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Comparison of Long-Acting G-CSF (PD-Lasta) with Short-Acting G-CSF (PD-Grastim) in Neutrophil Recovery Following Consolidation Chemotherapy with High-Dose Cytarabine in Acute Myeloid Leukemia: A Randomized Clinical Trial

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ABSTRACT

Background: Acute myeloid leukemia (AML) patients are often neutropenic as a result of their disease alone or following their chemotherapy. In this randomized clinical trial the efficacy of Iranian short-acting (PD-Grastim) and long-acting G-CSF (PD-Lasta) were compared in term of time to recovery from neutropenia in de novo AML patients following the consolidation chemotherapy.
Materials and Methods: Patients (n = 51) received one or two courses of Cytarabine and Daunorubicin as an induction. If complete remission was achieved, the treatment was followed by high-dose Cytarabine as consolidation chemotherapy. Twenty four hours after the consolidation chemotherapy, patient were randomized to receive either daily short-acting G-CSF (PD-Grastim) (300 µg/kg) or single-dose long-acting G-CSF (PD-Lasta) (6 mg).
Results: The median time to recovery of neutrophils was 11.00 and 13.00 days for short-acting G-CSF (PD-Grastim) (n=22) and long-acting G-CSF (PD-Lasta) (n=29) groups, respectively (U=186.5, P>0.05 two-tailed). Incidence of adverse effects was similar in both short-acting G-CSF (PD-Grastim) and long-acting G-CSF (PD-Lasta) groups.
Conclusion: Overall, data show that Iranian long-acting G-CSF (PD-Lasta) was not significantly different with Iranian short-acting G-CSF (PD-Grastim).

Keywords: Neutropenia; Acute Myeloid Leukemia; Granulocyte colony-stimulating factor (G-CSF)

INTRODUCTION

Neutropenia is the most common cause of death in Acute Myeloid Leukemia (AML) patients receiving chemotherapy. In recent years, use of widespread antibiotics is a major success in treatment of post chemotherapy infectious disease however infections can still occur as a result of neutropenia and lead to morbidity and mortality in AML patient receiving chemotherapy[1,2]. Thus, new therapeutic strategies are needed for management of these neutropenic patients.

Since 1980s, with introduction of bone marrow stimulating cytokines, a new method of

treatment was found. The synthetic granulocyte-colony stimulating factor (G-CSF) with the brand name Filgrastim was the first myeloid growth factor that was approved by FDA[3]. Previous studies have shown that simultaneous administration of G-CSF with cycles of chemotherapy is associated with reduction in the duration of neutropenia, antibiotic use, and hospitalization[1,4,9]. Because of short half-life of Filgrastim and the need of daily injection, long-acting recombinant G-CSF have been produced by addition of polyethylene glycol (PEG) to G-CSF. The mechanism of action of both drugs are same except that G-CSF is cleared by kidney while Peg-G-CSF clearance is regulated by neutrophils [5]. Therefore, clearance of Peg-G-CSF has a direct relation with neutrophil count. The single subcutaneous injection of Peg-G-CSF is as equal as 5-7 subcutaneous injections of G-CSF for increasing neutrophil count following the chemotherapy [6–11].

In most studies long-acting G-CSF (Peg-G-CSF) was used for prevention and treatment of neutropenia in patients with solid tumors though few studies have focused on hematologic malignancy patients under chemotherapy. It has been shown that daily injection of Filgrastim can increase the neutrophil count and reduce the severity of neutropenia in AML patients following the chemotherapy[12,13]. Another study on AML patients also showed the non-inferiority of Filgrastim compared to Pegfilgrastim in treatment of chemotherapy induced neutropenia [14,15].

The aim of this study was to demonstrate the non-inferiority of a new brand long-acting G-CSF (PD-Grastim, produced by Pooyesh darou; Iran) compared to short-acting G-CSF (PD-Grastim, produced by Pooyesh darou; Iran) in AML patients with neutropenia following the high-dose Cytarabine consolidation chemotherapy.

MATERIALS AND METHODS

Study population

This randomized clinical trial was done on adult patients (at least 15 years old) with de novo AML and Eastern Cooperative Oncology Group (ECOG) performance status≤2. The Table 1 shows the inclusion and exclusion criteria for this study. About 51 patients entered into the study and 22 (43.1%) received daily short-acting G-CSF (PD-Grastim) and the other 29 (56.9%) received one dose of long-acting G-CSF (PD-Lasta) 24 h after high-dose Cytarabine as consolidation chemotherapy. Due to a number of complications, seven patients were excluded from short-acting G-CSF group.

This study evaluated the effect of an Iranian short-acting G-CSF (PD-Grastim) in comparison with long-acting G-CSF (PD-Lasta). First, patients received one or two cycles of chemotherapy with Cytarabine (100mg/m2, D1-D7) and Daunorubicin (45mg/m2, D1-D3) as induction (7+3 regimen). If the patient achieved complete remission high dose of Cytarabine (>55y, 2 gr/m2, q12H, D1-D3 and <55y, 3 gr/m2, q12H, D1-D3) was infused as consolidation treatment. Twenty four hours after the last dose of chemotherapy patients were randomized to one of two treatment groups. The first and the second study group received one daily short acting G-CSF (PD-Grastim) (300 µg/kg) and long-acting G-CSF (PD-Lasta) (6mg) respectively. None of the patients received antibiotic prophylaxis according to our department protocol. The patients were monitored daily for 21 days after the first dose of short-acting G-CSF (PD-Grastim) and long-acting G-CSF (PD-Lasta) injections. Time to recovery from neutropenia (ANC<1.5×10^9/L) was calculated from the first day of drug injection until the first of two consecutive post-nadir ANC values ≥1.5×10^9/L. Patients who did not develop neutropenia were considered recovered at day 1. Time to recovery was censored for patients who did not recover from neutropenia.

Efficacy measurements

The Data were collected by taking a daily CBC test and measuring the absolute neutrophil count for each patient in case of neutropenia (ANC≤1.5×10^9/L). In addition for evaluating any adverse effects (etc. bone pain, fatigue, headache and fever), a daily questionnaire was collected from each patients.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age 15-65	Secondary AML
Denovo AML	ECOG performance status≥3
Achieved complete remission after induction chemotherapy	Have any effective disease (such as cardiovascular disease, renal disease, liver disease, pulmonary disease, diabetes, high blood pressure etc.) or receiving drugs and continuous treatment
Received high dose of Cytarabine in consolidation chemotherapy	

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Ethical consideration

The study was approved by ethics committee of IBTO and the ministry of health in agreement with Declaration of Helsinki and good clinical practice (IR.TUMS.REC.1394.507). The trial was registered on the Iranian Registry of Clinical Trials (IRCT) Web site with registration number IRCT2015072623349N1. Written informed consent was obtained from all patients before any study-related procedure was performed.

Statistical analysis

Data was analyzed with SPSS software version 18 and presented as mean ± SD or median with interquartile range (IQR). The Shapiro-Wilk test was used to check the normality of data. The Mann-Whitney test was employed to compare the incidence of febrile neutropenia and the time to recovery from neutropenia variables. A level of $P<0.05$ was considered to be a threshold for statistical significance.

RESULTS

Patients

Baseline demographic and patient characteristics at the time of treatment are shown in Table 2. Fifty-one patients were randomized into the trial, twenty-two patients (10 male, 12 female) treated with short-acting G-CSF (PD-Grastim) and twenty-nine patients treated (22 male, 7 female) with long-acting G-CSF (PD-Lasta). The mean age of patients were 46.5 (SD 14.1) and 42.3 (SD 13.3) years for the short-acting G-CSF (PD-Grastim) and long-acting G-CSF (PD-Lasta) groups, respectively. The majority of patients (14 patients in PD-Lasta group and 24 patients in PD-Grastim group) had intermediate cytogenetics. Cytogenetic data were not available in five patients.

Table 2: Demographics and disease characteristics

Characteristics	PD-Grastim (n=22)	PD-Lasta(n=29)
Age, years		
Mean (SD)	46.5 (14.1)	42.3 (13.3)
Range	15-65	15-65
Sex, n (%)		
Male	10 (41.4)	24 (82.8)
Female	12 (58.6)	5 (17.2)
*Cytogenetic, n		
Intermediate	14	24
Favorable	3	4
Unfavorable	1	-

*Cytogenetic data were not available in five patients

All patients (100%) in short-acting G-CSF group and 27 patients (93.1%) in long-acting G-CSF (PD-Lasta) group developed neutropenia after consolidation chemotherapy. The Mann-Whitney test showed no statistically significant difference in incidence of neutropenia between short-acting G-CSF (PD-Grastim) and long-acting G-CSF (PD-Lasta) (Mdn_1=4.29, n_1=22, Mdn_2=3.71, n_2=29, U=252.0, P>0.05 two-tailed) groups.

Time to recovery from neutropenia

The estimated median time to ANC recovery was 11.00 and 13.00 for short-acting G-CSF (PD-Grastim) and long-acting G-CSF (PD-Lasta) groups, respectively.

The Mann-Whitney test showed no significant difference in time to ANC recovery between two groups (n_1=22, n_2=29, U=186.5, P>0.05 two-tailed) (Figure 1). ANC recovered in all patients except 3 patients during our follow up in long-acting G-CSF (PD-Lasta) group.

Incidence of adverse event

As shown in Table 3, the most frequently reported adverse events were bone pain and fever. Thirteen patients (59.1%) in short-acting G-CSF (PD-Grastim) group and twelve patients (41.4%) in long-acting G-CSF (PD-Lasta) group experienced bone pain. Three patients (13.6%) in short-acting G-CSF (PD-Grastim) group and three patients (10.3%) in long-acting G-CSF (PD-Lasta) had fever.

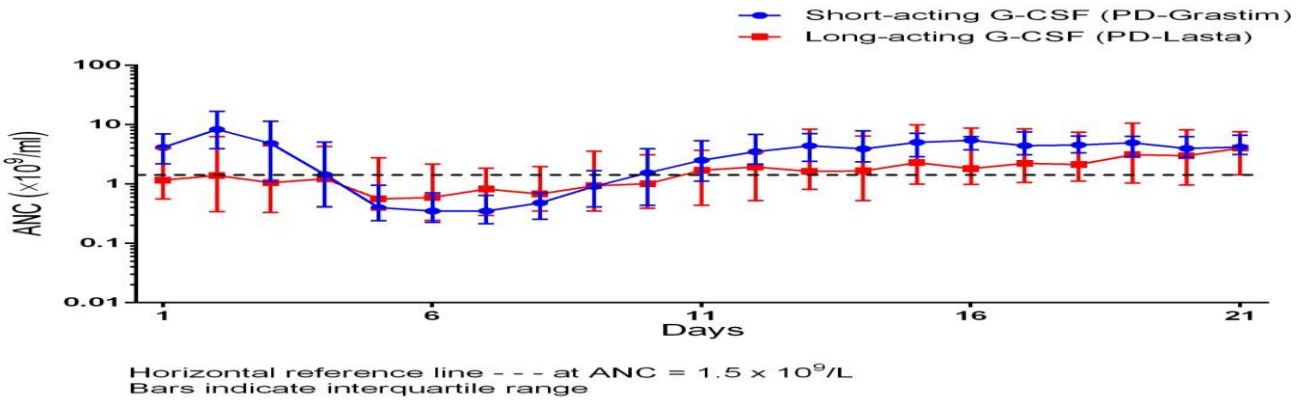

Figure 1. Median absolute neutrophil count (ANC) for short-acting G-CSF (PD-Grastim) and long-acting G-CSF (PD-Lasta) recipients following the consolidation chemotherapy

Table 3: Incidence of adverse events

Complication	PD-Grastim (n=22)	PD-Lasta (n=29)
Fever, *n (%)*	3 (13.6%)	3 (10.3%)
Bone pain, *n (%)*	13 (59.1%)	12 (41.4%)
Fatigue, *n (%)*	1 (3.4%)	1 (3.4%)
Headache, *n (%)*	1 (3.4%)	1 (3.4%)

DISCUSSION

Post chemotherapy neutropenia is the most common cause of morbidity and mortality in cancer patients[16,17]. Recent studies indicate that administration of short or long-acting G-CSF can increase WBC and decrease neutropenia duration, usage of antibiotics and hospitalization of patients after chemotherapy [18–20]. The current study is a randomized non-inferiority trial comparing efficacy and safety of Iranian long-acting G-CSF (PD-Lasta) with Iranian short-acting G-CSF (PD-Grastim) in treatment of post-chemotherapy neutropenia.

The population under study consisted of patients with acute myeloid leukemia (AML) that were hospitalized and received high dose cytarabine as treatment consolidation.

We found no significant difference in the severity of neutropenia and the time to recovery of neutrophils in long-acting G-CSF (PD-Lasta) group compared to short-acting G-CSF (PD-Grastim) group. The most common complaints of patients were bone pain and fever. Data showed no significant difference in occurrence of these adverse events in long-acting G-CSF (PD-Lasta) compared to short-acting G-CSF (PD-Grastim) groups. Result of our study support previous findings that the time to recovery of neutrophils and rate of adverse events were not significantly different between short-acting and long-acting G-CSF groups[14,21–23]. Due to different prognosis and response to chemotherapy secondary AML cases were excluded from the study.

The limitations and problems we faced in this study were few numbers of patients with AML (due to low incidence of the disease) and even fewer numbers of patients who met our inclusion criteria. Also, limited studies were available for

treatment of AML patients in comparison with other types of cancer by using long-acting G-CSF. By considering the effectiveness of both PD-Grastim and PD-Lasta, we suggest performing a cost-benefits analysis for comparing PD-Grastim and PD-Lasta with Filgrastim and Pegfilgrastim.

CONCLUSION

In conclusion, this trial demonstrated that there was no significant difference between Iranian long-acting G-CSF (PD-Lasta) in comparison with Iranian short-acting G-CSF (PD-Grastim) regarding neutrophil recovery.

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