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Research Article

Comparison of fixed dose pegfilgrastim and daily filgrastim after autologous stem cell transplantation in patients with multiple myeloma autografted on a outpatient basis

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Abstract

Different authors have explored the feasibility of autografting patients with multiple myeloma (MM) on an outpatient basis. Peg-filgrastim (PEG), a long-acting recombinant G-CSF, has similar efficacy when compared to conventional G-CSF for chemotherapy-induced neutropenia, but little is known about its use in the autologous stem-cell transplantation (ASCT) setting, namely in patients programmed to be autografted on outpatient basis. In this study, we compared therapeutic results in terms of hematopoietic recovery, non-hematologic toxicity, duration of hospitalization and percentage of hospital readmission between patients receiving either conventional G-CSF or PEG. Thirty-eight MM patients (48 autografts) received PEG, given at a single dose of 6 mg at day +5 from stem cell infusion, while 81 (113 autografts) received G-CSF from day + 2 up to stable neutrophil recovery. The conditioning regimen was high dose melphalan in all patients. The median age and the median number of CD34 + cell infused were comparable between the two groups. Overall, a second hospital admission was required in 36 procedures out of 161 (32%). Febrile neutropenia (FN) and severe mucositis were the most frequent causes of hospitalization. There was no statistically significant difference as percentage of hospital readmission is concerned: in the PEG group readmission was needed in 6 out of 48 autografts (12%) as opposed to 30 out of 113 (26%) in the G-CSF subgroup, *p*: 0.06. The median time of hospital stay for readmitted patients was identical for the two subgroups (9 days vs. 9 days, *p*: 0.94). Finally, one case of transplant related mortality occurred in the whole patient series (0.6%).

In conclusion, ASCT on an outpatient basis is feasible and safe in patients with MM, the majority of whom are manageable at home. The administration of single dose PEG results in no different outcome in terms of safety and efficacy as compared to 8 days of G-CSF.

Keywords: multiple myeloma; autologous stem cell transplantation; PEG filgrastim; outpatient

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Introduction

High-dose chemoradiotherapy followed by autologous stem-cell transplantation (ASCT) has become common practice for different hematologic malignancies [1,2]; in particular, in younger patients with multiple myeloma (MM), ASCT has been shown to prolong disease free and overall survival in patients with newly diagnosed disease and, therefore, it is currently considered as part of the gold standard therapy at least up to the age of 65 years [3–5]. Toxicity and mortality associate with ASCT have been reduced; thanks to several factors, principally the use of mobilized peripheral blood stem cells, administration of granulocyte colony-stimulating factor (G-CSF) after progenitor cells infusion and improvement of prophylactic antibiotic regimen [6,7]. Notwithstanding, in most cases the procedure of ASCT still requires long hospitalization during the aplastic phase, which is expensive and lead to the risk of hospital infections as well as to increasing pressure on available hospital beds. Therefore, different authors have successfully explored the possibility of performing ASCT on an outpatient basis. In particular, three basic models have been proposed: an early discharge model, a delayed admission model and a comprehensive, or total, outpatient model [8–10]. Whatever the model, the safety of such a procedure has been demonstrated either in patients with hematologic malignancies or in those with solid tumours, with substantial reduction of costs and more satisfying quality of life, namely in motivated patients having the physical and psychological capability

and desire of being autografted in this manner. In most studies aimed at exploring the feasibility of ASCT on outpatient basis, filgrastim has been administered by starting on the day after stem cell infusion. More recently, Peg-filgrastim (PEG), a G-CSF form characterized by an increased plasma half-life, has been approved for clinical use and its efficacy has been definitively demonstrated either for the management of febrile neutropenia (FN) after conventional chemotherapy, or in the setting of bone marrow aplasia induced by conditioning regimen during ASCT [11,12]. In this study, we describe clinical characteristics and treatment results from a series of 38 patients (48 autografts) affected by MM, who were autografted on an outpatient basis by using a single dose PEG administered on day +5 from the day of stem cell infusion. In addition, results from a comparison of therapeutic results in terms of hematopoietic recovery, non-hematologic toxicity, duration of hospitalization and percentage of hospital readmission between patients receiving either conventional G-CSF or PEG are also reported.

Patients and methods

From January 2008 to December 2009, 38 patients diagnosed as having MM in partial (PR) or complete remission (CR) were programmed to receive ASCT on an outpatient basis by using PEG, given at a single dose of 6 mg at day +5 from stem cell infusion. There were 23 male and 15 female patients, the median age being 59 years (range 47–72). In all, 21 patients had MM IgG and 10 MM IgA, while light chains MM was diagnosed in 7 cases (five *k* type and two lambda type); according to Durie and Salmon classification system, at diagnosis 12 patients were in stage IIA, 20 in stage IIIA and 6 in stage IIIB. In 32 patients, ASCT was part of first-line therapy, while 6 patients were in first or subsequent relapse after first line treatment including ASCT. At the time of autograft, all patients were in performance status 0–1 according to WHO criteria, without concomitant cardiac or respiratory diseases requiring specific treatment. Renal function was normal in all cases. Ten patients received double ASCT either as part of first line therapy or after relapse, so that the total number of autografting procedures was 48.

The control group, which included 80 patients with MM, in whom the modalities of ASCT were similar, the only difference being the administration of filgrastim instead of PEG from day +2 up to stable neutrophil recovery. In detail, these patients, autografted between January 2003 and December 2007, had a median age of 57 years (range 43–70); 49 were males and 31 females. As in PEG subgroup, patients were given ASCT only if atleast in PR after front line or salvage therapy. According to Durie and Salmon classification system, at diagnosis, 13 patients were in stage IIA, 52 in stage IIIA and 15 in stage IIIB. In 70 patients [13], ASCT was part of first-line therapy, while 8 patients were in first or subsequent relapse after first line treatment including ASCT. Sixty-one patients received a single ASCT, while 21 received double ASCT for a total number of 113 autografting procedures. Prerequisites for the admission to the outpatient program included for both subgroups the presence of a caregiver (spouse, close friend or family member), patient's adherence and living within 45-min travelling distance from the hospital. Accordingly, the outpatient procedure was actually performed in 161 out of 195 autografts for MM (82%).

At the time of autograft, all patients were in performance status 0–1 according to WHO criteria, without concomitant cardiac or respiratory diseases requiring specific treatment. Renal function was normal in all cases. The conditioning regimen consisted of high-dose melphalan (HDM) at 200 mg/m^2 (Mel200) for patients aged 65 years or less and 140 mg/m^2 (Mel140) for those older than 65 years.

Main characteristics of patients managed with PEG and controls are summarized in Table 1. In particular, there was no difference between the two groups as to median number of CD34 positive (CD34+) cells infused (5.8 for PEG and 5.9 for G-CSF, *p*: 0.67), percentage of conditioning with Mel200 and Mel140 (81%/19% for PEG vs. 82%/18% for controls, *p*: 0.87), percentage of first and second ASCT (82%/18% for both subgroups, *p*: 0.98) and median age at transplant: 59 years for PEG (range: 42–69) vs. 57 (range: 39–79) for controls, *p*: 0.31. In addition, the status at autograft in terms of results of pre-ASCT therapy was comparable (*p*: 0.68).

To receive ASCT, patients were admitted to the hospital on day −2 to receive pretransplant fluid load, on day −1

Table 1. Patients' characteristics

	PEG	Controls	*p* value
Patients number	38	93	na
Transplants number	48	113	na
Median age (range)	59 (42–69)	57 (39–70)	0.31
Myeloma type			
IgG	21	58	
IgA	10	25	0.23
Light chain	6	10	
Non secretory	1	0	
Melphalan: 200/140	39/9 (81%/19%)	93/20 (82%/18%)	0.87
Transplant: 1st/2nd	38/10 (82%/18%)	93/20 (82%/18%)	0.98
Median number of CD34+ cells infused (×10E6/l)	5.8 (2.5–9.3)	5.9 (2.8–10.2)	0.78

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they were given a conditioning regimen, on day 0 CD34+ cells were infused and on day +1 patients were programmed to be discharged. All patients received high-dose chemotherapy and stem cell infusion in single or double conventional rooms in the absence of any isolation procedure. At discharge, instructions were given for proper body hygiene and hand washing for all people in direct contact with the patient. The strategy to prevent vomiting and nausea included Granisetron and did not change between 2003 and 2009. Blood samples were taken three times a week at home by a nurse and analysed at the hospital's clinical chemistry unit. The patient was asked to take his/her temperature frequently to ensure that he/ she did not develop septic shock or acute respiratory distress syndrome. The clinic was open from 8 AM to 5 PM, 7 days a week; after-hours patients had access to transplant physician for medical emergencies by cellular phone. A daily phone call from a physician from the transplant unit was included into the protocol. The antimicrobial prophylaxis consisted of ciprofloxacin (500 mg t.i.d.) beginning when the neutrophil count was >1000/dl and continued until fever occurred, infection was documented or until neutrophil recovered to 1000/dl. Criteria for blood and platelet transfusion included hemoglonin >8 gr/dl and platelet <20 × 10E9/l, respectively. No antiviral or antifungal prophylaxis was administered. The criteria for admission included FN with concomitant hypotension or other life threatening complications (>38.5), intractable nausea, vomiting or diarrhoea, severe mucositis needing total parenteral nutrition (TPN) and/or narcotic analgesics as well as any other WHO grade III or IV side effect.

Results

Overall, after obtaining informed consent, 38 consecutive patients programmed to be autografted for MM were enrolled in the PEG study. Ten patients received a double ASCT, so that the total number of autografts was 48. Of note, all patients accepted the outpatient program and all were discharged on day +1 following PBSC infusion as programmed. There was no case of transplant-related mortality (TRM) and in all patients a full engrafment was achieved. The median time to obtain ANC >500/cmm and platelets >20000/cmm was 12 days (range: 9–14) and 11 days (range: 9–15), respectively. All patients were given PEG on day +5 and no patient needed a second PEG administration. Transfusional support consisted of a median of 0 packed RBC units (range: 0–2) and 0 platelet units (range: 0–2). Patients non-readmitted needing blood or platelets were transfused at the Day Hospital Unit. Overall, the rate of readmission was of 12% (6 patients); causes of hospitalization included WHO grade III–IV oral mucositis needing TPN in three cases, fever of unknown origin (FUO) requiring large-spectrum antibiotics in two cases and WHO grade III diarrhoea in one patient.

In the control group, including 93 patients and 113 autografts, 29 patients (26%) needed readmission. Causes of hospitalization were substantially similar to those reported for the PEG subgroup (40% mucositis requiring TPN, 28% FUO managed with wide spectrum antibiotics, 15% diarrhoea). In addition, in this subgroup, occasional reasons of hospital readmission included patient's anxiety (two cases), nausea and vomiting (two patients) and relatives' desire (one patient). Patients treated with G-CSF received a median of 8 doses (range: 5–13). In this subgroup, one case of transplant related mortality was recorded, due to fatal septic shock. Overall, (FN) was registered in 32 procedures (20%). The median number of days of fever >38.5°C was 4 (range: 1–7); either the occurrence of FN or the median number of days with fever did not differ between the two groups. Most cases of FN were managed at home with intravenous ceftriaxone, given the absence of hypotension or other life threatening complications. Finally, narcotic analgesics (morphine derivatives) were used in all cases of grade 3–4 stomatitis, which easily resolved in all patients at the resolution of neutropenia. Of interest, as shown in Table 2, hematopoietic recovery was comparable between the two groups; in particular, no statistically significant differences were found as neutrophil and platelet recovery as well as load of supportive therapy are concerned. In addition, the incidence of grade 3–4 mucositis was comparable (18% vs. 20%, *p*: 0.34).

Overall, the rate of readmission was higher for the control group as opposed to PEG subgroup (26% vs. 12%,); however, the difference did not reach the level of statistical significance (*p*: 0.06).

For further analysis, independently from the myeloid growth factor received, we considered separately two groups of patients, the former consisting of patients who did not need readmission (H1), the latter including patients who were readmitted to the hospital (H2). The median duration of hospitalization was 4 days for the H1 group and 9 days (range: 8–20) for the H2 group. The difference is highly statistically significant, *p*: 0.001. Of note, there

Table 2. Hematopoietic recovery and non hematological toxicity

	PEG	Controls	*p* value
Days to ANC > 0.5 ×10E9/l	12 (9–14)	11 (8-15)	0.75
Days to platelet count > 20 × 10E9/l	11 (9–15)	12 (10–16)	0.80
No of RBC Units (median, range)	0 (0.2)	0 (0–3)	0.97
No. of platelet units (median, range)	0 (0–2)	0 (0–1)	0.87
FUO	16/48 (34%)	33/113 (29%)	0.88
Mucositis (WHO > 2)	12/48 (20%)	20/113 (18%)	0.34
TRM	0/48 (0%)	1/113 (0.8%)	0.90

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was no correlation between the melphalan dose, age and pretransplant serum albumin level with the rate of second hospitalization. In addition, in the subgroup conditioned with 200 mg melphalan no difference was observed in readmission for patients below or over the median age (57 years, range: 47–60).

Discussion

In the recent years, the introduction of different new drugs has significantly improved the prognosis of patients with MM [14–16]. Notwithstanding, ASCT still remains a mainstay of therapy atleast in patients aged up to 65 years. In addition, for patients who fail to achieve VGPR or CR according to EBMT criteria, a second procedure is still recommended [6,7]. Accordingly, despite availability of new agents, there is an increasing demand for ASCT resulting in an increasing pressure on available hospital beds. On this basis, different authors have explored the feasibility of autografting patients affected by different hematologic malignancies, mainly lymphoproliferative disorders, on an outpatient basis. However, the ease of administration of HDM as well as the lack of excessive extramedullary toxicity, including nausea and vomiting, renders patients with MM more suitable for outpatient management. In the present study, we describe an outpatient program based on the early discharge model for the management of aplastic phase following HDM for patients with MM. Of note, while in many studies outpatients were housed in residential facilities located close to the hospital, in this series patients not readmitted did spend the aplastic phase entirely at home. In a previous study, dealing with a limited number of 28 patients [17], we demonstrated that such a procedure was feasible and safe in a patient population with a median age of 57 years. Of note, there were no cases of TRM and percent of re-hospitalization was 36%. All patients received filgrastim at a fixed dose of 300 ug from day +2 up to stable neutrophil recovery.

In this study, on a series of 38 patients accounting for a total of 48 autografting procedures, we adopted an identical outpatient approach by replacing filgrastim with PEG (one single administration of 6 mg on day +4), after stem cell infusion. The choice of giving PEG on day +4 derives by pharmacokinetic considerations; it is well known that the clearance of PEG is strictly related to the level of circulating neutrophils [18–19], therefore we speculated that delaying PEG at day +4 after stem cell infusion, when most patients begin to develop neutropenia, would result in a higher efficacy. Of interest, in our series of PEG treated patients percent of re-hospitalization was only 12%, which is consistently lower than that we observed in the control group, including 80 patients and 118 autotransplants in whom filgrastim had been used. While such a difference does not reach the level of statistical significance, in this regard, two considerations should be made: first of all, hematopoietic recovery and need for supportive treatment were no different between the two groups; secondly, the incidence of non-haematological toxicity was comparable. In particular, there were no differences in the occurrence of mucositis, vomiting and nausea and infections, which represented the more frequent causes of hospitalization in the PEG as well as in the control group. It is conceivable that the lower rate of re-hospitalization we did observe in the PEG subgroup was dependent on the period of transplant rather than the hematopoietic myeloid growth factor we employed; in other words, given that patients of PEG subgroup were autografted more recently, the possibility of a progressively increased expertise and confidence of the medical team with the outpatient procedure should be taken into account.

Obviously, patients not readmitted experienced a significantly shorter stay in the hospital as compared to the readmitted group (4 vs. 9 days, p: 0.001). However, also including patients needing re-hospitalization, when we compared median hospital stay of the 118 patients programmed to ASCT on an outpatient basis to a group of 21 MM patients previously autografted on an entire inpatient setting, the difference remains highly statistically significant (6 vs. 19 days, p: 0.003), suggesting a clear advantage for the outpatient approach.

Overall, in our experience administration of PEG was safe and had at least comparable efficacy to that of filgrastim. However, apart from the obvious improvement of compliance and convenience of a single injection for patients and healthcare professionals, no advantages for PEG were seen in hematopoietic recovery with respect to the standard use of filgrastim; in particular, no relevant clinical effects on occurrence and severity of FN and/or severe infections. Notwithstanding, our experience does clearly suggest that the single administration is particularly convenient in the outpatient procedure.

In conclusion, our data confirm that ASCT on an outpatient basis is feasible and safe in patients with MM, the majority of whom are manageable at home. The administration of single dose PEG is better accepted by patients and healthcare professionals, even though it results in no different outcome in terms of safety and efficacy as compared to 8 days of G-CSF.

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