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Delayed molgramostim administration after autologous peripheral blood stem cell transplantation does not add any benefit regarding hematological engraftment and supportive therapy requirements: A prospective randomized trial

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ABSTRACT

The administration of hematopoietic growth factors after autologous peripheral stem cell transplantation is still controversial. In this prospective, randomized trial we aimed to investigate the impact of GM-CSF after the transplantation with G-CSF mobilized peripheral blood stem cells with respect to hematological engraftment and supportive therapy requirements. Thirty-one patients with solid and hematological malignancies were randomized in one group (n=16) receiving GM-CSF (Molgramostim, Leucomax; Sandoz-Schering-Plough Laboratories, Paris, France) from day 7 post transplant until neutrophil recovery (absolute neutrophil count >0.5x10^9/L on three consecutive days) or in another group (n=15) receiving no GM-CSF. All patients received total CD34+ cells more than 2x10^6/kg. The patients in both groups were comparable for age, sex, time between diagnosis and transplantation, total numbers of pretransplant chemotherapy regimens, previous radiotherapy, tumor type (solid or hematological) and numbers of total CD34+ cells infused. There was no difference between cytokine and no-cytokine group with respect to leukocyte engraftment (11.9±2.2 vs. 11.9±2.9 days, respectively; p=0.936), platelet engraftment (12.6±3.6 vs. 11.9±3.9 days, respectively; p=0.691), number of days with parenteral antibiotherapy (10.8±4.7 vs. 11.9±3.7 days, respectively; p=0.662), number of days with fever over 38.1 °C (6.3±4.3 vs. 5.0±3.0 days, respectively; p=0.551), the use of red cells (2.6±1.7 vs. 2.9±1.0 units, respectively; p=0.623), the use of platelet transfusions (1.2±1.0 vs. 1.3±1.0 units, respectively; p=0.773), duration of posttransplant hospitalization (13.1±2.7 vs. 13.5±2.6 days, respectively; p=0.435). This randomized trial suggested that the administration of GM-CSF from day 7 until engraftment after autologous peripheral blood stem cell transplantation did not add any evident clinical benefit in terms of engraftment duration and supportive therapy requirements. [Turk J Cancer 2006;36(2):57-63].

KEY WORDS:

Molgramostim, high dose chemotherapy, autologous peripheral stem cell transplantation

INTRODUCTION

Nowadays autologous peripheral blood stem cell transplantation (APBSCT) is performed with increasing frequency in several malignancies. There is a general agreement that, compared to autologous bone marrow transplantation, APBSCT is associated with faster hematological engraftment, shorter hospitalization duration and decreased supportive therapy requirements (1-4).

It is well-established that the administration of hematopoietic growth factors (GM-CSF or G-CSF) accelerates neutrophil recovery in patients undergoing high-dose therapy followed by autologous bone marrow transplantation. In addition, there is evidence that the infusion of autologous peripheral-blood stem cells (PBSC) accelerates engraftment in comparison to patients who receive bone marrow alone. However, few data are available regarding the ability of hematopoietic growth factors (HGF) to accelerate engraftment further in patients who receive PBSC following high-dose therapy. Depending on the recent studies, G-CSF after APBSCT has beneficial effects in terms of hematological engraftment and supportive therapy requirements and that delaying its administration is a cost-effective and logical approach (5-9). But there are only few studies to reach conclusive results for GM-CSF.

MATERIALS AND METHODS

Thirty-one patients, who underwent autologous peripheral blood stem cell transplantation (APBSCT), were randomized to receive GM-CSF (Molgramostim, Leucomax; Sandoz-Schering-Plough Laboratories, Paris, France) or not to receive it. The study was approved by the local ethic committee. Written informed consent was obtained from all patients.

Patients

The diagnoses of the enrolled patients were breast cancer (n=13), osteosarcoma (n=5), relapsed Hodgkin's disease (n=5), relapsed non-Hodgkin's lymphoma (n=4), relapsed testicular cancer (n=2), small cell lung cancer (n=1) and multiple myeloma (n=1). GM-CSF group consisted of 16 patients (10 female, 6 male; mean age of 36.8±12.4 years) and -GM-CSF group consisted of 15 patients (6 female and 9 male; mean age of 37.0±12.2 years). Four patients in the GM-CSF group and 5 patients in the -GM-CSF group received previous radiotherapy. One patient in the GM-CSF group and 2 in the -GM-CSF group underwent second transplant. Interval between diagnosis and transplantation (time to transplantation) was 452.5±446.1 days in the GM-CSF group and 930.3±151.5 days in the no GM-CSF group. The patients' characteristics are shown in table 1.

Stem Cell Mobilization and Apheresis

Recombinant human G-CSF (Filgrastim, Neupogen, Roche, Basel, Switzerland) was given at a total dose of 10-15 μg/kg/day with twice-daily s.c. injections, beginning fourteen days after the completion of the last cycle of induction chemotherapy and continuing until the collection of PBSC was completed. Using a continuous flow cell separator (COBE Spectra, Lakewood, CO, USA), the leukapheresis procedure was performed wit a three-way central catheter on days 4, 5 or 6. Each apheresis continued 4 to 6 hours every day. Single apheresis was sufficient for all but one patient (10). Harvested autologous plasma was mixed with dimethylsulfoxide (DMSO) to yield a final DMSO concentration of 10%. The final suspension was transferred into freezing bag and frozen to -100 ºC using a computerized freezing device (R 201 Planar) and then stored in liquid nitrogen at -196 ºC following standard methods.

Flow Cytometry

CD34+ cells in the leukapheresis product were enumerated by flow cytometry (FACScan; Becton Dickinson, Heidelberg, Germany) using direct CD34 immunofluorescence. A minimum of 1×10^6 mononuclear cells was incubated for 30 minutes at 4 ºC with fluorescence conjugated to fluorescein isothiocyanate (Becton Dickinson, Heidelberg, Germany). The gated percentage of CD34+ cells was multiplied by the absolute MNC of the apheresis product to yield and absolute CD34+ cell count for each apheresis.

High-Dose Chemotherapy Regimens

Conditioning regimens included: CNV for breast cancer (n=13): Cyclophosphamide 2.4 g/m^2, mitoxantrone 35 mg/m^2, etoposide 250 mg/m^2/d ×6 days; BEAM for Hodgkin's and non-Hodgkin's lymphoma (n=9): BCNU 300 mg/m^2, etoposide 200 mg/m^2/d ×4 days, Ara-C 200 mg/m^2/d ×4 days, melphalan 140 mg/m^2; ICE for testicular cancer, osteosarcoma, lung cancer (n=8): Ifosfamide 2.5

g/m^2/d ×6 days, carboplatin 250 mg/m^2/d ×6 days, etoposide 250 mg/m^2/d x6 days; CEP for breast cancer with lung metastasis (n=1): Cyclophosphamide 60 mg/kg/d ×2 days, etoposide 200 mg/m^2/d ×6 days, carboplatin 200 mg/m^2/d ×6 days; L-PAM for multiple myeloma: Melphalan 140 mg/m^2.

Stem Cell Transplantation and GM-CSF Administration

At the time of transplantation (day 0), stem cell bags were quickly thawed at bedside and immediately infused intravenously through a central catheter. After transplantation the patients were randomized in cytokine or no cytokine group. In the cytokine group, the patients received 5 μg/kg/day recombinant human GM-CSF (Molgramostim, Leucomax; Sandoz-Schering-Plough Laboratories, Paris, France) by intravenous route from day 7 until leukocyte counts exceeded 1×10^9/L for 3 consecutive days.

Evaluation of Posttransplant Reconstitution of Hematopoiesis

Leukocyte count greater than 1×10^9/L was documented as leukocyte engraftment, neutrophil count greater than 0.5×10^9/L as neutrophil engraftment, and platelet count grater than 50×10^9/L as platelet engraftment.

Posttransplant Supportive Therapy

Single donor thrombopheresis was performed as needed to keep the platelet number above 20×10^9/L. Erythrocyte transfusion was performed to keep the hemoglobin level above 8 g/dL. All blood products were irradiated (2500 cGy) and transfused via leukocyte filter. Fever was defined as any temperature elevation over 38.1 ºC or fever over 38.0 ºC lasting at least one hour. Posttransplant hospitalization duration was documented as the period elapsed from reinfusion to discharge.

Statistical Analysis

Statistical analysis was performed using a statistical software (SPSS for Windows, version 9.0, SPSS Inc., USA). Mann-Whitney U test was used for comparison of distribution of values for unpaired series such as age, number of patients enrolled, time to transplantation, number of previous chemotherapy cycles, number of total nucleated cells, number of CD34+ cells, time to leukocyte and platelet engraftment, number of febrile days, number of days with parenteral antibiotherapy, number of erythrocyte and platelet units transfused. Chi-square test was used for comparison between groups regarding gender, history of previous radiotherapy, preparative regimens and type of malignity. If the expected frequency in table cells was under 5 or total sample size was under 20, Fisher's exact test was used. The p value was considered statistically significant if <0.05.

RESULTS

Patients

Between +GM-CSF and –GM-CSF group there were no statistically significant difference regarding age (36.9±12.4 vs. 37.0±12.2 years, respectively, p=0.968), gender (χ^2=1.519, p=0.210), history of previous radiotherapy (χ^2=0.261, p=0.704), time to transplantation (452.5±446.1 vs. 930.3±1510.5 days, respectively, p=0.527), number of pretransplant chemotherapy cycles (107 vs. 127, respectively, p=0.519), number of solid and hematological tumors (χ^2=2.761, p=0.135) as shown in table 1.

Leukapheresis Findings

Between +GM-CSF and –GM-CSF group, number of collected total nucleated cells (12.4±3.5×10^8/kg vs. 14.6±7.5×10^8/kg respectively; p=0.937) and numbers of total CD34+ cells infused (6.3±2.3×10^6/kg vs. 9.3±7.9×10^8/kg respectively; p=0.384) were not different. All patients received total CD34+ numbers above 2×10^6/kg (Table 2).

Hematological Engraftment

Between two groups there was no difference with respect to leukocyte engraftment (11.9±2.2 vs. 11.9±2.9 days respectively; p=0.936) or platelet engraftment (12.6±3.6 vs. 11.9±3.9 days; p=0.691) (Table 3).

Supportive Therapy Requirements

Between +GM-CSF and –GM-CSF group, number of days with parenteral antibiotherapy (10.8±4.7 vs. 11.9±3.7 days, respectively; p=0.662), number of days with temperature over 38.1 °C (6.3±4.3 vs. 5.0±3.0 days, respectively; p=0.551), the use of red cells (2.6±1.7 vs. 2.9±1.0 units, respectively; p=0.623), the use of platelet transfusions (1.2±1.0 vs. 1.3±1.0 units, respectively; p=0.773), duration of posttransplant hospitalization (13.1±2.7 vs. 13.5±2.6 days, respectively; p=0.435) were not different (Table 3).

Table 1
Patient characteristics

Characteristics	+GM-CSF group	-GM-CSF group	P value
Number of patients	16	15	
Gender (M/F)	6/10	9/6	0.2101*
Mean age	36.81	37.00	0.9682**
Diagnosis			
Solid tumor	13	8	0.1351*
Breast cancer	9	4	
Osteosarcoma	3	2	
Lung cancer	1	0	
Testicular cancer	0	2	
Hematological malignancy	3	7	0.1351*
Hodgkin's disease	1	4	
Non-Hodgkin's lymphoma	2	2	
Multiple myeloma	0	1	
Previous radiotherapy (n of patients)	4	5	0.7041*
Previous chemotherapy (n of total cycles)	107	127	0.5192**
Preparative regimen			
CEP	1	-	
ICE	4	4	
CNV	8	4	
BEAM	3	6	
Melphalan	-	1	
Time to tx (days)	452.50±446.137	930.26±1510.472	0.5272**

BEAM: BCNU, Etoposide, Ara-C, Melphalan; ICE: Ifosfamide, Carboplatin, Etoposide; CNV: Cyclophosphamide, Mitoxantrone, Etoposide; CEP: Cyclophosphamide, Etoposide, Carboplatin; Tx: transplantation
**p value calculated with Chi square*
***p value calculated with Mann-Whitney U test*

Table 2
Characteristics of apheresis products

		+GM-CSF group	-GM-CSF group	P value*
Apheresis volume (cm^3)	Mean±SD	215.6±65.1	213.3±55.0	0.950
	Median	200.0	200.0	
Total nucleated cells ($\times 10^8$/kg)	Mean±SD	12.4±3.5	14.6±7.5	0.937
	Median	12.3	11.0	
CD34+ ($\times 10^6$/kg)	Mean±SD	6.3±3.0	9.3±7.8	0.384
	Median	5.3	7.9	

**Calculated with Mann-Whitney U test*
SD: Standard Deviation

Table 3
Hematological engraftment days and supportive therapy requirements

Parameters		+GM-CSF group	-GM-CSF group	P value*
Leukocyte engraftment (days)	Mean±SD	11.9±2.2	11.9±2.9	0.936
	Median	11.0	12.0	
Platelet engraftment (days)	Mean±SD	12.6±3.6	11.6±3.9	0.691
	Median	12.5	12.0	
Number of febrile days	Mean±SD	6.3±4.3	5.0±3.0	0.551
	Median	6.0	5.0	
Number of days on parenteral antibiotherapy	Mean±SD	10.8±4.7	11.9±3.7	0.662
	Median	12.0	12.0	
Use of red cells (units)	Mean±SD	2.6±1.7	2.9±1.0	0.623
	Median	2.5	3.0	
Use of platelet transfusions (units)	Mean±SD	1.2±1.0	1.3±1.0	0.773
	Median	1.0	1.0	
Posttx hospitalization (days)	Mean±SD	13.1±2.7	13.5±2.6	0.435

**Calculated with Mann-Whitney U test*
SD: Standard Deviation

DISCUSSION

Posttransplant use of hematopoietic growth factors (HGF) have established value in following situations: patients receiving bone marrow infusion, patients receiving peripheral stem cells with total CD34+ cell number below 2×10^6/kg, patients receiving stem cells mobilized without HGF, patients with graft failure (11-18). However, their use after APBSCT is still controversial. There are only few studies addressing posttransplant GM-CSF use, which gives a special value to our study.

Advani et al. (19), randomized sixty-nine consecutive patients with Hodgkin's or non-Hodgkin's lymphoma to receive GM-CSF (36 patients) or placebo (33 patients) and found that administration of GM-CSF beginning on the day of autologous hemotopoietic stem cell transplantation in patients with lymphoma resulted in accelerated myeloid recovery, particularly in patients who received peripheral blood stem cells and nonpurged bone marrow, and was associated with a decreased incidence of bacterial infections. Delayed engraftment (neutrophils less than 500/mm^3 at day 30) occurred in 26% and 17% of the placebo and GM-CSF groups, respectively, and correlated with the absence of detectable myeloid progenitor cells (colony-forming units-granulocyte macrophage, CFU-GM) (P <0.001) in marrow aspirate specimens obtained on day 15. Time to platelet independence, hospitalization period, severe adverse reactions, relapse, and disease-free survival rates did not differ significantly between the two groups. In this study, GM-CSF was administered after stem cell infusion collected without any cytokine.

In a placebo-controlled randomized trial, Legros et al. (20) evaluated the hematological and clinical effects of r-Hu GM-CSF after high-dose chemotherapy (HDC) followed by GM-CSF-mobilized PBPC transplantation. Fifty patients with poor prognosis malignancies were randomized in a double-blind study to receive either GM-CSF or placebo after HDC followed by PBPC rescue. For all patients, PBPCs were recruited using a combination of VP-16 (300 mg/m^2 on days 1 and 2), cyclophosphamide (3 g/m^2 on days 3 and 4) and GM-CSF (5 micrograms/kg as from day 5). No differences were demonstrated between the two groups in median time to neutrophil or platelet recoveries. There was no significant difference between the GM-CSF group and the placebo group in terms of the median duration of post-transplant hospitalization, the number of days on antibiotic treatment, the number of infections and red blood

cell or platelet transfusion requirements. There was a significant difference with an advantage for the placebo group in the mean duration of febrile days (p=0.01). Finally it was concluded that the administration of GM-CSF in patients transplanted with GM-CSF-mobilized PBPC was not associated with a clinical benefit in terms of time to engraftment, numbers of documented infections, transfusion requirements and mucositis grading. The results of this study are similar with ours, but the study design is different. GM-CSF was used after infusion of stem cells that had been collected with GM-CSF. Also GM-CSF had no additive benefit after GM-CSF priming.

In other studies suggesting beneficial effects of GM-CSF after APBSCT, the patients received CD34+ cells below 2×10^6/kg or apheresis is performed without any HGF. It seems that primed peripheral blood stem cells with HGFs enhance marrow engraftment and they have no additive effect after transplantation.

We concluded that the administration of GM-CSF from day 7 until engraftment to patients transplanted with autologous peripheral blood stem cells does not add any evident clinical benefit in terms of engraftment duration and supportive therapy requirements. Even of no statistical importance, in the +GM-CSF group there were more febrile episodes (6.3±4.3 vs. 5.0±3.0 days; p=0.551) and longer platelet engraftment times (12.6±3.6 vs. 11.9±3.9 days; p=0.691), which may be explained as an adverse action of GM-CSF.

Regarding the high cost of GM-CSF, its posttransplant controversial benefit and potential adverse effects, we suggest that they must be used only in selected cases.

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