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Original Article

Evaluation of Engraftment and Adverse Effects of Granulocyte Colony Stimulating Factor versus PEG Granulocyte Colony Stimulating Factor in Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation

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Abstract

Hematopoietic stem cell transplantation (HSCT) is an effective treatment for many hematological malignancies. Engraftment is the foremost step in the autologous hematopoietic stem cell transplantation (AHSCT) process in which different granulocyte colony-stimulating factors with various administrations are used. In this study, we evaluated and compared the efficacy and side effects of two forms of recombinant granulocyte colony-stimulating growth factors (GCSF) ,GCSF and Peg GCSF, In this randomized clinical trial, 60 consecutive patients with multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma who underwent AHSCT were included, the average age of the patients was 55; the patients were then divided into two groups so the comparison of efficacy and side effects between the two methods become achievable. The local ethical committee approved the study with the code of SB2019:210291, and the Helsinki declaration was respected across the study. In the first group, patients received peg GCSF at a dose of 6 mg on day five, and the second group received GCSF started with 5µg/kg from day 5. We compared engraftment time and adverse effects in the two groups. Our study demonstrated no difference between the two groups regarding need for transfusion and infection complications; also, the two groups did not differ in terms of the flue-like syndrome, the type of infection and the recorded number of febrile neutropenia. Mean leukocyte engraftment days were 10.97 ± 1 and 11.1 ± 1.1 that was similar in both groups (P=0.328). Mean platelet engraftment days were 11.03 ± 2.4 and 11.1 ± 2.4 without significant difference (P=0.714).it was concluded that *Pegfilgrastim* has the same efficacy and safety profile in comparison to *Filgrastim.* Therefore, since Pegfilgrastim has a easier method of injection and can simplify the HSCT process.

Keywords: Stem Cell Transplantation, GCSF, PEG-GCSF, Engraftment, Adverse Effect, Autologous, HSCT.

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1. Introduction

Hematopoietic stem cell transplantation (HSCT) would result in more prolonged survival rates in certain types of hematologic malignancies, but bone marrow suppression and need for cellular replacement are amongst important debates. Progenitor stem cells are an important integrated part of this life saving process. Granulocyte-colony stimulating factor (G-CSF) is a critical cytokine affecting releasing and homing of hematopoietic stem cells; two recombinant types of the very mentioned are GCSF and Peg-GCSF [1-6] GCSF is usually prescribed daily due to its short half-life of 3-4 hours, whilst Peg-GCSF which is prescribed for a single dose based on its long half-life of two weeks [7-10]. This drug is used as an adjuvant therapy short-after stem cells transfusion to shorten the duration of severe neutropenia and decrease the infectious side effects [11, 12]. Different types of GCSF with various injection methods have been used in HSCT setting, also in some studies, different doses are evaluated. Generally; GCSF is the drug of choice in HSCT setting after stem cell infusion. Some evidence has shown that single dose injection of PEG-GCSF may have good efficacy and outcomes in stem cells' engraftment in autologous HSCT [12-15]. Since the Pegylated form is only injected once and has the benefit of a more long-lasting effect due to its longer half-life it may facilitate the HSCT process for the patients. Our study purpose was to compare the effects of short-acting routine form of GCSF versus PEG-GCSF in HSCs engraftment in transplantation process alongside considering the pharmaceutical adverse effects in Taleghani BMT center in Tehran.

2. Materials and Methods

In this randomized clinical trial, 60 consecutive patients with multiple myeloma, Hodgkin's, and non-Hodgkin's lymphoma with an average age of 55 (24-65 years), who underwent autologous hematopoietic stem cell transplantation (HSCT) were divided into two groups. The local ethical committee approved the study with the code of SB2019:210291, and the Helsinki declaration was respected across the study. Also, the informed consent form was received from all patients. All the patients who were eligible for AHSCT between 18-70 years old entered the study. According to ECOG criteria, inclusion criteria were patients needing to AHSCT (multiple myeloma Hodgkin and non-Hodgkin lymphoma) and optimal performance. The exclusion criteria were patients with inappropriate performance and lack of desire for participation in the study. Eligible patients initially underwent stem cell harvesting and received conditioning chemotherapy with routine protocols in the

HSCT ward and then were randomly divided into two groups. In the first group, patients received PEG-GCSF (Pegagen®) at a dose of 6 mg subcutaneously on days +5 and +9, the second group received GCSF 5μg/kg IV infusion during 20 minutes from day +5. Patients who didn't have any increase in White blood cell count after day +10, the dose of GCSF was doubled. Both study groups were assessed for engraftment of WBC, RBC and platelets .Side effects according to NCI (national cancer institute) toxicity grading were also recorded. The same physician checked all patients for complications (fever, headache, flue-like, etc.). CBC and kidney function tests were evaluated daily, liver function tests were measured three times per week. Engraftment day was determined the day in which a platelet count >20000/u and absolute neutrophil count > 500/μl were detected from the patient, and the duration of admission was calculated from the admission day to the day of discharge. Data analysis was done by SPSS version 25.0 software. The used tests were Kolmogorov-Smirnov, Independent-Sample-T, Fisher, Chi-Square, Man-Whitney, and Repeated-Measure-ANOVA. The P values less than 0.05 were considered statistically significant.

3. Results and Discussion

From Sep 2017 to May 2018, 68 patients enrolled in the study. Sixty patients were divided into two groups and 8 patients were excluded from the study. Demographic and background data are demonstrated in Table 1. The disease's remission status was similar in both groups (P=0.216). The bone marrow status was the same (P=0.157). Eight patients (26.7%) in the Peg-GCSF group and one patient (3.3%) in the GCSF group had radiation therapy history showing a significant difference (P=0.026). No patients were using myelotoxic agents. No patient had a headache. The flu-like syndrome has differed across the groups (P=0.024), and all six subjects with this side effect were in the GCSF group. Bone pain (P=0.197) and fever (P=0.243) were the same across the groups (Table2). The mean febrile days were 6.3 ± 4.3 days and 2.4 ± 1.7 in GCSF and peg_GCSF groups respectively with a significant difference (P=0.022). Infection rate and transfusion requirements were similar between the groups (P > 0.05). The number of used packed cells were alike across the groups (P=0.144). The mean required platelet infusions were 9 ± 6s.04 and 7.1 ± 5.4, in GCSF and peg_GCSF groups respectively which was the same across the groups (P=0.354).

The mean leukocyte engraftment days were 10.97 ± 1 and 11.1 ± 1.1 that was alike across the groups (P=0.328). The mean platelet engraftment days were 11.03 ± 2.4 and 11.1 ± 2.4 without a difference (P=0.714). Antibiotic usage was the same across the groups (P=0.243). The mean duration of antibiotic use was 6 ± 3.7 and 4 ± 2.5 days in GCSF and peg_GCSF groups respectively without a difference (P=0.263).

In this study, Peg GCSF and GCSF showed no difference in mean leukocyte engraftment

days that was 10.97 ± 1 and 11.1 ± 1.1 respectively in two groups, and mean platelet engraftment days were 11.03 ± 2.4 and 11.1 ± 2.4 without a difference. Also, the need for transfusion and the infection complication were the same, and the two groups did not differ in terms of the flu-like syndrome, the type of infection, the duration of febrile neutropenia. The total cost for peg-GCSF was lower than GCSF in this study. One of our goals was to reduce the job burden of our nurses; replacing the traditional form of GCSF with its pegylated form helped us through reaching our goal as it needed only two single doses in comparison to GCSF which needed daily injections with same results for platelet and leukocyte engraftment. Vanstraelen *et al.* assessed 20 consecutive patients with lymphoma or multiple myeloma receiving a single 6-mg dose of Peg GCSF on day one post-transplant to a historical control group of 60 patients receiving daily GCSF 5 microgram/kg starting on day one post-transplant similarly and reported no difference in neutrophil engraftment or fever between two drugs [12]. In another study by Mathew e al , among 164 patients in two groups of Peg GCSF and GCSF, it was found that Peg GCSF led to faster engraftment, lower febrile neutropenia, and low antibiotic-therapy days [13]. However, in our study, engraftment and antibiotic use were similar between the groups, and only febrile days were different. In another study by Martino *et al.* Peg GCSF use resulted in 961USD cost-saving per patient [14]. Although the exact cost effectiveness evaluation was not included in our study but it seems that it could be a positive point in peg -GCSF usage in HSCT setting. Probability to cost saving were also seen in our study. A comparative study by Green *et al.* of Peg GCSF versus GCSF showed that fever and infections were the same across the groups. Nevertheless, in our study, the febrile days showed a significant difference (P=0.022) [15]. In other studies, Peg GCSF single dose and GCSF, multiple doses had the same safety profile, but the duration of febrile neutropenia and total length of febrile days have differed as well as our study [16,17]. The infection rate has differed between groups in the study, but it has differed in our study. This difference may be due to various antibiotic protocols in different studies. Jagasia *et al.* [16] reported no side effects among 28 patients who received Peg GCSF and the GCSF and Peg GCSF groups. Neutrophil engraftment has differed between groups [16,17] . However, similar to our study the adverse effects were the same. For this matter selection of treatment for each patient is case-dependent. Vanstraelen *et al.* reported no difference between Peg GCSF and GCSF for fever and infection [12].

4. Conclusion

In our study, Peg GCSF showed similar efficacy and safety comparable with GCSF considering easier process for both patients and nurses. However, in our study, GCSF doses were prescribed in the 5th and 9th days, and in the majority of other studies, the first and fifth days were considered. Based on the obtained results, it may be concluded that GCSF and

Peg-GCSF have the same efficacy in engraftment after high dose chemotherapy however, further studies with larger sample size and multi-center sampling would develop more definite results.

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Tables:

Table 1. Demographic and background data of included cases.

Variable		PEG-GCSF Group	GCSF Group	P-value
Age		60.5 ± 13.4	50.5 ± 13.4	0.135
Sex	Male	18 (60%)	16 (53.3%)	
	Female	12(40%)	14(46.7%)	0.602
Chemotherapy courses number		1.4 ± 0.7	1.7 ±0.8	0.124
Background disease	Multiple Myeloma	21 (70%)	20 (66.7%)	
	Hodgkin Disease	5 (16.7%)	7 (23.3%)	
	Ewing Sarcoma	1 (3.3%)	1 (3.3%)	0.817
	Non-Hodgkin lymphoma	2 (6.7%)	1 (3.3%)	
	T Cell Lymphoma	1 (3.3%)	1 (3.3%)	
CD34+ cells dose (10^6/kg)		4.1 ± 2.6	3.6 ± 3.02	0.136

Table 2. Complications of the study groups.

	PEG GCSF group	GCSF group	P-value
Headache	-	-	-
Flue like syndrome	-	20%	0/024
Bone pain	13/3%	26/7%	0/197
Fever	33/3%	20%	0/243

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