What are the Factors Affecting Survival After Autologous Stem Cell Transplantation in Patients with Multiple Myeloma?

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Abstract

Introduction: High-dose chemotherapy (HDC) and autologous stem cell transplantation(ASCT) still remains in the treatment of myeloma patients even during the period of new agents. **Materials and Methods:** We analysed the prognostic affect of pretransplant characteristics and transplant modalities on response, in 150 autologous transplant of 144 multiple myeloma (MM) patients who were transplanted in our centre between 2008 to 2017. We evaluated the affect of age, type of MM, previous treatment regimens, status pre and postfrom transplantation, time of ASCT, neutrophil and platelet engraftmant days, dose of reinfused CD34+ cells, plasma cell infiltration, international staging system(ISS) and Durie -Salmon stage at diagnosis. We examined the affect of these status on overall survival(OS) and eventfree survival(EFS). **Results:** The median OS and EFS after transplanation were 41 and 28 months, respectively. Median OS after the diagnosis was 57 months. Transplant-related mortality was 3,3%. We found that the lower β2- microglobulin levels,lower ISS stage,lower plasma cell infiltration, achievement good responds at the $+100^{th}$ day of post transplant were statistically significant independent predictor factors for longer EFS and OS. When the patients were given chemotherapy regimen with bortezomib before transplantation, these patients were seen to be a better response rate. There was showed a relationship between the using of bortezomib before transplantation with EFS($P = 0.017$), but there was no relationship with OS. **Conclusions:** Our analysis confirms HDCT-ASCT as an effective and safe therapeutic strategy in multiple myeloma patients. This results were independent of age, first line treatment regimens and renal insufficiency. Patients with a high ISS stage were found to have shorter survival($P = 0.002$). However, the EFS and OS were longer of the patients whose have good response at the 100th day of transplantation($P = 0,002$, $P = 0,02$).

Keywords: Autologous stem cell transplantation, event-free survival, multiple myeloma, overall survival

INTRODUCTION

Multiple myeloma (MM) is the primary type of hematological malignancy originating from the plasma cells. MM is an incurable disease. The traditional chemotherapeutic regimens such as melphalan and prednisone have been recommended treatment for patients with MM for many years. Only a very limited portion of patients achieve a complete response (CR) with the traditional therapy, with a median survival of approximately 3 years. During the past decade, the high-dose chemotherapy (HDC) and autologous stem cell transplant (ASCT) have been used for myeloma patients.[1,2] Randomized and nonrandomized studies have suggested an association between ASCT results and high-dose melphalan with higher remission rates and prolonged survival. The positive effect of ASCT was particularly evident in a subgroup of patients with favorable characteristics at the time of diagnosis who achieved CR after transplantation. It also offers benefit in patients with resistant myeloma disease.[3-6] As part of the present study, we have evaluated the results of ASCT of the patients with MM. We examined the prognostic influence

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How to cite this article: Solmaz S, Acar C, Seyhanlı A, Sevindik OG, Piskin O, Ozcan MA, *et al*. What are the factors affecting survival after autologous stem cell transplantation in patients with multiple myeloma? Indian J Transplant 2020;14:57-62.

Access this article online

Quick Response Code:

Website:
www.ijtonline.in

DOI:
10.4103/ijot.ijot_15_19

Table 1: Baseline patient characteristics

	n (%)
Patients	144 (100)
Age (years), median (range)	55 (26-70)
Gender	
Male	92 (61.3)
Female	58 (38.7)
Type	
IgG	85 (56.6)
IgA	32 (21.4)
Light chain	24 (16)
Nonsecretory	2 (1.3)
Multiple plasmacytoma	7 (4.7)
ISS stage	
I	45 (30)
II	52 (34.7)
III	64 (33.3)
Not evaluated	3 (2)
Durie-Salmon stage	
IA	18 (12)
IIA	32 (21.3)
IIB	5 (3.3)
IIIA	65 (43.4)
IIIB	27 (18)
Not evaluated	3 (2)
First-line treatment	
VAD	110 (73.3)
Cyclophosphamide-dexamethasone	30 (20)
Bortezomib-dexamethasone	10 (6.7)
Mobilization regimens	
Cyclophosphamide/G-CSF	134 (89.3)
Plerixafor/G-CSF	9 (6)
G-CSF	7 (4.7)
Conditioning (mg/m²)	
Melphalan 200	125 (83.3)
Melphalan 140	25 (16.7)
Death	38 (25)

ISS=International staging system,
VAD=Vincristine-adriablastin-dexamethasone,
G-CSF=Granulocyte-colony-stimulating factor

of pretransplant characteristics and transplant modalities, retrospectively.

MATERIALS AND METHODS

Study design

Between August 2008 and September 2017, a total of 144 patients with MM underwent ASCT at Dokuz Eylul University Hospital, Department of Hematology. The data were collected electronically and from the patient files in medical archives, retrospectively. Baseline patient characteristics are shown in Table 1. The majority of the patients had one or two lines of prior pretransplantation chemotherapy (CT) (range: 1–3) (vincristine-adriablastin-dexamethasone [VAD] therapy, bortezomib-dexamethasone, cyclophosphamide-dexamethasone, and lenalidomide-dexamethasone therapies). The first-line treatment regimens are shown in Table 1. At the

time of transplant, 11.3% of patients were in CR, 56.7% (*n*: 86) of them were in a very good partial response (VGPR), 29.3% (*n*: 43) of them presented a partial response (PR), and 2.7% (*n*: 4) had refractory or progressive disease. However, a secondary ASCT was planned in six patients due to late relapse of the disease. The median time interval between diagnosis and transplant was 13 months (range: 3–117 months).

Hematopoietic stem cells were mobilized using intravenous cyclophosphamide and granulocyte-colony-stimulating factor (G-CSF), only G-CSF and plerixafor-GCSF. Peripheral blood stem cells were collected with 1–4 apheresis procedure (mean: 1.7) following mobilization regimens. Apheresis was initiated on the recovery of CD34+ cells to 10>µL. The minimum goal CD34+ stem cell dose for the collection was $>2 \times 10^6$ CD34/kg for each autologous transplantation.

The conditioning regimen for hematopoietic cell transplantation (HCT) consisted of melphalan 140–200 mg/m². Melphalan was given at a dose of 200 mg/m² in 125 patients (83.3%) and a reduced dose of 140 mg/m² in 25 patients (16.7%) because of reduced creatinine clearance (<50 ml/min).

The International Myeloma Working Group (IMWG) uniform response criteria (2006) were applied for the evaluation of disease status. For the aim of analysis, patients who achieved a CR, very good partial response (VGPR), and partial response (PR) were regarded to have chemosensitive disease. Patients with the progressive or refractory disease before the transplant were described to have a chemoresistant disease. Transplant-related mortality (TRM) was taken to be the death for any reason other than relapsed disease or progression occurring within the first 100 days post-ASCT. Relapse or progression was defined as the worsening of the disease status at the time of transplant and meeting the IMWG criteria for progressive disease.[7] Event-free survival (EFS) was defined from the time of transplant until relapse or progression. Overall survival (OS) was measured from the date of transplant to death due to any reason. However, OS from the time of diagnosis was also evaluated, and the OS analysis considered death from any reason as an event.

Procedures followed were in accordance with ethical standards. The study involves retrospective analysis of data and there was no human intervention.

The study used anonymized data from registries authorized by the regional ethics committees for the respective transplant center.

Statistical analysis

Descriptive statistics were used for baseline characteristics, transplant-related factors, and posttransplant outcomes. Differences in the distribution of variables between patient subsets were analyzed using Pearson's Chi-square test/Correlation test/Student's *t*-test. The response rate of the patients was assessed using the McNemar test for paired categorical variables. OS and EFS were estimated using the

Kaplan–Meier method, log-rank test, which was employed to determine differences in survival and events. The median follow-up time was calculated using the Kaplan–Meier method for potential follow-up. The Cox regression method was used to identify significant predictors of survival outcome. All statistical analyses were two-sided tests with 0.05 as the critical level of statistical significance, and P values were reported.

RESULTS

We analyzed a total of 150 autologous transplantation of 144 MM patients between August 2008 and September 2017 retrospectively. The median age was 55 ± 8.5 (26–70) with a 92/58 male/female ratio. The median number of the infused CD34+ cells was 7.5×10^6/kg (1.5–31×10^6/kg). A total of 122 patients received $>5 \times 10^6$ CD34+ cells/kg, as 28 patients received $<5 \times 10^6$ CD34+ cells/kg. There was no relationship between the basic characteristics of the patients at diagnosis and the number of mobilization day. The median time to platelet engraftment was 13.9 days (9–30), whereas the median time to neutrophil engraftment day was 11.5 days (8–17). The number of infused CD34+ cells and the stage of disease at the transplantation were predictive of the time to neutrophil

Table 2: The status of the disease were pretransplant and on the 100th s of posttransplant

	n (%)
Status of the pretransplant	
CR	17 (11.3)
VGPR	86 (56.7)
PR	43 (29.3)
Progressive/refractory	4 (2.7)
Status of the posttransplant	
CR	59 (39.3)
VGPR	54 (36)
PR	27 (18)
Progressive/refractory	10 (6.7)

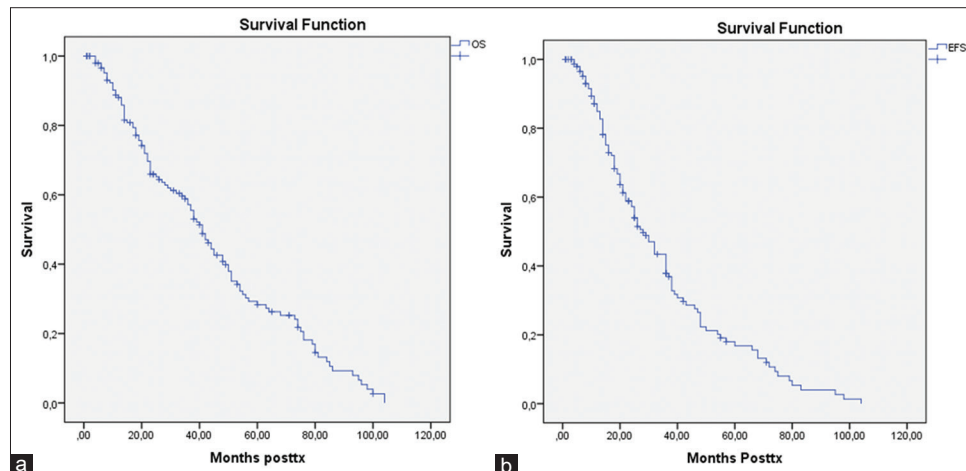CR: Complete response, VGPR: Very good partial response, PR: Partial response

engraftment ($P = 0.0001$, $P = 0.032$), while only the number of infused CD34+ cells was predictive of the platelet engraftment day ($P = 0.006$). However, there was no relationship between the applied conditioning regimen with the neutrophil and platelet engraftment days.

The median follow-up was 52 months (range: 8–132 months). The overall response rate was 93.3%. Remission statuses after the transplant were as follows: CR in 59 patients (39.3%), VGPR in 54 patients (36%), PR in 27 patients (18%), and progressive/refractory disease in ten patients (6.7%) out of 150 patients. The status of the disease pretransplant and on the 100th-day posttransplant is shown in Table 2. The 100th-day TRM was 3.3% (5/150 patients): five patients died of sepsis caused by febrile neutropenia.

The median OS was 41 months, and the median EFS was 28 months, whereas the median survival from diagnosis was 57 months [Figure 1]. The estimated probability of 5-year OS and EFS is 46.7% and 19%, respectively.

The pretransplant status of disease did not significantly affect either EFS or OS ($P = 0.35$, $P = 0.1$). Response to ASCT was correlated with the EFS and OS ($P = 0.001$, $P = 0.04$). Patients who achieved a CR after ASCT had a longer OS and EFS than others (median OS and EFS were 58 months and 49 months, respectively). β_2 microglobulin at diagnosis was a predictive factor. The low levels of β_2 microglobulin (<3 mg/l, 39 patients) had a longer median EFS and OS ($P = 0.08$, $P = 0.028$), international staging system (ISS) was detected at diagnosis. There was a significant correlation between the ISS stage at diagnosis with EFS and OS. Patients with Stage II and III ISS were found to have shorter median EFS and OS ($P = 0.05$, $P = 0.002$) [Figure 2].

The patients with Durie Salmon (DS) Stage 2b and 3b were found to have shorter median survival. However, there was no correlation between the DS stage at diagnosis and OS or EFS ($P = 0.4$, $P = 0.3$). There was a significant correlation between the OS and plasma cells ratio ($P = 0.05$). The median OS for the patients with plasma cells <30% was 69 months

Figure 1: The overall survival (a) and event-free survival times (b) from diagnosis all patients

Solmaz, *et al.*: Factors affecting survival after autologous stem cell transplantation
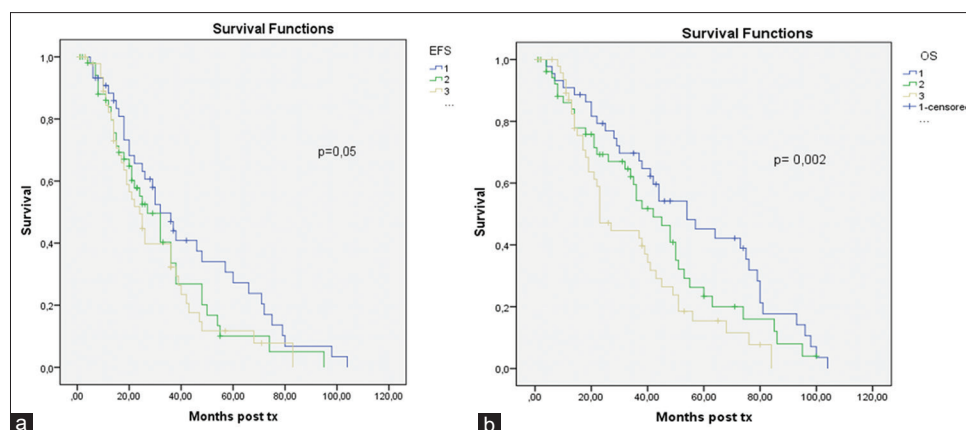

Figure 2: The overall survival (a) and event-free survival times (b) according to the international staging system

versus 57 months for patients with plasma cells >30%. However, there was no statistical significance between EFS and the ratio of plasma cell infiltration (*P* = 0.06), the lower infiltrate of plasma cells at diagnosis was associated with the development of CR and VGPR posttransplant (*P* = 0.001). Age was found to influence neither OS nor EFS. The median OS for patients <60 and ≥60 years was 42 and 40 months (*P* = 0.26). We compared two age groups (one group: <60 vs. ≥60, another group: <60, 60–65 and ≥65) but found no statistical significance regarding the OS and EFS. The median OS for patients <60, 60–65, and ≥65 years was 41, 44, and 36 months (*P* = 0.77), respectively. The time from the diagnosis to transplant was found to influence both EFS and OS (*P* = 0.0001, *P* = 0.021). If this time is short, their survival was longer. The patients who received melphalan (mel) 200 mg/m^2 in the conditioning regimen were found to have a longer median OS (*P* = 0.003) (in the mel 200 mg/m^2: 42 vs. in the mel 140 mg/m^2: 22 months). However, there was no relationship with EFS (*P* = 0.059; 30 vs. 21 months). As the length of hospital stay decreased, the OS and EFS were found to be longer (*P* = 0.007, *P* = 0.04). However, EFS was found longer in women, yet there was no correlation with OS (*P* = 0.019 vs. 0.43).

Patients were divided into two groups. In the first group (*n*: 12), all patients received 2–4 cycles of VAD or cyclophosphamide-dexamethasone CT before ASCT (before the availability of novel drugs). In the second group (*n*: 138), patients received bortezomib/dexamethasone for a median of four (3–6) cycles, after two cycles of VAD, or cyclophosphamide-dexamethasone CT before ASCT. VGPR and CR rates were 50% and 67.3% in only CT induction and bortezomib-CT induction groups, respectively. Overall response rates, defined as partial remission or better response, were 91% and 98% in only CT induction and bortezomib-CT induction groups, respectively (*P* = 0.26). Overall response rates after transplantation, defined as partial remission or better response, were 75% and 95% in only CT induction and bortezomib-CT induction groups, respectively (*P* = 0,029). In conclusion, the patients who received an addition of bortezomib to CT at the pretransplantation seems to have a better response rate probably. There was a relationship between the pretransplantation use

of bortezomib with EFS (*P* = 0.017); however, there was no relationship with OS (*P* = 0.6). While the EFS of the patients receiving bortezomib before the transplantation was 29 months, the EFS of the other patients was 14 months.

The type of disease, levels of albumin and creatinine at the diagnosis, the neutrophil and platelet engraftment days, and the infused CD34+ cells dose did not affect either OS or EFS.

DISCUSSION

Although novel treatment regimens have changed the treatment landscape of MM patients throughout the past decade, HDM and ASCT have so far remained an integral part of the myeloma treatment. However, ASCT is not curative, and most patients relapse in a median time of 3 years. In this study, we present the results of a retrospective analysis of patients with MM, who were autologous transplantation in our center. The posttransplant median OS and EFS were 41 and 28 months, respectively, while the median survival from diagnosis was 57 months; our results are compared with the data reported in the relevant literature. Although the median OS from diagnosis is almost 5 years, in a study by Terpos *et al.*, the median OS and EFS after transplant was found 50 and 21 months. However, another study showed that the median OS and EFS were 61.7 and 35.4 months, respectively.[8,9] The 100-day TRM was 3.3% in our study. Our results are similar to the survival rates reported by other studies; median EFS, median OS, and TRM ranged 25–42 months, 47.8–67 months, and 3%–7%, respectively, in different studies.[3-5,10]

The status of disease before autologous transplantation was a prognostic factor for OS and EFS in the literature. The patients with refractory disease had a better response after transplantation.[11,12] However, in this study, the status of disease before transplantation did not significantly affect either EFS or OS. Our result was driven by a small number of patients with refractory disease. This result was also found in the study by Terpos *et al.*[13] However, the posttransplantation status of disease was strongly associated with both EFS and OS in our study. Patients who achieved a CR have a longer OS and EFS than others. Our results confirm the results reported by other studies. The response that achieves a CR after an autologous transplant has an important on EFS and OS.[8,13,14]

Just as Terpos' study, we also found that the low infiltrate of plasma cells at the time of diagnosis predicts improved EFS and OS.[8] This was associated with the achievement of CR and VGPR posttransplant. Another study showed that pretransplant levels of paraprotein and the plasma cell infiltration of the bone marrow were associated with the achievement of CR after transplantation.[15] Furthermore, β_2 microglobulin levels, DS stage, and ISS stage at diagnosis were associated with OS and EFS in the literature.[8,16] Yet another study showed that there was no correlation between β_2 microglobulin levels and survival.[16,17] In this study, low β_2 microglobulin at diagnosis indicated improving EFS and OS. Patients with the ISS Stage II and III were found to have shorter median EFS and OS. However, there was no correlation between the DS stage at diagnosis with OS and EFS.

Nevertheless, the conditioning regimen is not standardized. As to which one is the less toxic and the most effective regimen, this is still an open question. In a recent randomized study, MEL140-TBI was as effective as MEL200 alone but more toxic. The authors concluded that MEL200 was less toxic and at least as effective as MEL140-TBI, considering MEL200 to be the standard conditioning regimen. There is also some evidence that patients treated with melphalan 200 mg/m^2 conditioning have a longer OS.[18] A single MEL-based auto-SCT following older induction regimens typically produce a CR in 20%–40% of patients and a median progression-free survival time of 2.5–4 years.[19] In this study, many patients received melphalan 200 mg/m^2 as a conditioning regimen. Only 25 patients had melphalan 140 mg/m^2. The patients that were administered melphalan 200 mg/m^2 have had a longer median OS.

Advanced age has been shown to be a poor prognostic factor in many trials using HDC and ASCT. Moreover, another study showed that age at a cutoff value of 60 years predicts survival independently.[11,20] We evaluated OS and EFS using 60 years as a cutoff point and found no difference in survival between the results of the groups. Reece *et al*. also found that EFS and OS were similar for myeloma patients younger than 60 years and older than 60 years who underwent an ASCT.[21] ASCT was also summarized in older myeloma patients, and the survival was reduced in the ≥70 age group. However, this analysis was based on overall mortality.[22,23] When we compared the results of OS and EFS after ASCT between the three different age groups, namely <60 years, 60–64 years, and ≥65 years, no significant difference was found in our study. Our data showed that patients over the age of 65 years can benefit from ASCT in patients with MM.

The optimal timing of HCT and ASCT is not clear. Yet based on our results, when this time was short, their survival was longer. There was no difference in EFS and OS between early or late timing of transplant in the literature.[8,24]

There were no well-structured studies related to the effect of the first-line treatment regimens on the results of ASCT in myeloma patients. In our study, we found no difference regarding survival between patients who received VAD as the first-line treatment regimen compared with others. This result was similar in other studies as well.[8,13] However, the patients with the addition of bortezomib to CT at the pretransplantation appear to have a better response rate. There was a relationship between the pretransplant use of bortezomib with the EFS. The importance of ASCT as a part of the first-line of therapy in MM has also been confirmed in the era of novel drugs.[25]

Conclusions

We have shown that HDC with ASCT is an effective and safe treatment in patients with myeloma. The outcome of ASCT is independent of age, first-line treatment regimens, or renal insufficiency. Response to ASCT, plasma cell infiltration at diagnosis, β_2 microglobulin levels and ISS stage at diagnosis, and the time from diagnosis to ASCT predict for both OS and EFS, while the conditioning regimen predicts for OS. Finally, the addition of bortezomib to CT at the pretransplantation significantly correlated with EFS.

Financial support and sponsorship

Conflicts of interest
There are no conflicts of interest.

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