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The effect of CD 34+ stem cell dose on both short-term and long-term outcomes of autologous stem cell transplantation in multiple myeloma

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Abstract

Aim: In this single-center, retrospective study, we aimed to evaluate the effect of CD34+ stem cell dose on hematologic recovery and long-term outcomes such as progression-free survival and overall survival after autologous stem cell transplantation (ASCT).

Materials and Methods: In this study, 282 patients with MM, who underwent ASCT between January 2014 and October 2021 were evaluated. The patients were divided into 2 groups according to the infused cell dose. Patients who received $\leq 5x10^6$/kg CD34+ cells were defined as group A. Patients who received $>5x10^6$/kg CD34+ cells were group B. The outcome of ASCT including the time of neutrophil/platelet engraftment, febrile neutropenia status, transplant-related mortality (TRM) at 100 days, duration of hospitalization and survival status were examined in both groups.

Results: There were 118 (41.8%) patients in group A and 164 patients (58.2%) in group B. The median neutrophil engraftment was 12 (7-26) days in A group, 11 (6-28) days in B group. The median platelet engraftment was 12 (6-40) and 11 (6-29) days in group B. There were statically significant different in both group for neutrophil and platelet engraftment time (p=.001 and .002, respectively). The median hospitalization time was 16 (10-53) days and 15 (6-83) days in group A and B, respectively. The hospitalization time was statistically significantly different in two groups (p<.012). The mean OS was 53.1±4.2 months in group A and 58.2±3.5 in group B which was not statistically significant difference (p=.841). The mean PFS was 11.8±1.3 months in group A and 19.1±1.4 months in group B which was statistically significant difference in 2 groups (p<0.001).

Conclusion: Infusion of $>5x10^6$/kg CD34+ stem cells (median dose 9,6 $x10^6$/kg) may have a favorable effect on short-term outcomes of transplantation, including short-term neutrophil engraftment, short-term platelet engraftment, and short-term hospitalization. Additionally, progression-free survival may be positively affected by high dose, but upper limit should be defined by new study.

Introduction

Multiple myeloma [MM] is characterized by plasma cell proliferation in the bone marrow constituting approximately 10% of hematological malignancies and 1% of all cancers [1]. Despite new targeted therapies, MM is still an incurable disease, and autologous stem cell transplantation [ASCT] following high-dose therapy after induction therapy is the standard and cornerstone treatment for fit and young patients [2,3].

Infused CD34+ stem cell dose is one of the main factors affecting transplantation's short-term and long-term outcomes. The presence and duration of neutrophil and platelet engraftment, duration of hospitalization, and transplant-related mortality [TRM] are the short-term outcomes of ASCT, whose result is related to the dose of CD34+ stem cells. [4-6]. The recommended minimal dose of CD34+ cells for ASCT is $\geq 2.0 \times 10^6$/kg [7]. In the literature, infused CD34+ stem cell dose $<2.0 \times 10^6$/kg was associated with delayed hematologic recovery [8]. The minimum infused CD34+ stem cell dose is clear, but the

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maximum dose is not so clear yet. Some studies reported high amount of infused CD34+ stem cells are associated with a short engraftment time in both platelet and neutrophil engraftment [9]. The CD34+ stem cell dose >5-6x10^6/kg was associated with fast recovery, and a decrease in the amount of blood transfusion [10,11] . In the retrospective study, the platelet count was not observed below 20x10^9/L; platelet replacement was not required with the CD34+ stem cell dose between 15.8 and 25. 1x10^6/kg [12].

In this single-center, retrospective study, we aimed to evaluate the effect of CD34+ stem cell dose on hematologic recovery and long-term outcomes such as progression-free survival and overall survival after ASCT.

Materials and Methods

Patients

In this retrospective study, 282 patients with MM, who underwent ASCT between January 2014 and October 2021 were evaluated. Patients who underwent a tandem transplant or a second transplant due to progression or relapse were excluded. This study was approved by our center Ethics Committee (Inonu University Ethical Committee, approval number: 2021/2755) which was conducted in accordance with the principles of the Declaration of Helsinki. Patients' age at the time of transplantation, gender, M protein type, disease stage at diagnosis, number of induction treatment lines, induction treatment protocols, the time from diagnosis to transplantation, disease status before transplantation, the dose of CD34+ stem cells infused, the time of neutrophil/platelet engraftment, febrile neutropenia status, transplant-related mortality (TRM) at 30 days, duration of hospitalization and survival status were examined retrospectively from hospital registers and patients' clinical records.

Disease score was determined by the International Staging System (ISS) [13]. Remission status before transplantation was assessed based on the International Myeloma Working Group (IMWG) criteria [14].

Study design

The patients were divided into 2 groups according to the infused CD34+ stem cell dose. The cut-off for the CD34+ cell dose was determined as 5x10^6/kg. Patients who received ≤5x10^6/kg CD34+ stem cells were defined as group A. Patients who received >5x10^6/kg CD34+ stem cells were group B.

Induction treatment

Bortezomib plus cyclophosphamide plus dexamethasone (VCD) was mostly used for induction treatment before the transplantation. Vincristine plus doxorubicin A plus dexamethasone (VAD) alone or VAD plus VCD were other induction treatments because of the drug reimbursement policy. In case of refractory disease after the induction therapy, immunomodulatory drugs (IMiDs) based therapy (VRD: bortezomib, lenalidomide, dexamethasone; RD: lenalidomide, dexamethasone; PD: pomalidomide, dexamethasone) and 2nd generation proteasome inhibitors (PIs) based therapy (CRD: carfilzomib, lenalidomide, dexamethasone) were used before the transplantation.

Transplantation

Melphalan was used for the conditioning regimen in all patients and administered as a single dose on day +2. Melphalan was administered at 200 mg/m^2 to fit and young patients, and 140 mg/m^2 was administered to fragile patients or patients with a glomerular filtration rate of less than 60 mL/min/1.73 m^2. Stem cells were infused on day 0. CD34+ stem cell counts were measured by flow cytometry method after the leukapheresis. However, cell viability was not routinely tested before the cell infusion in our clinic. Primary endpoints of study were hematologic recovery (neutrophil/platelet engraftment and febrile neutropenia), duration of hospitalization and TRM. Secondary endpoint was the comparison of both groups for OS and PFS.

Definition of outcomes

The neutrophil engraftment was specified as ''A neutrophil count was achieved 0.5×10^9/L and more for 3 consecutive days after transplantation". *The time of platelet engraftment* was accepted as the platelet count greater than 20×10^9/L without transfusion for 3 consecutive days after the transplantation. *Progression-free survival (PFS)* was calculated as the time from the first day of ASCT to the disease progression or death due to any cause. *Overall survival (OS)* was calculated from the first day of ASCT until death or last fallow-up time.

Statistical analysis

The program of IBM SPSS Statistics Version 22.0 (Armonk, NY, USA: IBM Corp.) statistical software package was used in all analyses. 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. Mann-Whitney U 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. Bonferroni method was used to compare the column rations of the multinominal variables found to be significant in the chi-square test. Kaplan-Meier test was used for OS and PFS analyses and curves. The predictors of OS and PFS were compared using the log-rank test. Multivariate analyses of predictors of survival were performed using the Cox regression test. The statistically significant was defined as p value <.05.

Results

Baseline characteristics

A total of 282 patients were included in this study. The mean age at the time of transplantation was 58±8.9 and 169 (59.9%) of them were male. More than half of the patients (58.5%) had IgG M-protein type. Disease status at the transplantation was CR in 120 (42.6%) patients, VGPR in 135 (47.9%) patients, PR in 25 patients (8.9%) and refractory disease in 1 (0.4%) patient. VCD therapy (69.1%) was used mostly for induction treatment followed by VAD plus VCD (11.0%), VCD plus VRD (7.1%), VCD

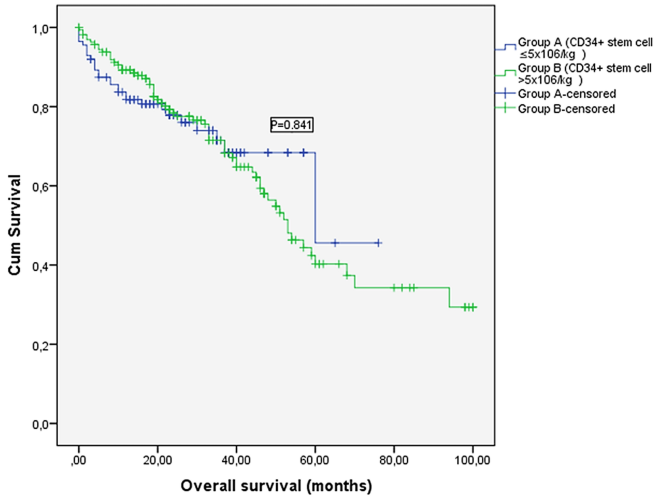

Figure 1. Kaplan Meier curve for overall survival according to the dose of CD34+ stem cells.

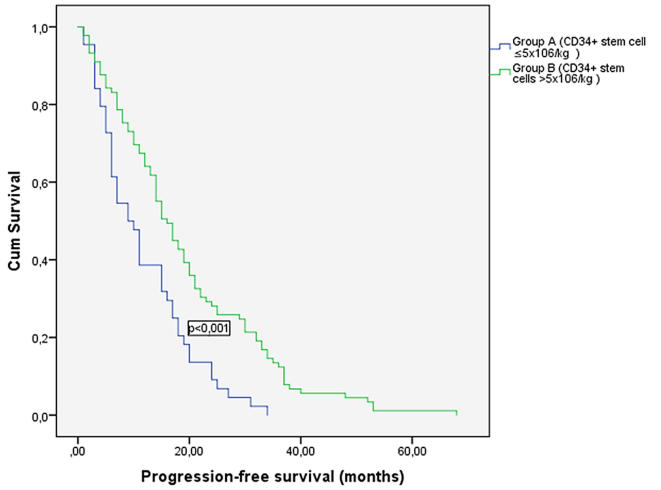

Figure 2. Kaplan Meier curve for progression-free survival according to the dose of CD34+ stem cells.

plus RD (4.6%) and VAD (4.3%). The priory treatment line was 1 in 210 (74.5), 2 in 66 (23.4%) and 3 in 6 (2.1%) patients. IMiD based therapy was used in 40 (14.2%) patients before the ASCT, 10 (25%) of them was received more than 4 cure. The median the time from diagnosis to ASCT was 4 (1-125) months. The median infused CD34+ stem cell dose was 6.33x10^6/kg (1.70 x10^6/kg-40.76 x10^6/kg) in all cohort. In group A and B, the median infused CD34+ stem cell dose was 3.98 x10^6/kg (1.70 x10^6/kg -4.98 x10^6/kg) and 9.6 x10^6/kg (5.1 x10^6/kg - 40.76 x10^6/kg), respectively. The age, gender, M protein type, the stage at the time of diagnosis, the prior therapy line, and prior therapy associated with IMiD were statistically similar in both groups (p>.05). The response status at the time of ASCT and induction treatment were statically significant difference in 2 groups (p=.01 and p=.001, respectively). The number of patients who received VAD monotherapy and VAD plus VCD was higher in group B than in group A. The clinical and demographic characteristics of patients at the time of transplantation in each group are summarized in Table 1.

Table 1. The clinical and demographic characteristics of patients at the time of transplantation in both groups.

Variables	Group A (%)	Group B (%)	p value
Gender			
Male	74 (62.7)	95 (57.9)	.461
Female	44 (37.63	69 (42.1)	
The mean age, years*	58.76±8.4	57.8±9.2	.457
M protein type			
IgA	19 (17.3)	31 (19.1)	.684
IgG	69 (62.7)	94 (58.0)	
Kappa	8 (7.3)	16 (9.9)	
Lambda	14 (12.0)	19 (11.7)	
Others	0	2 (1.2)	
Stage			
ISS 1	12 (12.0)	32 (21.8)	.071
ISS 2	44 (44.0)	67 (45.6)	
ISS 3	44 (44.0)	48 (32.7)	
Disease status**			
CR	36 (32.1)^a	81 (49.7)^b	.010
VGPR	66 (58.9)^a	67 (41.1)^b	
PR	10 (8.9)^a	15 (9.2)^a	
Number of prior therapy line			.562
1	87 (77.7)	118(72.0)	
2	23 (20.5)	42(25.6)	
3	2 (1.8)	4(2.4)	
Induction therapy**			
VAD	0 (0.0)^a	12 (7.9)^b	<.001
VAD+VCD	4 (4.0)^a	26 (17.1)^b	
VCD	86 (86.0)^a	104 (68.4)^b	
VCD+VRD	10 (10.0)^a	10 (6.6)^a	
Prior IMiD therapy			
Yes	21(18.8)	19(11.6)	.117
No	91(81.3)	145(88.4)	
Number of IMiD cure			
≤4	16 (76.2)	14 (73.7)	.999
>5	5 (23.8)	5 (26.3)	
The median time to ASCT from diagnosis, months	4 (1-58)	4 (2-125)	.835

Abbreviations: CR; complete response, VGPR; very good partial response, PR; partial response, ISS; International staging system, VAD; vincristine plus doxorubicin A plus dexamethasone, VCD; bortezomib plus cyclophosphamide plus dexamethasone, VRD; bortezomib plus lenalidomide plus dexamethasone, IMiD; immunomodulatory drugs. *mean ± standard deviation **Bonferroni method: ^{a,b}; Values without a common superscript letter in the same row significantly differ.

The outcomes of transplantation

In all cohorts, the median neutrophil and platelet engraftment durations were 11 days (11.00-28.00) and 11.5 (6.00-

40.00) days. Febrile neutropenia occurred in 153 (54.3%) patients, and the median hospitalization time after ASCT was 15 days (6-83). The median neutrophil engraftment was 12 (7-26) days in the A group and 11 (6-28) days in the B group. The median platelet engraftment was 12 (6-40) and 11 (6-29) days in group B. There were statically significant differences in both groups for neutrophil and platelet engraftment time (p=.001 and .002, respectively). The median hospitalization time was 16 (10-53) days and 15 (6-83) days in groups A and B, respectively. The two groups' hospitalization time was significantly different (p<.012). The outcomes of ASCT according to the CD34+ stem cell dose was shown in Table 2.

Survival analysis

At the mean follow-up of 58.9±3.1 months, 1-year, 2 years, and 5 years OS rate were 86.1%, 77.9% and 46.3%, respectively in all cohorts. The 1-year, 2 years, and 5 years PFS were 57%, 23.7% and 0.7%, respectively in all patients. During the follow-up time, 32.2% patients died and the rate of TRM 5.3% at first 100 days in all patients.

The mean OS was 53.1±4.2 months in group A and 58.2±3.5 in group B which was not statistically significant difference (p=.841) (Figure 1). The mean PFS was 11.8±1.3 months in group A and 19.1±1.4 months in group B which was statistically significant difference in 2 groups (p<.001) (Figure 2). In univariate analyses, the febrile neutropenia status, the infused dose of CD 34+ stem cell, and the duration of neutrophil engraftment were detected as prognostic factors on PFS. The presence of febrile neutropenia (HR: 1.46 95%CI: 1.02-2.09, p=.039) and low CD34+ stem cell dose (≤5x10^6/kg) (HR: 1.90 95% CI: 1.29-2.79, p=.001) were adverse prognostic impact on PFS in multivariate analyses (Table 3).

Table 2. The outcomes of ASCT according to the dose of CD34+ stem cell dose.

Variables	Group A (%)	Group B (%)	p value
The median neutrophil engraftment time, day (min-max)	12 (1.0-26.0)	11 (6.0-28.0)	.001
The neutrophil engraftment times			.018
≤11 days	53 (47.7)	102(62.6)	
>11 days	58 (52.3)	61(37.4)	
The median platelet engraftment time, day (min-max)	12.00 (6.0-40.0)	11.00(6.0-29.0)	.002
The neutrophil engraftment times			.010
≤11 days	46 (41.4)	94 (57.7)	
>11 days	65 (58.6)	61 (37.4)	
The median hospitalization time, day	16 (10-53)	15 (6-83)	.012
The febrile neutropenia			
Yes	65 (58)	83 (50.6)	.269
No	47 (42)	81 (49.4)	
Transplant related mortality (first 100 day)			.175
Yes	9 (8)	6 (3.7)	
No	103 (92)	158 (96.3)	
The mean overall survival, months*	53.1±4.2	58.2±3.5	.841
The mean progression-free survival, months*	11.8±1.3	19.1±1.4	<.001

* mean ± standard deviation.

Discussion

High dose chemotherapy followed by ASCT has become the standard treatment modality in the treatment of MM. The dose of CD34+ stem cells is one of the most important factors affecting the success of transplantation results [6]. In this study, we analyzed the effect of CD34+ stem cell dose on the short and long-term outcomes of ASCT in patients with MM. In our study, it was observed that neutrophil engraftment time, platelet engraftment time and hospitalization time were statistically significantly shorter in the group with high CD34+ stem cell count (p=.001, p=.01 and p=.012, respectively). In a retrospective study by Tricot G et al. in 225 multiple myeloma patients in 2015, the statistically significant association was reported between the number of CD34+ stem cells and the recovery of both granulocytes (p = .0001) and platelets (P = .0001) [15]. Klaus J et al. divided 508 multiple myeloma patients into 2 groups as CD34+ count ≥6.50×10^6 and CD34+ <3.00×10^6. Leukocyte and platelet engraftment times were statistically shorter in the first group (p<.001). The dose of transplanted CD34+ stem cells could not be shown to have a significant effect on transplant-related death, overall survival, or CR/PR rates at 100 days. It has been reported that a high amount of CD34+ stem cell count accelerates hematological recovery and shortens the hospitalization time [9]. Celikzencir et al. investigated the effects of CD34+ and CD34+CD133+ stem cell ratios on mobilization and clinical outcomes. A statistically significant relationship was reported between CD34 + stem cell numbers / kg and neutrophil engraftment times (median CD34 + stem cell counts: 4.55x10^6/ kg, neutrophil engraftment time (days) median: 11 days (p <0.001). Additionally, they reported that the ideal amount of stem cells in adult patients was 4.57 x10^6/ kg in ASCT [16].

In the retrospective study by Karakulak EA et al. in which two groups were compared in terms of OS and engraftment times according to the number of CD34+ stem cells. A negative correlation was reported between CD34+ stem cell counts and neutrophil and platelet engraftment times (p<.001). A statistically significant positive correlation was reported between the two groups in terms of OS in the group with CD34+ stem cell count ≥5 × 10^6 /kg of CD34+ (p = .009) [17]. In our study, the mean OS was 53.1±4.2 months in group A and 58.2±3.5 in group B which was not statistically significant difference (p=.841).

Sarici A et al. divided 223 multiple myeloma patients into two groups, group A: cyclophosphamide plus filgrastim, group B: filgrastim alone, according to the pre-ASCT mo-

Table 3. The univariate and multivariate analyses for progression-free survival.

	Univariate analyses			Multivariate analyses		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Gender	1.279	0.893-1.832	.180			
Age	1.017	0.999-1.035	.069			
ISS 1			.347			
ISS 2	1.273	0.766-2.115	.351			
ISS 3	1.457	0.877-2.421	.146			
Response status	1.252	0.889-1.763	.199			
Number of prior therapy line						
1			.581			
2	0.952	0.637-1.423	.810			
3	1.793	0.566-5.684	.321			
Prior IMiD therapy (Yes vs No)	1.249	0.700-2.229	.451			
Febrile neutropenia (Yes vs No)	1.470	1.031-2.096	.033	1.464	1.020-2.099	.039
CD 34+ stem cell dose ($\leq 5x10^6$/kg vs $>5x10^6$/kg)	1.946	1.330-2.846	.001	1.900	1.291-2.796	.001
Neutrophil engraftment day ($\leq$11 vs >11)	1.459	1.013-2.099	.042	1.230	0.842-1.795	.285
Platelet engraftment day ($\leq$11 vs >11)	1.348	0.958-1.898	.087			

Abbreviations: ISS; International staging system, IMiD; immunomodulatory drugs.

bilization regimen. The number of CD34+ stem cell collected in group A was reported to be significantly higher. Despite higher CD34+ stem cell counts, patients in group A had a higher risk of developing febrile neutropenia during mobilization and hospitalization times compared to patients in group B ($p<.001$) [18]. In our study, the median hospitalization time was 16 (10-53) days and 15 (6-83) days in group A and B, respectively. The hospitalization time was statistically significantly different in two groups ($p<.012$).

In the study reported by Zannetti BA et al. they divided the patients into 3 groups as low-dose cyclophosphamide, intermediate-dose cyclophosphamide and only G-CSF in the pre-ASCT mobilization regimen. Although the amount of CD34+ stem cell collected at low doses was not significantly different between the three groups, it was statistically less in the $\geq 8 \times 106$/kg group in the G-CSF group ($p<.001$). Concomitant total CD34+ stem cells collected $\times 10^6$/kg, the median number was statistically lower in the group given only G-CSF ($p<.001$). A statistically significant increase in CD34+ stem cell count was observed in the cyclophosphamide received groups. However, higher febrile neutropenia (16.3%) and need for hospitalization (20%) were reported in the intermediate dose cyclophosphamide group [19]. In our study, febrile neutropenia was occurred in 153 (54.3%) patients and the median hospitalization time after ASCT was 15 days (6-83).

A surprising result was reported in the study reported by Lebel E et al. At a mean follow-up of 74 months, PFS of 33.7 months ($p=0.038$) was detected for the group <8 versus a low PFS of 24.1 months in the group with $\geq 8x10^6$/kg CD34+ stem cells, while no difference was found in OS ($p=.612$) [20]. In our study, the mean PFS was 11.8±1.3 months in group A and 19.1±1.4 months in group B which was statistically significant difference in 2 groups ($p<.001$).

Limitations

Limiting features of our study which can be listed as being retrospective, relatively low number of patients, and short follow-up period of the patients. Multicenter, prospective studies should be carried out to define especially for the upper limit and for the lower limit of stem cell doses.

Conclusion

Infusion of $>5x10^6$/kg CD34+ stem cells (median dose 9.6 $x10^6$/kg) may have a favorable effect on short-term outcomes of transplantation, including short-term neutrophil engraftment, short-term platelet engraftment, and short-term hospitalization. Additionally, progression-free survival may be positively affected by high dose, but upper limit should be defined by new study.

Ethical approval

The study was approved by Inonu University Ethical Committee (approved number: 2021/2755 and date: 30.11.2021).

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