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Hematology and Disorders
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ISSN: 2836-3582 RESEARCH ARTICLE

Cyclophosphamıde–Etoposıde + G-csf Compared to G-csf alone in Perıpheral Blood Stem Cell Mobılızatıon for Multıple Myeloma

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Received Date: 09 November 2022; **Accepted Date:** 25 November 2022; **Published date:** 22 December 2022.

Citation: Aysun Halacoglu, (2022). Cyclophosphamıde–Etoposıde + G-csf Compared to G-csf alone ın Perıpheral Blood stem cell Mobılızatıon for multıple Myeloma. Journal of Hematology and Disorders (JHD). 1(2). 10.58489/JHD.001.

Abstract

Background: Multiple myeloma (MM) is the leading indication of autologous hematopoietic stem cell transplantation (AHSCT). There are different regimens used for peripheral blood stem cell mobilization in MM. A minimum of 2 × 106 CD34 + cells/kg are needed for engraftment. This study that present a comparison of the mobilization outcomes Cyclophosphamide-Etoposide (Cy-Et) + granulocyte-colony stimulating factor (G-CSF) group and G-CSF alone group. Patients and methods: This study has been performed in a retrospective manner. 110 patients with diagnosed MM who underwent stem cell mobilization at Memorial Sisli Hospital between the years of 2013 and 2018 were evaluated. We retrieved data on patient demographics, disease status at mobilization, treatment characteristics, stem cell mobilization, collection and post AHSCT outcomes. For mobilization, 70 patients received cyclophosphamide 1250 mg/m2 for 2 day, etoposide 100 mg/m2 for 3 day and G-CSF 10 mcg/kg/day from day 4 onwards and 40 patients received G-CSF alone. Results: In 98 of 110 patients (89.1%) first mobilization trial was successful. Four patients in the Cy-Et group (5,7%) and eight patients in the G-CSF alone group (20%) were mobilized three times (p=0.001). The number of CD34 in peripheral blood was significantly higher in Cy-Et group (94±14) than G-CSF alone group (54±7) (p=0.04) on the stem cell mobilization time. Stem cell collection was higher in the Cy-Et group (13.8 × 106 CD34 + cells/kg) compared to the G-CSF alone group (8.8× 106 CD34 + cells/kg) (p =0.001). The median time to neutrophil engraftment was 11 and 13 days in Cy-Et group and G-CSF alone group respectively (p=0.014). The median time to platelet engraftment was 15 and 17 days in Cy-Et group and G-CSF alone group respectively (p=0.006). Median 360 ml stem cells in Cy-Et group and 470 ml stem cells in G-CSF alone group were collected and this difference was statistically significant (P=0.001). Conclusion: In conclusion, this study was demonstrated that Cy-Et + G-CSF mobilization provides a higher peripheral CD 34 count, less apheresis sessions, less volume, more stem cell mobilization, earlier neutrophils and platelet engraftment for patients with MM and eligible for AHSCT. Today, Cy-Et + G-CSF mobilization is a really useful method than G-CSF alone.

Keywords: *Stem Cell, Mobilization, Multiple Myeloma*

Introductıon

Multiple myeloma (MM) is a malignant disease that occurs with an uncontrolled, clonal increase of plasma cells in the bone marrow (1). MM is the leading indication of autologous hematopoietic stem cell transplantation (AHSCT) worldwide (2). High-dose melphalan followed by AHSCT is the standard treatment for MM in eligible patients after induction therapy (3). There are different regimens used for peripheral blood stem cell mobilization in MM, however, there is no consensus as to the optimal mobilization regimen for the MM. A minimum of 2 × 106 CD34 + cells/kg are needed for engraftment (4).

This study that present a comparison of the mobilization outcomes Cyclophosphamide-Etoposide (Cy-Et) + granulocyte-colony stimulating factor (G-CSF) group and G-CSF alone group.

Materials and Methods

Patients and methods

This study has been performed in a retrospective manner. 110 patients with diagnosed MM who underwent stem cell mobilization at Memorial Sisli Hospital between the years of 2013 and 2018 were

evaluated. All patients gave informed consent for all aspects of AHSCT. We retrieved data on patient demographics, disease status at mobilization, treatment characteristics, stem cell mobilization, collection and post AHSCT outcomes (Table1-2). For mobilization, 70 patients received cyclophosphamide 1250 mg/m2 for 2 day, etoposide 100 mg/m2 for 3 day and G-CSF 10 mcg/kg/day from day 4 onwards and 40 patients received G-CSF alone. Prophylactic antibiotic was given from day +5 till absolute neutrophil count was more than 500 x ×106 /L. Stem cell collection began when CD34+ was over 10 cells/µL. All ethical considerations were strictly followed in accordance with the Helsinki Declaration.

Definitions

Poor mobilization are a collection of 2 ×106 CD34+ cells/kg body weight. Neutrophil engraftment was defined neutrophil count of 0.5 × 109 /L on 3 consecutive days. Platelet engraftment was defined platelet count of 20 × 109 /L on 7 consecutive days without platelet transfusion.

Statistical Analyses

SPSS statistics 20 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Comparisons of categorical variables in groups were tested by Chi-square or two-tailed Fisher's exact tests. All P values 0.05 were considered significant.

Results

One hundred and ten patients were included in this study. The median age was 55 (31–71) years at the time of the diagnosis. No significant difference was observed in baseline characteristics between groups, including the disease control and previous therapies.

In 98 of 110 patients (89.1%) first mobilization trial was successful. Four patients in the Cy-Et group (5,7%) and eight patients in the G-CSF alone group (20%) were mobilized three times (p=0.001).

The number of CD34 in peripheral blood was significantly higher in Cy-Et group (94±14) than G-CSF alone group (54±7) (p=0.04) on the stem cell mobilization time.

Stem cell collection was higher in the Cy-Et group (13.8 × 106 CD34 + cells/kg) compared to the G-CSF alone group (8.8× 106 CD34 + cells/kg) (p =0.001).

The median time to neutrophil engraftment was 11 and 13 days in Cy-Et group and G-CSF alone group respectively (p=0.014). The median time to a platelet count > 20.000 x 109/L for more than 7 days without transfusion was 15 and 17 days in Cy-Et group and G-CSF alone group respectively (p=0.006).

Median 360 ml stem cells in Cy-Et group and 470 ml stem cells in G-CSF alone group were collected and this difference was statistically significant (P=0.001).

Discussion

This single-center, retrospective study involving 110 MM patients who underwent stem cell mobilization, present a comparison of the mobilization outcomes Cy-Et + G-CSF group and G-CSF alone group.

Although different agents are used for stem cell mobilization in MM, there is no consensus on the most appropriate option. Plerixafor can be used in stem cell mobilization by evaluating its side effects, cost-benefit ratio and availability in suitable patients (5, 6). Today, Plerixafor comes to mind in case of failure of first-line mobilization regimens. In this study, adequate mobilization was achieved in all patients without the need for plerixafor use in any of the patients.

In a study (7), two groups that were applied Cy + GCSF and Et + GCSF for stem cell mobilization in MM were compared and more stem cells were obtained in the group mobilized with Et than in the group mobilized with Cy. In our study, more stem cell mobilization was achieved in the Cy-Et group than in the GCSF alone group.

In this study, in the stem cell mobilization process, there was no increase in infection processes in the Cy-Et group, contrary to expectations, compared to the GCSF alone group, and Cy-Et was easily tolerated by all patients. This may be related to the fact that the disease was under control before transplantation in patients who were planned for transplantation.

Some previous studies (8-10) used GCSF alone or Cy + GCSF as a mobilization regimen in MM. However, mobilization insufficiency is around 10-20%. In this study, adequate mobilization was performed in a single session in 89.1% of the patients. Mobilization was required 3 times in 5.7% of the patients in the Cy-Et group and in 20% of the patients in the GCSF alone group.

In a study of 91 MM patients in the literature (11), 42 patients were mobilized with a novel pegylated form of the recombinant G-CSF filgrastim, 49 patients were mobilized with filgrastim, and it was shown that more stem cell mobilization and earlier engraftment were achieved with the pegylated form. The combination of Cy-Et with pegylated form filgrastim is a candidate to be the current cost-effective mobilization option in MM.

In the literature (12), in a multicenter study of 422 MM patients, it was shown that low-dose Cy provides

optimal mobilization when Cy is 2 g/m2 and ≥ 3 g/m2 and GCSF alone is used. In this study, when Cy was used with total 2.5 g/m2 and Et, more effective mobilization was achieved than GCSF alone. In addition, in this study, no hemorrhagic cystitis or neutropenic infection was reported due to the use of Cy during stem cell mobilization in MM in previous studies (13-14).

In this study, the fact that more stem cell mobilization was obtained with less apheresis in the Cy-Et group offers an advantage especially for tandem transplantation in MM. Also, earlier neutrophil and platelet engraftment was obtained in the Cy-Et group compared to the GCSF group alone, which may provide a cost advantage due to earlier post-transplant discharge and less hospital stay.

Conclusions

In conclusion, this study was demonstrated that Cy-Et + G-CSF mobilization provides a higher peripheral CD34 count, less apheresis sessions, less volume, more stem cell mobilization, earlier neutrophils and platelet engraftment for patients with multiple myeloma and eligible for ASCT. Today, Cy-Et + G-CSF mobilization is a really useful method than G-CSF alone. Further randomized, prospective studies with larger sample size and clinical, laboratory and histopathological data from such studies are required to support the results of this study.

Compliance with ethical standards

All ethical considerations were strictly followed in accordance with the Helsinki Declaration.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Table 1: Patients Characteristics

Variable	Cy-Et Group (N=70)	GCSF Alone Group (N=40)	*P* value
Median age (range)	62 (31-69)	63 (56-71)	0.74
Sex, n (%)			
Female	34 (48.5%)	18 (45%)	0.12
Male	36 (51.5%)	22 (55%)	
Myeloma Type, n (%)Ig			
G/kappa	28 (40%)	18 (45%)	
Ig G/lambda	14 (20%)	8 (20%)	
Ig A/kappa Ig	10 (14.3%)	5 (12.5%)	
A/lambdaIg	7 (10%)	3 (7.5%)	
M/kappa Ig	4 (5.7%)	2 (5%)	
M/lambda	2 (2.9%)	-	0.94
Kappa	3 (4.2%)	2 (5%)	
Lambda	2 (2.9%)	2 (5%)	
Induction Treatment, n (%)			
Bortezomib Lenalidomide	60 (85.7%)	35 (87.5%)	
Carfilzomib	8 (11.4%)	4 (10%)	0.30
	2 (2.9%)	1 (2.5%)	
Stage (R-ISS), n (%)I			
II	32 (45.7%)	22 (55%)	
III	21 (30%)	13 (32.5%)	0.47
	17 (24.3%)	5 (12.5%)	
Premobilization Status, n (%)			
Complete Response	16 (22.9%)	10 (25%)	
Very Good Partial ResponsePartial	39 (55.7%)	18 (45%)	
Response	10 (14.3%)	9 (22.5%)	0.21
Minor Response / Stable Disease	5 (7.1%)	3 (7.5%)	

Table 2: Stem cell mobilization outcomes

Variable	Cy-Et Group (N=70)	GCSF Alone Group (N=40)	*P* value
Total CD34+ stem cell collected, x10^{6}cells/kg, median	13.8	8.8	0.001
Peak peripheral blood CD34 counts, range	94±14	54±7	0.04
CD34+ stem cell volüme (ml), median	360	470	0.001

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