Original Paper

Comparison of 10 and 20 μg/Kg/day PD-Grastim in Stem Cell Mobilization in Patients with Hematologic Malignancies Candidate for Autologous Stem Cell Transplantation

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ABSTRACT

Introduction: Today, autologous peripheral blood stem cell transplantation is considered as a substitute procedure for Autologous bone marrow transplantation. Treatment with G-CSF mobilizes $CD34^+$ HSCs from bone marrow into peripheral blood and could be used as a marker for hematopoietic stem cells mobilization and subsequent apheresis. **Methods:** In this study, 60 patients that had hematologic malignancies were randomly categorized into the two groups and were given PD-grastim (group A: 20 μg/kg/day and B: 10 μg/kg/day) to evaluate 10 and 20 μg/kg/day of PD-grastim in stem cell mobilization for autologous transplantation. Their $CD34^+$ cell enumeration was carried out when leukocyte count was reached above 10000 cells/μl. Apheresis was also carried out when $CD34^+$ count was reached above 16 cells/μl. **Results:** Results of the groups A and B were statistically analyzed and there was a meaningful statistical difference in gender, drug taking day numbers, apheresis numbers, hospitalization period and injected blood units. Based on the results, group A patients had lesser hospitalization period and apheresis number than group B. **Conclusion:** This indicates that utilization of PD-grastim at dose 20 μl/kg/day has better therapeutic effects on the patients with hematologic malignancies and could be considered as the major therapeutic regimen.

INTRODUCTION

Bone marrow transplantation is now hematopoietic transplantation (HCT) that includes transplantation of hematopoietic stem and progenitor cells from related (autologous) or histocompatible unrelated (allogenic) donors (1). Autologous HCT is carried out using cryopreserved hematopoietic cells to restore bone marrow function after high dose chemotherapy especially for the patients with lymphomas or multiple myeloma (2). Previously, hematopoietic cells where obtained through collection of large volume of bone marrow for both autologous and allogenic transplantations. Although pre-clinical data demonstrated that G-CSF can mobilize hematopoietic cells into blood stream in large numbers (3). High dose chemotherapy in combination with autologous stem cell transplantation (ASCT) is considered as a preferential procedure for a variety of hematologic malignancies such as multiple myeloma (MM), non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (4). Randomized clinical studies have demonstrated advantage of mobilized stem cells in peripheral blood rather than bone marrow for ASCT (5).

Collecting of adequate number of $CD34^+$ cells is a suitable procedure for predicting chance of success and rate of hematopoietic recovery (6). There are evidences that the minimum dose of $2×10^6$ cell/Kg of $CD34^+$ cells is essential for successful hematopoietic recovery and sustained transplantation (7). Recent investigations have revealed that optimum dose of $≥5×10^6$ cell/Kg of $CD34^+$ cell resulting in faster and predictable hematopoietic and platelets recovery (8).

PBSC mobilization and harvesting include multiple steps in the patients affected with hematologic malignancies. The initial step is utilization of chemotherapy drugs that have both anti-tumor effects and stress to recruit HSC from the bone marrow (9). One to two weeks later white blood cells count is reached the minimum amount and subcutaneous utilization of recombinant G-CSF during neutropenia is used for both stem cell mobilization and neutropenic infection inhibition. By recovery of WBC above $1×10^9/L$, the patients undergo leukapheresis once or twice by blood cell separator to collect adequate amount of PBSC for durable transplantation and restore the function of bone marrow (10). The quality of

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each leukapheresis is determined by enumeration of CD34+ cells by flow cytometry or of cologenic cells by colony forming unit of granulocyte macrophage (CFU-GM) culture assay (11). G-CSF can induce some short term side effects. Although most of them are not serious but are uncomfortable such as: malaise, nausea, night sweats and bone pain (12). Although, some more serious side effects have been reported like splenic rupture, interstitial pneumonitis, pulmonary infiltrates, lung fibrosis and respiratory distress syndrome (13). Some studies have revealed that higher dose than 10 µg/kg/day of G-CSF can be more efficient in CD34+ cells harvesting (14). In two other studies, 20 and 50 µg/kg/day of G-CSF were efficient in CD34+ cells harvesting that resulted in reduced apheresis number to achieve 2.55×106 CD34+ cells/kg (15). Investigations have shown that 10-16 µg/kg/day of G-CSF causes to high yield of CD34+ cells in day 4 or 5 after treatment with G-CSF. It has been reported that higher dose of G-CSF (32 µg/kg/day) is more effective than lower dose (32 µg/kg/day) in weak mobilizers (16). Michael and et al revealed that 25 µg/kg/day resulted in mobilization increase in the patients were incapable for harvesting sufficient amount of CD34+ cells (17).

The aim of this study is comparison of 10 and 20 µg/kg/day of G-CSF in mobilization of stem cells for autologous transplantation (18).

MECHANISM OF MOBILIZATION

The mechanism of HSC mobilization has not been completely understood. G-CSF has likely indirect effect on mobilization of HSC and progenitor cells. This phenomenon was proved using chimeric mouse that has not G-CSF receptor. In these mice, hematopoietic progenitors lacking G-CSF receptor were mobilized similar to those expressed the receptor (19). Although, the mice all hematopoietic cells lacking G-CSF receptor were completely unsuccessful in mobilization suggesting that hematopoietic cells response to G-CSF is required for mobilization but its effect is as indirect manner (20).

It is believed that resident HSC in a niche in the bone marrow regulate their growth, survival and differentiation (21). It is needed to break down the bond between niche and HSC hematopoietic stem cell for mobilization. A series of retentive factors have been identified that the most important ones are very late antigen (VLA)-4/VCAM1 adhesive interaction and CXCL12/CXCR4 chemo-attractive interaction. There are important evidences that these interactions are broken during HSC mobilization induced by G-CSF and these barriers breakage is sufficient for mobilization (12)

It has been shown that neutrophils are required for HSC mobilization. It is supposed that neutrophilic proteolytic enzymes are essential for breakage of microenvironment retentive factors such as CXCL12 and VCAM1. These molecules are cleaved by protease activity of neutrophil in a similar manner upon G-CSF utilization and prevention of these enzymes reduces mobilization (22). VCAM1 cleavage is not occurred in the mouse lacking protease that suggesting VCAM1 is not essential for mobilization upon G-CSF utilization. In contrast both functional CXCL12 and CXCR4

were reduced in these mice (23). The only protease that has distinct role in HSC mobilization is aminodipeptidase, CD26, that its deletion reduces hematopoietic progenitor mobilization but not completely (12). CXCL12 is a target of CD26 but CD26 also cleaves many other cytokines and chemokines including G-CSF (24).

Therefore, one part of mobilization is mediated by proteases that cleave interaction among the expressed adhesion molecules on stem cells and their ligands surface in bone marrow stroma and another part is mediated by non-proteolytic mechanism regulating molecular expression of stroma cell-derived factor 1 (SDF-1) at mRNA level (25) (Figure 1).

PATIENTS AND METHODS

In this study, the patients with hematologic malignancies that were candidate for autologous transplantation were randomly divided into two distinct groups (groups A and B). The group A patients were injected by 10 µg/Kg/day PD-grastim and the group B patients were injected by 20 µg/Kg/day PD-grastim to mobilize and harvest stem cells from peripheral blood. The patient's selection criteria were as follow: the patients affected with hematologic malignancies, autologous transplantation candidate, the patients which their functional states were ECOG=0-2, having the age under 65, having functional liver and kidney.

Study circumstances were explained completely for the patients and they signed satisfaction letter. The drugs were given during hospitalization period. The patients were divided into two groups randomly after chemotherapy when their leukocytes count reached under 1000 cells/µl and they were then injected by G-CSF at doses 10 and 20 µg/Kg/day as subcutaneously for 5-7 days.

Their leukocyte count and biochemical panel (K, Na, CBC, uric acid and …) were checked daily. When leukocyte count was reached above 10000 cells/µl enumeration of CD34+ and MNC (mononuclear cells) were carried out. If CD34+ cells count was above 16 cells/µl and MNC count was above 15%, the patient was then prepared for cell separation. The patients were undergone apheresis by haemantic
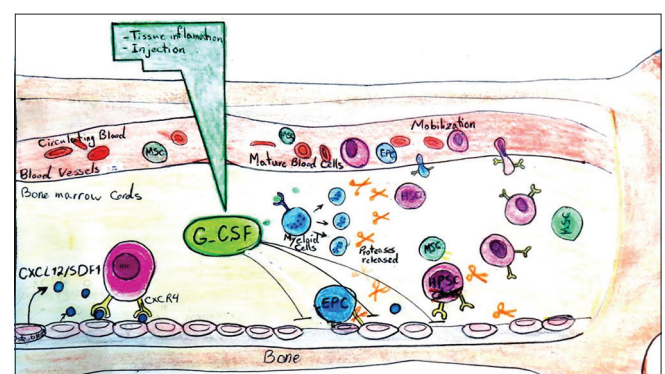

Figure 1. Molecular mechanism of HSCs mobilization. G-CSF triggers HSC mobilization thorough two main routes. One rout is mediated by proteases releasing from myeloid cells and another routes is mediated by CXCL12/SDF-1 expression attenuation in osteoblast cells

MCS+ device and the achieved samples were collected and stored in specific bag. Two samples amount of 2 ml in sterile tube were sent to count CD34+ and MNC cells and flow cytometry analysis was taken on CD34+ cells.

RESULTS AND DISCUSSION

Sixty patients were randomly classified in two drug groups with determined doses and the results were compared based on them. Thirty patients were located in the group A and were given PDgrastim 20 µg/Kg twice a day and the remained thirty patients were located in the group B and were given PD-grastim 10 µg/Kg twice a day.

The average age of the studied patients in this study was 39.63 years with standard deviation 14.11. Among sixty patients, 23 patients (38.3%) were female and 37 (61.7%) were male. The average weight of the studied patients was 67.96 Kg with standard deviation 12.71. The average drug taking days by the patients was 19.30 days with standard deviation 14.76 although the average of drug taking days in the group B patients was lesser than the group A (Table 1).

The average number of apheresis days for the studied patients in this study was 1.79 with standard deviation 0.92. 14 patients from the group A and 6 patients from the group B had one day apheresis. Chi-square test showed there is a meaningful statistical difference in one-day apheresis distribution between the two groups (p-value: 0.02). 15 patients from the group A and 22 patients from the group B had two-day apheresis. Chi-square teat showed there was no a meaningful statistical difference in two-day apheresis distribution between the two studied groups (p-value: 0.06)

but the achieved p-value proximity to 0.05 shows the most patients of the group B that have taken the dose 10 µg/Kg had tendency to have two-day apheresis. One patient from the group A and two patients from the group B had three-day apheresis. Chi-square test showed there was no a meaningful statistical difference in three-day apheresis distribution between the two groups (p-value: 0.55) (Table 1). The average of neutrophil number reaching time above 500/mm³ in all of the patients was 10.40 days with standard deviation 1.48 days while the average of platelet number increasing time above 20000/mm³ in all of the patients was 12.24 days and the average of white blood cells number in the all studied patients was 8829.06/mm³ (Table 1). Received blood and platelet unit numbers have been shown in Figure 2. The average of hospitalization period of the all studied patients
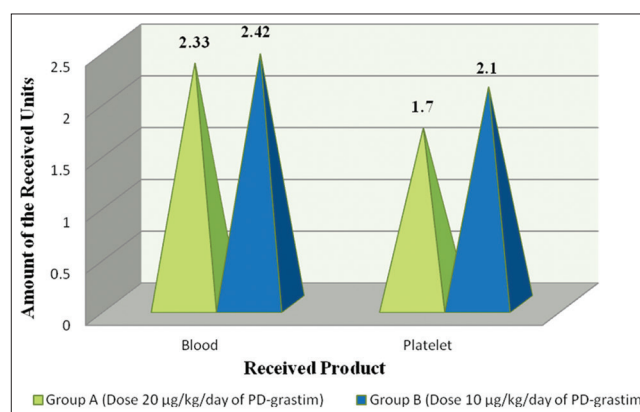
Figure 2. Comparison of the received blood and platelet unit numbers by the patients

Table 1. Statistical comparison of the results between the groups A and B

Character	Lowest	Highest	Average		Statistical deviation		p-value
			Group A	Group B	Group A	Group B	
Age (Year)	13	67	38.54	39.98	13.56	13.45	0.75
Gender	-	-	F: 7	F: 16	-	-	0.012
			M: 23	M: 14			
Weight (Kg)	43	92	68.65	67.33	10.57	14.81	0.81
Drug taking number (day)	4	73	24.19	14.57	18	8.71	0.011
Apheresis number	-	-	1.57	1.87	0.56	0.50	0.03
Platelet number increasing time >20000/mm³ (day)	8	23	12.68	11.79	2.96	2.35	0.25
Average of white blood cells count (mm³)	2600	37400	8468.15	9203.85	4307.11	7003.74	0.64
CD34+ cells count (mm³)	0	21	3.47	2.96	3.79	3.37	0.61
Mono nuclear cells number (cells/Kg)	2	51	7.85	6.00	9.19	3.14	0.33
Mono nuclear cells percent (cells/Kg)	2	93	74.47	73.88	10.45	17.39	0.88
Received blood number (Unit)	0	10	2.33	3.07	2.42	2.44	0.25
Received platelet number (Unit)	0	9	1.70	2.10	1.95	2.59	0.50
Hospitalization period (Day)	15	57	28.07	32.53	7.88	8.09	0.03

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was 31.67 days with standard deviation 8.16 days although the patients that received drug at dose 20µg/Kg had lesser hospitalization period. None of the patients were died during the study time (Table 1). CD34$^+$ cells number had been recorded for 14 patients out of 60. The average of CD34$^+$ cells number was 3.22 cells/kg with standard deviation 3.56 cells/kg. Among the all studied patients in this study, CD34$^+$ cells number were according to: in 33 patients above 2.5 cells/Kg, in 3 patients equal to 5 cells/Kg, in 3 patients above 5 cells/(patients 6, 18 and 21). 23 patients from the group A and 10 patients from the group B achieved CD34$^+$ cells number above 2.5cells/kg in their first day apheresis. Based on Chi-square test this statistical difference was meaningful (p-value: 0.001) (Table 1).

Based on significance of the cell number 2.5 cells/kg as a prognosis border, results of the disease progression comparison in the patient with CD34$^+$ cells number above 2.5 cells/kg and under 2.5 cells/kg were as follow (26): 13 patients who had CD34$^+$ cells number above 2.5 cells/kg and 11 patients who had CD34$^+$ cells number under 2.5 cells/kg had antibiotic demand during their hospitalization. Chi-square statistical test showed there was no a meaningful difference in antibiotic demand between the two studied groups (p-value: 0.78) (Table 2).

The average of hospitalization period in the patients who had CD34$^+$ cells number above 2.5 was equal to 26.39 days with standard deviation 7.28 days and in the patients who had CD34$^+$ cells number under 2.5 was equal to 35.07 days with standard deviation 6.68 days. The student t-test showed this statistical difference was meaningful (p-value: 0.000) (Table 2). The average of the injected blood units to the patients who had CD34$^+$ cells number above 2.5 was equal to 2.63 units with standard deviation 1.88 units and the average of the injected blood units to the patients who had CD34$^+$ cells number under 2.5 was equal to 3.27 units with standard deviation 2.85 units. The student t-test showed this statistical difference was meaningful (p-value: 0.03), (27), (Table 2). The average of the injected platelet units to the patients who had CD34$^+$ cells number above 2.5 was equal to 2.04 units with standard deviation 2.10 units and the average of the injected platelet units to the patients who had CD34$^+$ cells number under 2.5 was equal to 2.27 units with standard deviation 2.55 units. The student t-test showed this statistical difference was not meaningful (p-value: 0.20), (28), (Table 2).

In the patients group who had CD34$^+$ cells number above 2.5, none of the patients had no need for transplantation while in the patients group who had CD34$^+$ cells number under 2.5, two patients were not transplanted. Based on Chi-square test, there was no a meaningful statistical difference in being eligible for transplantation between the two studied groups (p-value: 0.23), (29), (Table 2). The most common diagnosis for the studied patients in both groups was multiple myeloma and then was Hodgkin. The rarest diagnosis in both groups was plasma cell leukemia. Chi-square statistical test showed no a meaningful statistical difference in the diagnosed disease distribution between the two groups (p-value: 0.36), (30), (Figure 3).

Among 60 studied patients, 24 patients (40%) needed to receive antibiotic during their hospitalization. Rest of the patients, 36 patients (60%), didn't need to receive antibiotic. There was no a meaningful statistical difference in need to receive antibiotic between the two studied groups (p-value: o.34) (Figure 4).

The rarest observed side effect in the all studied patients was facial edema and the most common side effect was bone-muscular pain and the headache. Chi-square test showed there was no a meaningful statistical difference in side effects distribution between the two studied groups (Figure 5).

Among 60 studied patients, 9 patients (14.8%) were not eligible for transplantation and 52 patients (85.2%) had
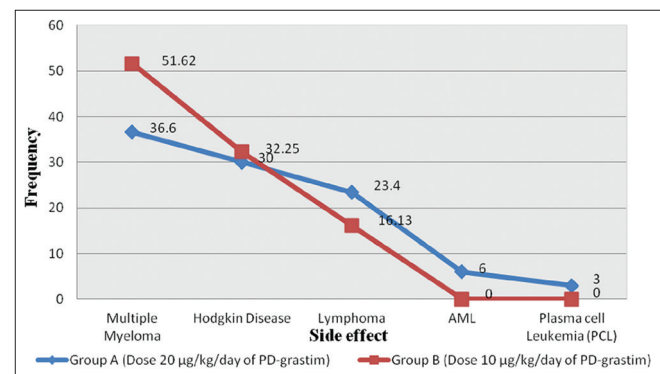

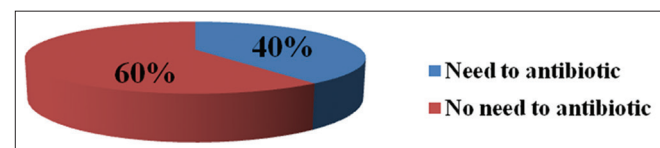**Figure 3.** Comparison of the diagnosed diseases of the studied patients

Figure 4. Antibiotic demand distribution of the studied patients

Table 2. Comparison of the patients with CD34$^+$ cell numbers above and under 2.5 cells/kg

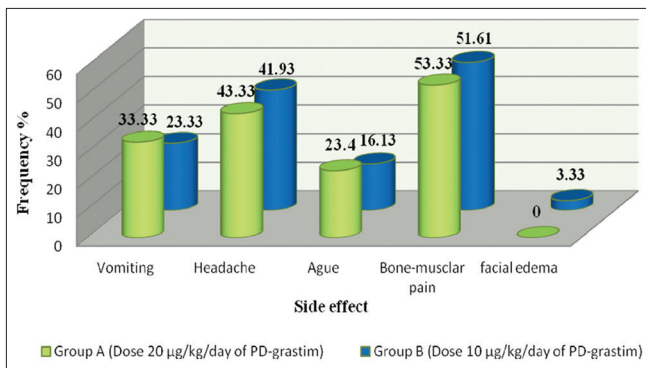| Character	Average		Statistical deviation		p-value
	Above 2.5 cells/kg	Under 2.5 cells/kg	Above 2.5 cells/kg	Under 2.5 cells/kg	
Antibiotic demand	13	11	-	-	0.78
Hospitalization period (day)	26.39	35.07	7.28	6.68	0.000
Injected blood (unit)	2.63	3.27	1.88	2.85	0.03
Injected platelet (unit)	2.04	2.27	2.10	2.55	0.20
Transplantation rejection	None	2	-	-	0.23

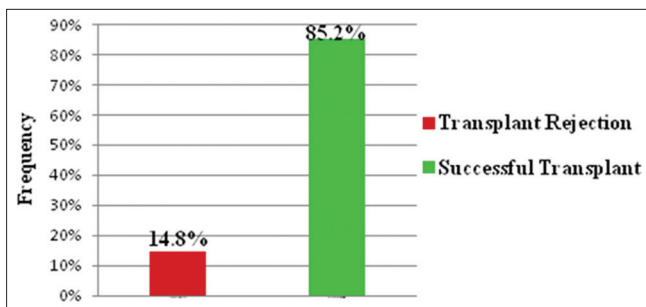**Figure 5.** Side effects comparison of the studied patients

Figure 6. Eligible for Transplantation distribution of the studied patients

successful transplantation. 4 patients (13.33%) from the group A and 5 patients (14.12%) from the group B not eligible for transplantation. Chi-square test showed there was no a meaningful statistical difference in being eligible for transplantation frequency between the two studied groups (p-value: 0.75) (Figure 6).

CONCLUSION

Over the last decade. the bone marrow was substituted with PBSCs as main source of hematopoietic stem cells that results in faster transplantation and recovery of functional durable bone marrow. Mobilization of PBSCs is the first step in this type of therapy (31).

Today, G-CSF is a routine therapeutic procedure to control neutropenia and morbidity reduction especially in cancer patients undergoing chemotherapy (32). G-CSF is also principle of transition of bone marrow into the peripheral blood as hematopoietic stem cell source for transplantation that increases safety, efficiency and applicability of the procedure (12). Although, G-CSF utilization is usual for HSC mobilization but hope for finding better procedures and new agents instead of GCSF is high (33).

Many agents are under investigation for efficient PBSC mobilization (31). New strategies specially those are focused on molecular mechanisms to recruit HSCs from bone marrow into the blood stream should be mentioned to investigate for new drug development (34).

Recent progresses suggest agents such as SDF-1 and CXCR4 as next generation candidates for PBSC mobilization especially for poor mobilizers (16).

In this study, possibility of transplant rejection and apheresis days number were lower in the higher dose of PD-grastim (group A) without increase of side effects. Thus, this procedure can be considered as a reliable method for stem cell mobilization in the patients with hematologic malignancies.

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