

Retrospective analysis of autologous stem cell transplantation outcomes in multiple myeloma patients with renal insufficiency

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Abstract

Aim: The most seen complication of multiple myeloma (MM) is renal insufficiency (RI). Although MM is known as one of the causes of reversible end-stage renal disease, these patients are usually not suitable for autologous stem cell transplantation (ASCT). We aimed in this study to reveal the clinical course of MM patients with renal insufficiency that underwent ASCT.

Materials and Methods: We included 25 MM patients with RI who has undergone ASCT in this study. Creatinine levels more than 2 mg/dL was defined as renal insufficiency at the time of diagnosis. For survival analysis, we included patients with a minimum 100 days post-transplantation follow-up.

Results: Median age was 56.6±7.9 (42-65) years. Melphalan was given 140 mg/m². Nine patients (36%) required dialysis at the time of diagnosis. Six patients became dialysis-free with induction therapy. After ASCT, none of the patients needed dialysis. Cox regression analysis showed a significant increase in disease-free survival (DFS) and overall survival (OS) times compared to patients with very good partial response in patients with complete response on the 100th day of ASCT (for DFS; 15.7 months vs 63.7 months, p=0.009 and for OS; 37.9 months vs 97.3 months p=0.01, respectively).

Conclusion: There are studies showing that ASCT performed with reduced dose of melphalan is a renal protective and effective method in patients with renal impairment. Our study confirms this thesis, as well as emphasizing the significant effect of CR on DFS and OS on the 100th day after transplantation in these patients.

Keywords: Autologous stem cell transplantation; multiple myeloma, renal insufficiency

INTRODUCTION

Ten percent of all hematologic malignancies constitute Multiple myeloma (MM). One of the most fearful complication of MM is renal insufficiency (RI) because of high risk of early mortality (1). Thirty percent of MM patients have RI at the time of diagnosis. There are many additional factors can cause renal impairment such as dehydration, hypercalcemia, hyperuricemia, infection and nonsteroidal anti-inflammatory drugs (NSAIDs). On the other hand, main mechanism of RI in MM results from excessive monoclonal free light chain (FLC) production that has also a possible cause to severe RI (2). Dialysis need is present at about 5% of patients with MM with severe RI (3-5).

Over the last few years, the research of the MM field has made major progress and numerous fascinating

novel drugs have being introduced. Despite the recent registration of these drugs, for eligible patients, such as young patients e.g., autologous stem cell transplantation (ASCT) still remains the standard method. There are numerous factors that can impact on the outcomes of ASCT such as disease phase, elevated β_2 microglobulin and lactate dehydrogenase levels (LDH), presence of renal impairment and cytogenetic abnormalities (6-8). Especially, presence of RI is associated with advanced stage disease, increased early mortality rates and hesitancy for use of high dose chemotherapy around clinicians (9). Moreover, there is no agreement if ASCT can completely abolish the negative effects of RI on the prognosis in patients with MM. From this point of view, the aim of our study is to share our experience on MM patients with underlying RI who received ASCT.

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MATERIALS and METHODS

Twenty-five myeloma patients who had 2 mg/dL or higher creatinine levels at the time of diagnosis whom underwent ASCT at the Eskisehir University Hospital Stem Cell Transplantation Unit between June 2008 and November 2013 were included in our study. All study subjects had a calculated creatinine clearance <60 mL/min at baseline. The tenets of Declaration of Helsinki were followed. Ethics committee approval was obtained from Eskişehir Osmangazi University Faculty of Medicine Ethics Committee with decision number 07, dated 09/01/2020, for this study. Patient records were analyzed retrospectively. Clinical and laboratory parameters such as age, sex, complete blood counts, creatinine and LDH levels, disease stage, and treatment response and dialysis requirement were recorded. All patients received Granulocyte colony stimulating factor (G-CSF) was used in order to mobilize hematopoietic stem cells into the peripheral blood for apheresis. Melphalan (140 mg/m²/day) was given over 1 or 2 days for the conditioning regimen. International Myeloma Working Group uniform response criteria was used to evaluate the response and progression rate (10). A neutrophil count of > 0.5x10⁹/L and a platelet count of at least >20x10⁹/L for consecutive 3 days was considered as hematopoietic engraftment.

Statistical Analysis

Statistical analyses were done by using commercially available software (SPSS version 20.0 Chicago, IL, USA). Median (range) depiction was used for data showing non-normal distribution during comparison (Mann-Whitney test). For the categorical data sets, Fisher exact test was used. Univariate Cox-regression analysis was used to analyze association between the survival time of patients and predictor variables. Overall survival (OS) analysis was performed by Kaplan-Meier curves (OS). P < 0.05 was accepted as the statistically significance level.

RESULTS

The median age for the study subjects was 56.6 (48-65) years. Patient characteristics are described in Table 1. Approximately half of the patients were kappa light chain multiple myeloma and had Durie Salmon stage IIB disease. Peripheral blood hematopoietic stem cells were mobilized by G-CSF alone (n=19 patients) or by G-CSF following chemotherapy (n=6 patients). The median count of collected CD34⁺ cells was 7.28 (range, 3.4-28.7x10⁶/kg). The median creatinine levels at the time of diagnosis, before transplantation and 100th days after transplantation were 4.3, 1.7 and 1.5 mg/dL respectively. Nine patients (36%) were dialysis-dependent at the diagnosis. Three patients still needed dialysis before transplantation in which primary cause for RI was MM. After transplantation, it was observed that all 3 patients became dialysis-free.

Table 1. Demographic characteristics of multiple myeloma patients with renal insufficiency

	Patients (n=25)
Age (year)	56.6 (48-65)
Sex (Female/Male) (%)	10/15 (40/60)
Type of Multiple myeloma (%)	Kappa light chain: 11 (44) Lambda light chain: 5 (20) IgG: 7 (28) IgA: 2 (8)
Durie Salmon Stage (%)	IB: 3 (12) IIB: 14 (56) IIIB: 8 (32)
ECOG performans status (%)	Grade 0: 2 (8) Grade 1: 7 (28) Grade 2: 12 (48) Grade 3: 4 (16)
Co-morbid diseases (%)*	Hypertension: 8 (32) Diabetes Mellitus: 5 (20) Coronary artery disease: 2 (8) Hepatosteatosi: 4 (16) Rheumatoid arthritis: 1 (4)
Creatinine levels at the time of diagnosis (mg/dl) (median)	4.3 (2-8.8)
Creatinine levels at the time of ASCT (mg/dl) (median)	1.73 (0.4-4.4)
Creatinine levels at the time 100 th day of ASCT (mg/dl) (median)	1.58 (0.3-3.9)
Dialysis requirement (at the time of diagnosis / at the time of ASCT) (n)	9 / 3
Serum calcium level (mg/dl)	11.6 (8.3-14.5)
Serum lactate dehydrogenase level (IU/ml)	424.6 (222-623)
Hemoglobin (gr/dl)	9.5 (5.4-13)
Platelet count (x10 ³ /uL)	159 (55-289)
Pre-transplant treatment regimens**	VAD (14 patients) VAD +VD (7 patients) VAD + VCD (4 patients)
Time to ASCT (months)	5.2 (3.8-7.1)

* None of the patients had chronic liver disease or heart failure; **VAD: Vincristine, Adriamycin, Dexamethasone; VD: Bortezomib, Dexamethasone; VCD: Bortezomib, Cyclophosphamide, Dexamethasone; ASCT: Autologous stem cell transplantation

Clinical and laboratory parameters affecting DFS and total survival were shown in Table 2. Patients categorized into 3 groups according to pre transplant and post-transplant 100th day remission status as patients in complete remission (CR), very good partial remission (VGPR) and partial remission/progression (PR). Pre-transplant rates of CR, VGPR and PR were 64% (n=16), 12% (n=3) and 24% (n=6), respectively. Median follow-up_in_surviving_patients_was_32_months (range: 18–106).

At the post-transplant 100th day, 15 patients (63.7%) achieved CR and 10 patients (15.3) reached VGPR. Disease-free survival (DFS) and overall survival (OS) were found to be statistically significantly higher in

patients with CR compared with VGPR. Time to relapse was found to be 4.2 times fewer (63.7 months vs 15.7 months) in patients with CR compared to patients with VGPR (p=0.009) (Figure 1). Likewise, overall survival rates were 2.6 times greater (97.3 months vs 37.9 months) in patients with CR compared to patients with VGPR (p=0.01) (Figure 2). Although not statistically significant, presence of pre-transplant CR status, light chain myeloma type, and the stage IIB disease (compared to stage IIIB), were the factors that was related with longer DFS and OS periods. No signs of severe drug toxicity or life-threatening febrile neutropenia were observed in patients.

Table 2. Clinical and laboratory parameters affecting disease-free survival and overall survival in multiple myeloma cases with renal insufficiency						
	Disease free survival (DFS) (months)	Hazard ratio for DFS	P value	Overall survival (OS) (months)	Hazard ratio for OS	P value
Remission status before ASCT	CR: 54.9	VGPR-CR: 1.8	0.187	CR: 86.5	VGPR-CR: 4.0	0.066
	VGPR: 20.5			VGPR: 44.2		
	PR: 14.6	PR-CR: 3.2	PR: 27.3	VGPR-CR: 4.9	0.001	
Remission status at the 100 th day of ASCT	CR: 63.7	VGPR-CR: 4.2	0.004	CR: 97.3	VGPR-CR: 14.8	
	VGPR: 15.7			VGPR: 37.9		
Type of Multiple myeloma	Kappa light chain: 48.6	Lambda light chain-Kappa light chain:0.7	0.498	Kappa light chain:72.2	Lambda light chain-Kappa light chain: 0.7	0.304
	Lambda light chain: 43.2			Lambda light chain: 53.7		
	IgG: 14.5	IgG-Kappa light chain: 1.8	IgG: 58.3	IgG-Kappa light chain: 1.3		
	IgA: 14.4	IgA-Kappa light chain :2.3	IgA: 26	IgA-Kappa light chain: 4		
Durie Salmon Stage	IIB: 35.2	IIB-IIB: 2.3	0.083	IIB: 57.6	IIB-IIIIB: 1.4	0.575
	IIIIB:16.6			IIIIB: 37.6		

CR: Complete response, VGPR: Very good partial response, PR: Partial response/Progression, ASCT: Autologous stem cell transplantation

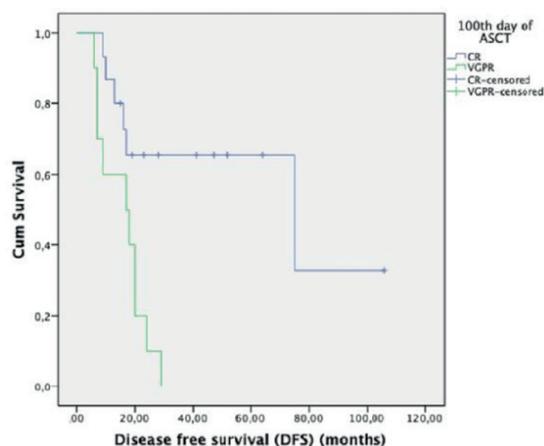


Figure 1. Kaplan Meier survival plot showing the effect of remission status on the 100th day of autologous stem cell transplantation on disease free survival for multiple myeloma patients with renal insufficiency.(CR=complete remission, VGPR:=ery good partial remission)

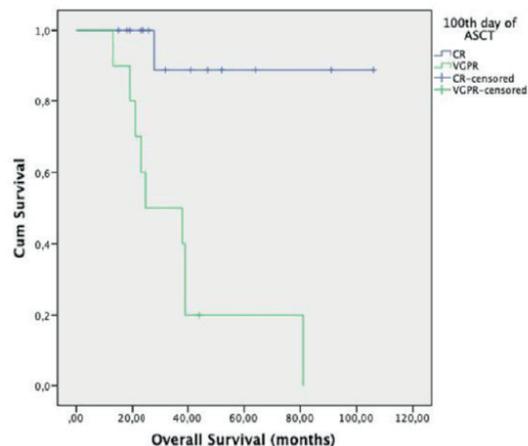


Figure 2. The effect of remission status on the 100th day after autologous stem cell transplantation of multiple myeloma cases with renal insufficiency to overall survival (CR=complete remission, VGPR=very good partial remission)

DISCUSSION

One of the best-known factors affecting survival in MM is RI, which is related with poor prognosis (11). Besides, these patients are not frequently considered suitable for ASCT (12). Some studies have shown that ASCT did not affect RI rates in MM patients (13). However, other studies showed that despite using low doses of conditioning regimen such as melphalan in myeloma patients with RI, ASCT is feasible and had comparable outcomes with those patients who has normal renal functions (14-16). Herein, we aimed to share our experience of the clinical progress of newly diagnosed myeloma patients with RI who underwent ASCT.

Our study demonstrated that reduced-dose melphalan in conjunction with ASCT can reverse dialysis-dependent RI due to MM. We used Melphalan 140 mg/m² for all 25 patients, 3 of them was dialysis dependent just before ASCT. All of these patients became dialysis-free after ASCT. In a study by Raab et al, ASCT reversed dialysis in 2 out of 17 patients (17). Similarly, Fakih et al reported that ASCT rescued 3 out of 24 patients from dialysis dependency (18). In contrast, Knudsen et al, reported that, ASCT did not make any difference for reversing dialysis dependence in 8 patients after transplantation. (13). Overall, the current findings in the literature show that patients who require dialysis at the time of ASCT will often need renal replacement in the post-transplant period.

Many reports showed that, because high dose (200 mg/m²) Melphalan is related with extreme toxicity, reduced doses of Melphalan (140 mg/m²), which has been similar outcomes, should use in myeloma patients with RI. In a single center study with 59 dialysis dependent patients, ASCT reversed the dialysis requirement in 13 out of 54 patients who lived more than 30 days (19). In this study, melphalan 200 mg/m² was started to first 27 patients but significant toxicity occurred, then, melphalan was decreased to 140mg/m² for the remaining subjects. In another study from Mayo Clinic, melphalan was started 140 mg/m² in 30 patients with advanced RI. One out of 15 of these patients who had been on dialysis recovered renal function (20). Our study confirms these findings that, renal impairment even dialysis dependent RI alone should not be an exclusion criterion for ASCT. Autologous transplant with reduced doses of melphalan could provide improved renal functions with minimal treatment related toxicity for these patients.

In our study, 100th day remission status was found related with significantly better DFS and OS rates. Also, despite a lack of statistically significance, presence of pre-transplant CR status, light chain myeloma type, and the stage IIB disease (when compared to stage IIIB), were the factors that was associated with longer DFS and OS. Moreover, in contrast to several reports (15,21), we were not able to show that the presence of RI is a risk factor, leading lower OS, because of our limited number of patients. In a recent study by Scheid et al. 1856 newly diagnosed MM

patients who underwent ASCT were analyzed(22). They showed, impaired renal functions at diagnosis (but not at transplant) are a poor risk factor for OS. In this study, overall negative effect of poor renal function on OS was not seen in PFS and multivariate analysis showed that GFR<30 at diagnosis, GFR<50 at transplant, disease stage \geq II and response < partial remission were significant risk factors that affect OS (22). In a recent study, Atlanger et al. reported the outcomes of a multi-center cohort of myeloma patients with or without RI both at the time of diagnosis and ASCT (16). No differences between the groups were observed in terms of PFS and OS rates. They hypothesize because new drugs have fewer nephrotoxicity, RI may not associate with inferior hematological outcomes anymore in innovative medications era. Our study was done at a time when many new generation drugs were not yet widely used. Despite this reality, our results seem comparable with current findings. All of our patients received at least 2 courses of VAD protocol (Vincristine, Adriamycin, Dexamethasone) as first line therapy before ASCT. Ten of 25 patients underwent bortezomib based therapy as second line treatment and then underwent to ASCT.

LIMITATIONS

There are some limitations of this study that must be addressed as follows; limited number of patients, lack of GFR normal control group, and retrospective nature of the study. Also, possible patient selection bias should be mentioned. Our patients were newly diagnosed patients with low co-morbidity index and only 2 of 25 patients had genetically poor prognostic factors.

CONCLUSION

We report the outcomes of 25 MM patients with RI and our data support that ASCT with reduced doses of melphalan is an effective, safety and striking therapy for these patients even in dialysis depending setting. Current guidelines emphasize that, careful patient selection is required, especially if ASCT is to be performed in patients with advanced RI. Our study also underlines the significant effect of CR on DFS and OS on the 100th day after ASCT in MM patients with RI.

Competing interests: The authors declare that they have no competing interest.

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