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The effect of preemptive use of plerixafor on stem cell mobilization in patients with lymphoma and multiple myeloma

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ABSTRACT

Objective: The aim of this study is to investigate the effect of the preemptive use of plerixafor in patients with lymphoma and multiple myeloma which was administered as a preemptive single dose to the patients who were determined to have a CD34+ cell count of <15/μL in the peripheral blood (PB) on the 4th day of mobilization.

Patients and Methods: Thirty-five patients who were administered plerixafor on the 4th day after granulocyte colony-stimulating factor (G-CSF) alone for stem cell mobilization between January 2020 and November 2021 were included. CD34+ stem cell counts in PB before and after plerixafor, the amount of CD34+ stem cells collected, and the outcome of transplantation was examined.

Results: The median CD34+ cell count in PB on the 4th day was 5.2/μL (0.1-13.4), which was determined to increase 206.6-fold (31.57-49347) to 924.80 /μL (295.00-5056) following the administration of plerixafor on the 5th day (Z=-5.160; r= – 872.2; p<0.0001). The number of apheresis sessions was 1 in all patients. The median collected CD34+ cell count was $5.90x10^6$/kg ($2.70x10^6$-$14.4x10^6$).

Conclusion: The use of preemptive plerixafor shows that it is an effective mobilization method by increasing the rate of stem cell collection at an effective dose and reducing the mobilization time/apheresis sessions.

Keywords: Apheresis, Stem cell, Mobilization, Plerixafor, Preemptive

1. INTRODUCTION

Autologous stem cell transplantation (ASCT) is the main treatment option in multiple myeloma (MM) and lymphoma both as first-line therapy and in the treatment of relapsed/refractory disease, providing high overall survival and disease-free survival outcomes[1, 2]. The amount of infused stem cells is of great importance in ASCT in terms of ensuring repeat recovery in the bone marrow. Although, the minimum recommended CD34+ stem cell dose for infusion is $2x10^6$/kg, the targeted effective dose for rapid recovery is $5x10^6$/kg[3-5].

Peripheral blood is used for stem cell collection in ASCT, given that it leads to rapid neutrophil and platelet engraftment and is a convenient method for patients. Various methods are used for the mobilization of stem cells into the peripheral blood. Granulocyte-colony stimulating factor (G-CSF) alone, one of these mobilization methods, or its combined use with chemotherapy, may lead to mobilization failures in rates of 15% to 30% [5-8]. Among the risk factors that cause mobilization failure have been cited as advanced age, agents used in previously administered treatments such as alkylating agents, fludarabine, lenalidomide, exposure to multiple lines of chemotherapy, radiotherapy history, lymphoma diagnosis, and bone marrow involvement [9, 10].

The CD34+ stem cells count in the peripheral blood before the apheresis procedure is crucial as an indicator of the effective dose of cell collection and mobilization failure. The targeted CD34+ cell count for an effective cell collection in the peripheral blood is >20/μL on the 5th day of mobilization. CD34+ cell counts below this threshold level result in lesser amounts of stem cells to be collected by apheresis, increase the number of apheresis steps, prolong the stem cell collection time,

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and increase the overall cost [11]. For this reason, plerixafor is applied preemptively if CD34+ stem cell count is determined to be below <10-15/μL in the peripheral blood count performed on the 4th day of mobilization, in order to reduce the mobilization failure associated with the use of G-CSF [12]. Both European Group for Blood and Marrow Transplantation (EBMT) and British guidelines support the use of preemptive application of plerixafor in cases where the peripheral blood CD34+ cell count is below 20/μL [4, 13].

Plerixafor is a selective, reversible CXCR4 (chemokine receptor type 4) antagonist, blocking the interaction of CXCR4 with SDF-1α (stromal cell-derived factor 1) in stem cells and facilitating the passage of CD34+ stem cells into peripheral blood with the synergistic effect of G-CSF[14]. The combined use of plerixafor and G-CSF was reported to be superior to the use of alone G-CSF in mobilizing hematopoietic stem cells without significant toxicity[15, 16].

In this study, we aimed to investigate the effect of plerixafor, which was administered as a preemptive single dose to the patients with both MM and lymphoma [non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL)] who were determined to have a CD34+ cell count of <15/μL in the peripheral blood count on the 4th day of mobilization.

2. PATIENTS and METHODS

Thirty-five patients who were administered a single dose of plerixafor preemptively on the 4th day after G-CSF alone for stem cell mobilization for ASCT between January 2020 and November 2021 were included in this study.

This study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics committee approval of the study was obtained from the Clinical Research Ethics Committee of Inonu University (approval date: 14.12.2021, and approval number: 2021/2844).

Patients' diagnoses, lines of treatments before mobilization, lenalidomide treatment, number of the lenalidomide cycles, CD34+ stem cell counts in the peripheral blood per microliter before and after administration of plerixafor, number of apheresis performed for stem cell collection, the amount of CD34+ stem cells collected after apheresis (x106/kg), the conditioning regimens, the duration of neutrophil and platelet engraftment, the status of febrile neutropenia, and durations of hospitalization were examined.

Duration of neutrophil engraftment was defined as the time from the day of stem cell infusion to the first of three consecutive days with an absolute neutrophil count ≥ 0.5×10^9/L. Duration of platelet engraftment was accepted as the time from the day of stem cell infusion to the first of three consecutive days with a platelet count greater than 20×10^9/L without transfusion. Additionally, febrile neutropenia was deemed to be present in the event of fever above 38 °C with a neutrophil count below 500/μl.

Duration of hospitalization was defined as the time from the first day of mobilization to discharge or death from any cause.

Transplant-related mortality was defined as the death that occurred in association with transplant complications and not in relation to any disease in the first 30 days after transplantation.

Mobilization Protocol

Granulocyte colony-stimulating factor was administered to the patients via subcutaneous injection at a dose of 10 μg/kg/day for 4 days. CD34+ cell count was measured by flow cytometry in the peripheral blood on the 4th day of mobilization. Plerixafor was administered subcutaneously at a dose of 0.24 mg/kg/day at 11.00 pm on the 4th day of mobilization to patients whose CD34+ cell counts in the peripheral blood were found to be <15/μL. The Navios EX flow cytometer (Beckman Coulter Inc, California, USA) device was used to measure the CD34+ cell counts. GCSF was applied at 7 am on the 5th day of mobilization, and stem cell collection was performed by apheresis 11 hours after the administration of plerixafor. Patients' CD34+ cell counts were re-measured via flow cytometry from peripheral blood before apheresis. It was aimed to collect a minimum of $2x10^6$/kg CD34+ cells with apheresis. Amicus (Fresenius-Kabi, Istanbul, Turkey) device was used for all stem cell collection procedures. Mobilization failure was defined as a CD34+ stem cell count of $<2x10^6$/kg after apheresis.

The stem cells collected were cryopreserved in lymphoma patients preserved via the addition of dimethyl sulfoxide (DMSO) at a concentration of 10% followed by freezing at a mechanical freezer at – 80°C. The bags containing the cryopreserved cells were thawed in a 37 °C water bath immediately before infusion and re-infused on day 0 following the application of the conditioning regimen.

The stem cells collected were infused without freezing in MM patients. For this reason, the collected CD34+ cells were stored in blood bags without DMSO at 4 °C for up to 72 hours and re-infused on day 0 following the application of the conditioning regimen.

Transplantation Protocol

A single dose of melphalan was administered to MM patients on day – 2 as the conditioning regimen. The melphalan dosage to be administered to the fit and young patients and to fragile patients or patients with a glomerular filtration rate of less than 60 mL/min/1.73 m^2 were determined as 200 mg/m^2 and 140 mg/m^2, respectively. Stem cells were infused on day 0.

BEAM (carmustine, etoposide, cytarabine, and melphalan) regimen was used in 13 lymphoma patients, whereas Bu/Cy/E (busulfan, cyclophosphamide, etoposide) regimen was used in two lymphoma patients and in one acute lymphoblastic leukemia (ALL) patient as a conditioning regimen. BEAM regimen was applied as carmustine on day –6 (300 mg/m2/day), etoposide from day–6 to –3 (100 mg/m2 every 12 h), cytarabine from day –6 to –3 (200 mg/m2 every 12 h), and melphalan on day –2 (140 mg/m2/day). Bu/Cy/E regimen was applied as busulfan (16mg/kg/day) from day – 7 to – 4, carmustine (200 mg/m2/day) on day – 7 and cyclophosphamide (120 mg/kg/day) on day-3 and

– 2, etoposide (400 mg/m2/day) on day – 3 and – 2. Stem cells were infused on day 0.

All patients received premedication comprising chlorpheniramine, methylprednisolone, and acetaminophen before stem cell infusion. G-CSF was started to be given on day +1 and continued to be given until neutrophil engraftment was achieved. All patients received acyclovir, levofloxacin, and fluconazole as prophylactic therapy.

Statistical Analysis

In descriptive analyses, numbers and percentages were used to express the categorical data, whereas mean ± standard deviation values, percentages, and histograms were used to express parametric and median (range, minimum-maximum) values were used to express non-parametric continuous data. Skewness-Kurtosis and Kolmogorov–Smirnov tests were used for parametric and non-parametric classification of the continuous data. Mann-Whitney U test or Wilcoxon Signed-Rank test was used for the comparisons of nonparametric continuous variables. Pearson's chi-squared test or the Fisher's Exact Test was used for the comparisons of categorical data. Wilcoxon Signed-Rank test was used to analyze the difference between the CD34+ count measurements performed on the 4th and 5th days of mobilization. The difference of the marginal means between the CD34+ count measurements performed on the 4th and 5th days of mobilization in respect of MM and other cases was compared via split-plot in time-repeated measures analysis of variance (ANOVA). Probability (p) values of <0.05 were deemed to indicate statistical significance.

3. RESULTS

A total of 35 patients who were administered preemptive plerixafor were included in the study. Twenty of them (57.1%) were diagnosed with MM, 15 (42,9%) with lymphoma [NHL: 8 (53,3%), HL: 7 (46,7%)]. The median age was 53 (range, 19-74) years. Only 7 (20%) patients were over 60 years. Sixteen (45.7%) patients were female, and 19 (54.3%) patients were male. There was no significant difference between the patient groups in terms of gender (p=0.807). The median number of treatments before mobilization was 2 (range, 1-6). Twenty-three (65.7%) patients received more than one line of treatment. It was determined that 9 (25.7%) patients, who were all MM patients, received lenalidomide treatment before mobilization, and that 5 of these patients received lenalidomide treatment for 4 cycles or more. All patients had a partial or better response to treatment at the time of mobilization. None of the patients had refractory disease. Demographic and clinical characteristics of the patients according to the diagnosis subtypes are shown in Table I. Analysis by the subtypes revealed that 93.3% of the lymphoma patients as compared to 45% of the MM patients received intense pre-mobilization treatment, that is more than one line of treatment, and that there was a significant difference between the patient groups in that respect.

Table I. *The demographic and clinical characteristics of the patients*

	Multiple Myeloma N: 20	Lymphoma N: 15	Total N: 35
The median age, years (range)	57 (40-74)	39 (19-66)	53 (19-74)
>60 years, at the time of mobilization (%)	6 (30%)	1 (6,7%)	7 (20%)
Gender			
Female (%)	10 (50%)	6 (40%)	16 (45,7%)
Male (%)	10 (50%)	9 (60%)	19 (54,3%)
The median prior therapy line (range)	1 (1-3)	2 (1-6)	2 (1-6)
>1 line therapy	9 (45%)	14 (93,3%)	23 (65,7%)
Prior lenalidomide therapy (%)			
Yes	9 (45%)	-	9 (25,7%)
No	11 (55%)	-	26 (74,3%)
< 4 lines	4 (44,4%)	-	4 (11,4%)
≥ 4 lines	5 (55,6%)	-	5 (14,3%)
Disease status at the time of mobilization (%)			
CR	11 (55%)	11 (73,3%)	22 (62,8%)
VGPR	5 (25%)	-	5 (14,3%)
PR	4 (20%)	4 (26,7%)	8 (22,9%)
Refractory disease	-	-	-
The median time from diagnosis to mobilization (months)	5 (2-185)	20 (4-104)	10 (2-185)
Mobilization regimen (%)			
Melphalan 200mg/m2	14 (70%)	-	14 (40%)
Melphalan 140mg/m2	6 (30%)	-	6 (17,1%)
BEAM	-	13 (86,7%)	13 (37,1%)
Bu/Cy/E	-	2 (13,3%)	2 (5,8%)
Transplantation (%)			
First	13 (65%)	13 (86,7%)	26 (74,3%)
Second or more	7 (35%)	2 (13,3%)	9 (25,7%)

CR: Complete response, PR: Partial response, VGPR: Very good partial response BEAM: Carmustine, etoposide, cytarabine, and melphalan Bu/Cy/E: Busulfan, cyclophosphamide, and etoposide

The median CD34+ cell count in the peripheral blood on the 4th day was determined as 5.2/μL (range, 0.1-13.4), which was determined to increase 206.6-fold (range, 31.57-49347) to 924.80 /μL (range, 295.00-5056) in the peripheral blood following the administration of plerixafor on the 5th day (Z=-5.160; r= – 872.2; p<0.0001) (Figure 1). No side effects were observed in any of the patients after the administration of plerixafor.

The effects of plerixafor in the lymphoma and MM groups is shown in Table II. There was no statistical difference between the two groups in terms of CD34+ count or the increase in the CD34+ count measured on the 4th day of mobilization, that is, before the administration of plerixafor, and on the 5th day of mobilization, that is, after the administration of plerixafor (p=0.840). In addition, there was also no significant difference between the lymphoma subgroups in terms of CD34+ count or the increase in the CD34+ count measured in the peripheral blood on the 5th day of mobilization (Figure 2).

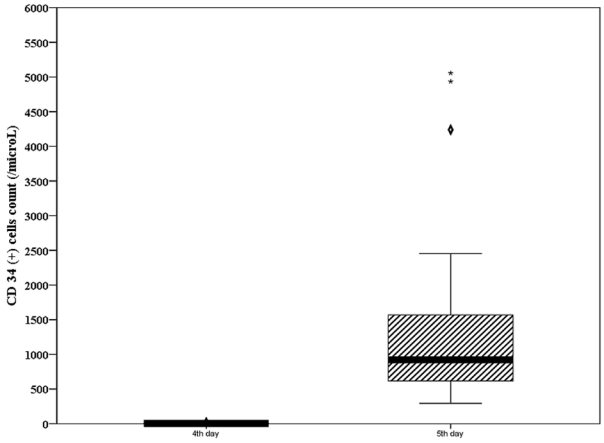

Figure 1. *CD34 (+) cell count of all patients were elavated on day 4 and on day 5 in peripheral blood. (Wilcoxon Signed rank Test; Z=-5.160; r= – 872,2; p<0.0001)*

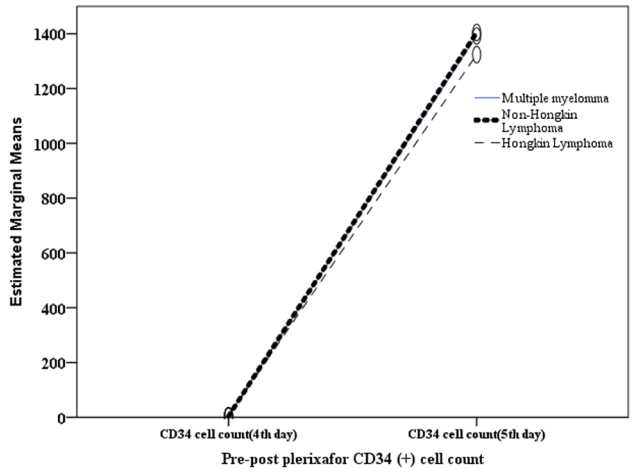

Figure 2. *Pre-post plerixafor CD34 count difference in the lymphoma and myeloma patients. Pre-post plerixafor CD34 count difference of the MM and lymphoma were not to be statistically different (two repeated measures of two groups ANOVA; p=0.840)*

Table II. *The effects of plerixafor in the lymphoma and multiple myeloma groups*

	Multiple Myeloma N: 20 (100%)	Lymphoma N: 15 (100%)	Total N: 35 (100%)	p-value
The median count of CD34/mL on +4th day (range)	5.1 (1.1-13.4)	5.2 (0.1-7.8)	5.2 (0.1-13.4)	0.317*
The median count of CD34/mL on +5th day (range)	1347.25 (295-5056)	803.6 (377.1-4934.7)	924.8 (295-5056)	0.208*
The mean difference of CD34/mL count between the 4th and 5th day	1385.9±1077.1	1302±1368.3	1349.9±1192.1	0.840**
The median fold increase with plerixafor	281.64 (31.57-884.76)	18.41 (98.81-49347)	206.6 (31.57-49347)	0.594*
The median collection CD34x10^6/kg (range)	7,.26 (2.70-14.4)	5.09 (3.6-14.3)	5.90 (2.70-14.4)	0.314*
Collection yield, x10^6/kg (%) <2 2-5 >5	 - 7 (35%) 13 (65%)	 - 6 (40%) 9 (60%)	 - 13 (37.1%) 22 (62.9%)	 >0999***

** Mann-Whitney-U ** A split-plot in time-repeated measures ANOVA *** Chi-square test*

Table III. *Transplantation outcome of lymphoma and multiple myeloma groups*

	Multiple Myeloma N: 20 (100%)	Lymphoma N: 15 (100%)	Total N: 35 (100%)
The median duration of neutrophil engraftment, day (range)	14 (9-19)	12 (9-17)	12 (9-19)
The median duration of platelet engraftment, day (range)	14 (11-43)	15 (11-21)	15 (11-43)
The rates of febrile neutrophile (%) Yes No	 11 (55%) 9 (45%)	 13 (86.7%) 2 (13.3%)	 24 (68.6%) 11 (31.4%)
The median duration of hospitalization, day (%)	21 (15-52)	27 (16-62)	24 (15-62)
Transplant-related mortality (%)	-	2 (13,3%)	2 (5,7%)

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In all patients, CD34+ stem cells were collected using apheresis only once. Mobilization failure was not observed in any patient. The median collected CD34+ cell count was 5.90x10^6/kg (range, 2.70x10^6-14.4x10^6). In 22 (62.9%) of the patients, the collected CD34+ stem cell count was above 5x10^6/kg. The difference in the count of cells collected between MM patients who received lenalidomide or not could not be given due to the small sample size.

Transplantation outcomes were shown in Table III. Neutrophil engraftment did not occur in two patients (1; NHL and 1; HL patient), whereas platelet engraftment did not occur in 3 patients (1; HL, and 2; NHL patient). There were two transplantation-related mortalities in the lymphoma group and none in the MM group. Two patients died due to coronavirus disease 2019 (COVID-19) infection. Accordingly, the transplantation-related mortality (TRM) rate of the study group was found as 5.7%.

4. DISCUSSION

CD34+ stem cell count measured in peripheral blood is an indicator of the efficiency of the stem cell collection by apheresis. The strong correlation between the two parameters is well established in the literature [11, 17]. In one of these studies, which was carried out with a view to investigating the use of CD34+ stem cell count in the peripheral blood on the day before stem cell collection by apheresis to predict poor mobilization, Szwajcer et al., determined 10/μL as the cut-off value to predict poor mobilization. Accordingly, CD34+ stem cell counts of less than 10/μL in the peripheral blood on the day before stem cell collection by apheresis predict poor mobilization. Additionally, it was determined that setting the cut-off value to a higher cell count of 15/μL reduced the possibility of poor mobilization. Therefore, it is recommended in patients at high risk for inadequate mobilization to add plerixafor to GCSF preemptively, that is, at the first step, not to prolong the apheresis procedure or to prevent remobilization[18]. In another study conducted with 397 patients undergoing ASCT, Sancho et al., investigated the cut-off value of CD34+ count in peripheral blood in respect of the preemptive or emergency use of plerixafor. Consequentially, they found with 90% sensitivity and 91% specificity that CD34+ cells count cut-off value of 13.8/μL indicates that the stem cells are collected at an effective dose (≥2x10^6 CD34 cells/kg). In the same study, 3% of the patients with a CD34+ cell count >20/μL in the peripheral blood before apheresis were found to have poor mobilization, as compared to 22% of the patients with a CD34+ cell count between 10/μL and 20/μL in the peripheral blood before apheresis, who were found to have poor mobilization[19]. Costa et al., determined that low CD34+ stem cell counts (<12/μL) in the peripheral blood on the 4th day of mobilization constituted a high risk for mobilization failure. In comparison, in our study, median CD34+ stem cell count in the peripheral blood on the 4th day of mobilization in patients treated with preemptive plerixafor was found as 5.1/μL (range, 1.1-13.4)[20].

In ASCT, the minimum CD34+ stem cell dose that should be infused is 2x10^6/kg in order not to prolong the duration of neutrophil and platelet engraftments and to reduce the risk of transplantation-related complications. Engraftment times are prolonged in transplantations performed with stem cell doses less than the said threshold value, which increases the duration of hospital stay, the risk of infection, and the amount of transfusion. The superiority of mobilization using G-CSF and plerixafor combined to mobilization using stand-alone G-CSF has been demonstrated in the literature, in terms of the stem cell count both in the peripheral blood and collected by apheresis [5, 21, 22]. In a study by Worel et al., in which the preemptive administration of plerixafor in MM and lymphoma patients undergoing ASCT has been investigated, the CD34+ stem cell count was found to be <20/μL in the peripheral blood of the patient group in which only GCSF was used for mobilization on the 4th day of mobilization. Based on this result, they used GCSF and plerixafor combination for mobilization attempts for a median number of one time (range, 1-4 times). Consequentially, the median collected CD34+ stem cell count was increased to 4.1 (range, 0.4-11.3) x10^6/kg with a median 5.9-fold (range, 1.2-26) increase after using plerixafor along with G-CSF for mobilization. The median number of apheresis performed for cell collection was one (range, 1-3) [22]. In another study, Micallef et al., used plerixafor upfront in patients whose CD34+ stem cell counts were found to be <10/μL (<20/μL, for those who were planning to have 2 transplants) in the peripheral blood on the 4th or the 5th day of mobilization. Consequentially, the median CD34+ stem cells collected after the use of plerixafor for mobilization on the 4th day of mobilization was found to be statistically significantly higher compared to the median CD34+ stem cells collected on the 5th day of mobilization after the use of plerixafor (6.1x10^6/kg and 7.8x10^6/kg, respectively, p<0.001). In the same study, the ratios of the collected stem cell count>2x10^6/kg and >4x10^6/kg were found to be statistically significantly higher in the patient group which was administered plerixafor on the 4th day of mobilization as compared to the patient group which was administered plerixafor on the 5th day of mobilization (93% vs. 84%, respectively, p<0.001; 99% vs. 95%, respectively, p<0.001)[23]. In our study, the median CD34+ stem cell count in the peripheral blood on the 5th day of mobilization following the preemptive administration of a single dose of plerixafor was determined to increase 206.6-fold (range, 31.57-49347) to 924.80 /μL (range, 295.00-5056). Additionally, the median collected CD34+ stem cells after a single apheresis session was found as 5.90 (range, 2.70-14.4) x10^6/kg. The ratios of the collected stem cell count>2x10^6 and >5x10^6/kg were found to be 100% and 62.9%, respectively, after the administration of a single dose of preemptive plerixafor.

In a study by Vishnu et al., conducted with 42 patients with MM and lymphoma undergoing ASCT, 18 (43%) patients were mobilized with alone GCSF, whereas 24 (57%) patients were mobilized with GCSF and plerixafor combined after the collected CD34+ stem cell counts in the peripheral blood on the 4th day of mobilization was found to be <10/μL. However, there was no statistically significant difference between the patient group that was administered alone GCSF and the patient group that was administered G-CSF and plerixafor combined in terms

of the duration neutrophil and platelet engraftment [neutrophil engraftment; 11 (range, 10-14) days vs. 11 (range, 8-13) days, p=0.93; platelet engraftment; 13 (range, 10-23) days vs. 13 (range, 10-47) days, p=0.47][24]. Similarly, Micallef et al., as well did not find any statistically significant difference between the patient group that was administered stand-alone GCSF and the patient group that was administered GCSF and plerixafor combined in terms of neutrophil and platelet engraftment times [23]. In our study, median neutrophil and platelet engraftment times were found as 12 (range, 9-19) days and 15 (range, 11-43) days, respectively, which are comparable to the respective findings reported in the literature.

The results of this study, in parallel with the relevant results reported in the literature, indicate that the preemptive use of plerixafor in stem cell mobilization is an effective and reliable mobilization method in increasing the rate of stem cell collection at an effective dose, decreasing the mobilization times and the number of apheresis sessions, and saving the patients from the risk of remobilization.

Compliance with Ethical Standards

Ethical Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki. The ethics committee approval of the study was obtained from the Clinical Research Ethics Committee of Inonu University (approval date: 14.12.2021, and approval number: 2021/2844).

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Conflict of interest statement: There are no conflicts of interest to declare.

Authors' contributions: AU and MAE: Conceptualization, AU, AS, SB, EH, EK and IK: Data curation and formal analysis, AU, AS, IB, SB, EK and IK: Investigation and resources, MAE, IB; EK and IK: Project administration, AU, SB, EH and AK: Software, MAE, EK, IK, IB and AU: Supervision, validation, visualization, AU and MAE: Writing – review and editing. All authors accepted the final version of the article.

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