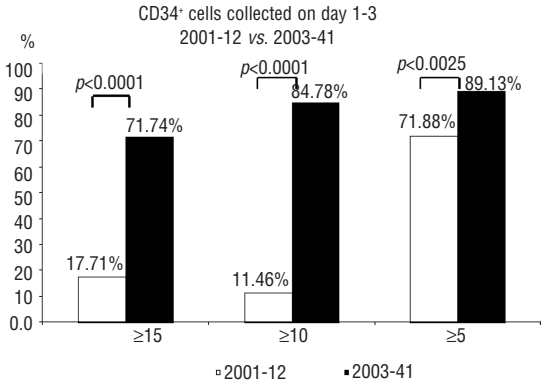


**Figure 1.** Percent of patients collecting 15, 10 and 5 million CD34 cells/kg, respectively with pegfilgrastim (black; 2003-41) or filgrastim (white; 2001-12) during the first 3 days of collection.

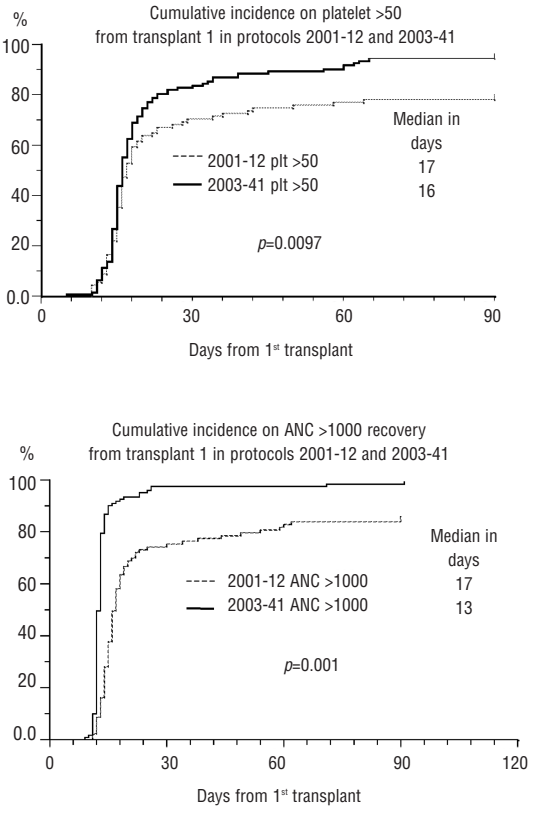


**Figure 2.** (A) Platelet recovery after transplant 1 was faster after mobilization with pegfilgrastim (full line; 2003-41) than with filgrastim (dotted line; 2001-12). (B) Recovery of ANC to >1000/mcL was faster after mobilization with pegfilgrastim (full line; 2003-41) than with filgrastim (dotted line; 2001-12) with transplant 1.

cells were infused; median number: 6.45 and 6.55×10⁶/kg respectively) (Figure 2A). The same difference was seen for a neutrophil recovery to 1×10⁹/L after the first ($p$<0.001) (Figure 2B), but also after the second ($p$<0.001) transplant.

### Toxicities of pegfilgrastim

The only grade 3 or higher non-hematologic toxicity directly related to pegfilgrastim was bone pain requiring more potent analgesics (codeine or morphine analogs) in 7 of 138 patients (5%). No cases of splenic ruptures were seen. Although not generated in the context of a randomized clinical trial design, the data clearly indicate that mobilization with chemotherapy and pegfilgrastim is at least as effective as mobilization with chemotherapy and filgrastim, and requires significantly less subcutaneous injections. Although the total number of CD34 cells collected was similar in both studies, the percentage of patients collecting >10 and 15×10⁶/kg CD34 cells in the first three days was significantly higher when mobilized with pegfilgrastim, resulting in a decrease of days of mobilization and thus a decrease in costs related to stem cell collection. There may also be some other advantages of mobilization with pegfilgrastim such as a more rapid recovery of platelet count to >50×10⁹/L, which we observed after the first transplant and in addition, a more rapid recovery of neutrophil count to >1.0×10⁹/L was seen after the first and second transplant. The absence of a difference in platelet recovery to 50×10⁹/L after the second transplant might be related to our practice of administering a higher number of CD34 cells with the second transplant to ensure robust hematopoiesis and thus better tolerance of post-transplantation consolidation and maintenance therapy. The benefit of mobilization with pegfilgrastim may especially be apparent in the setting of marginal hematopoietic stem cell reserve. Our study does not address the optimal dose of pegfilgrastim for chemotherapy-based peripheral blood stem cell collection. Successful mobilization of stem cells with or without chemotherapy has been observed with a single dose of 6 mg or 12 mg in myeloma patients.[10-12] These studies, however, were hampered by a small sample size. The choice of two doses of 6 mg of pegfilgrastim given on days 6 and 13 was based on pharmacokinetic data showing that a post-nadir neutrophil count of >1.0×10⁹/L or greater, was a surrogate marker for sub-therapeutic serum levels of pegfilgrastim.[13] The administration of two doses of pegfilgrastim assured therapeutic dose administration to all patients. Similar results, however, may be achieved with a single dose of pegfilgrastim. In addition, many centers have a lower target for CD34 cells/kg collection than we apply in our center; such a lower target can likely be achieved with a single dose of pegfilgrastim. Although not significant, probably due to the small sample size, more rapid post-transplantation recoveries of platelets (to >50×10⁹/L) and neutrophils (to more than 1×10⁹/L) were also observed by Bruns *et al.* in chemotherapy-mobilized patients with pegfilgrastim when compared to filgrastim, but only in patients receiving 6 mg, but not 12 mg.[11] In a retrospective study by Steidl *et al.* in newly diagnosed myeloma patients comparing mobilization with cyclophosphamide and either filgrastim or pegfilgrastim (single dose of 12 mg) an earlier recovery post-cyclophosphamide of leucocytes to >1×10⁹/L was seen in the pegfilgrastim-treated patients (12 *vs.* 14 days).[14] While severe toxicities related to pegfilgrastim administration are minimal and limited to bone pain, as with

filgrastim, occasional cases of splenic rupture have been reported after administration of pegfilgrastim, especially in healthy donors;[15-17] the incidence of bone pain with pegfilgrastim was not higher in our study than reported with filgrastim.[18,19] A comparable incidence of bone pain with pegfilgrastim and filgrastim was also reported in breast cancer patients.[20] Splenic rupture was not observed in our group of 140 patients.

In conclusion, peripheral blood stem cell mobilization post-chemotherapy is feasible and similarly effective with pegfilgrastim and filgrastim. Our data suggest greater ease and cost-effectiveness with pegfilgrastim, affording completion of collection in fewer days than with filgrastim. The optimal dose of pegfilgrastim in the context of chemotherapy still needs to be determined. Pegfilgrastim may become the standard growth factor to be used for stem cell mobilization with or without chemotherapy.

## Authorship and Disclosures

GT and BB designed the study; MZ, FVR and MCF were major contributors to the study, and AH and JS analyzed the data. The authors reported no potential conflicts of interest.

## References


1. Gianni AM, Siena S, Bregni M, Tarella C, Stern AC, Pileri A, et al. Granulocyte-macrophage colony-stimulating factor to harvest circulating haemopoietic stem cells for autotransplantation. Lancet 1989;2:580-5.
2. Barlogie B, Jagannath S, Vesole D, Tricot G. Autologous and allogeneic transplants for multiple myeloma. Semin Hemato 1995;32:31-44.
3. Tricot G, Jagannath S, Vesole D, Nelson J, Tindle S, Miller L, et al. Peripheral blood stem cell transplants for multiple myeloma: identification of favorable variables for rapid engraftment in 225 patients. Blood 1995;85:588-96.
4. Morris CL, Siegel E, Barlogie B, Cottler-Fox M, Lin P, Fassas A, et al. Mobilization of CD34+ cells in elderly patients (>/= 70 years) with multiple myeloma: influence of age, prior therapy, platelet count and mobilization regimen. Br J Haematol 2003;120:413-23.
5. Lord BI, Woolford LB, Molineux G. Kinetics of neutrophil production in normal and neutropenic animals during the response to filgrastim (r-metHu G-CSF) or filgrastim SD/01 (PEG-r-metHu G-CSF). Clin Cancer Res 2001;7:2085-90.
6. Molineux G. The design and development of pegfilgrastim (PEG-rmetHuG-CSF, Neulasta). Current Pharmaceut Design 2004;10:1235-44.
7. Lee CK, Barlogie B, Munshi N, Zangari M, Fassas S, Jacobson J, et al. DTPACE : an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. J Clin Oncol 2003; 21:2732-9.
8. Barlogie B, Anaissie E, van Rhee F, Haessler J, Hollmig K, Pineda-Roman M, et al. Incorporating Bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. Br J Haematol 2007;138:176-85.
9. Mills W, Chopra R, McMillan A, Pearce R, Linch DC, Goldstone AH. BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. J Clin Oncol 1995;13:588-95.
10. Hosing C, Qazilbash MH, Kebriaei P, Giralt S, Davis MS, Popat U, et al. Fixed-dose single agent pegfilgrastim for peripheral blood progenitor cell mobilization in patients with multiple myeloma. Br J Haematol 2006; 133:533-7.
11. Bruns I, Steidl U, Kronenwett R, Fenk R, Graef T, Rohr UP, et al. A single dose of 6 or 12 mg of pegfilgrastim for peripheral blood progenitor cell mobilization results in similar yields of CD34+ progenitors in patients with multiple myeloma. Transfusion 2006;46:180-5.
12. Fruehauf S, Klaus J, Huesing J, Veldwijk MR, Buss EC, Topaly J, et al. Efficient mobilization of peripheral blood stem cells following CAD chemotherapy and a single dose of pegylated G-CSF in patients with multiple myeloma. Bone Marrow Transplant 2007;39:743-50.
13. Yang BB, Kido A, Shibata A. Serum pegfilgrastim concentrations during recovery of absolute neutrophil count in patients with cancer receiving pegfilgrastim after chemotherapy. Pharmacotherapy 2007;27:1387-9.
14. Steidl U, Fenk R, Bruns I, Neumann F, Kondakci M, Hoyer B, et al. Successful transplantation of stem cells mobilized by chemotherapy and a single dose of pegylated G-CSF in patients with multiple myeloma. Bone Marrow Transplant 2005;35: 33-6.
15. Kuendgen A, Fenk R, Bruns I, Dommach M, Schutte A, Engers R, et al. Splenic rupture following administration of pegfilgrastim in a patient with multiple myeloma undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 2006;38:69-70.
16. Arshad M, Seiter K, Bilaniuk J, Qureshi A, Patil A, Ramaswamy G, et al. Side effects related to cancer treatment: CASE 2. Splenic rupture following pegfilgrastim. J Clin Oncol 2005;23:8533-4.
17. Hatzimichael E, Benetatos L, Stebbing J, Kapsali E, Panayiotopoulou S, Bourantas KL. Spontaneous splenic haematoma in a multiple myeloma patient receiving pegfilgrastim support. Clin Lab Haematol 2006;28:416-8.
18. Rowley SD, Donaldson G, Lilleby K, Bensinger WI, Appelbaum R. Experiences of donors enrolled in a randomized study of allogeneic bone marrow or peripheral blood stem cell transplantation. Blood 2001;97: 2541-8.
19. Kröger N, Renges H, Sonnenberg S, Krüger W, Gutensohn K, Dielschneider T, et al. Stem cell mobilisation in 16 μg/kg vs 10 μg/kg of G-CSF for allogeneic transplantation in healthy donors. Bone Marrow Transplant 2002;29:727-30.
20. Kubista E, Glaspy J, Holmes FA, Green MD, Hackett J, Neumann T, Pegfilgrastim Study Group. Bone pain associated with once-per-cycle pegfilgrastim is similar to daily filgrastim in patients with breast cancer. Clin Breast Cancer 2003;3:391-8.