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ORIGINAL ARTICLE

Impact of Pre-transplant and Post-transplant Remission Status of Patients on Survival in Newly Diagnosed Multiple Myeloma

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Abstract The overall survival (OS) in patients with multiple myeloma (MM) has increased in the last decade due to the introduction of proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies as well as an extensive combination of autologous stem cell transplantation (ASCT) for suitable patients. The objective of this study was to examine the impact of pre-transplant and post-transplant remission status of patients on survival in newly diagnosed multiple myeloma. Two hundred and four patients with newly diagnosed MM who received an ASCT in our HSC transplant center at Hacettepe University Hospital between the years of 2001 and 2018 were evaluated in a retrospective manner. The median follow-up period was 35.9 months (range 4.2–206.4) for the entire group. The 5-year OS for pre-transplant remission status CR/VGPR patients and pre-transplant remission status PR or less patients were 79% and 68%, respectively ($p = 0.09$). The 5-year PFS for pre-transplant remission status CR/VGPR patients and pre-transplant remission status PR or less patients were 62% and 45%, respectively ($p = 0.23$). The 5-year OS for post-transplant remission status CR/VGPR group was 72% and for post-transplant remission status PR or less group was 60% ($p = 0.02$). The 5-year PFS in post-transplant remission status CR/VGPR patients was 48% and post-transplant remission status PR or less patients was 36% ($p = 0.03$). This study focuses on determination of survival outcome based on the best response obtained before and after ASCT and particularly highlights the significance of reaching CR and VGPR.

Keywords Multiple myeloma · Complete remission · Very good partial response · Remission status

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Introduction

The overall survival (OS) in patients with multiple myeloma (MM) has increased in the last decade due to the introduction of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs) and monoclonal antibodies as well as an extensive combination of autologous stem cell transplantation (ASCT) for suitable patients [1, 2]. The combination of the novel agents, including PIs and IMiDs has produced good responses and improved survival in both newly diagnosed and relapsed/refractory MM [3, 4]. ASCT continues a complemantary part of MM therapy in the era of novel agents, with a phase 3 randomized controlled trial (RCT) showing the superiority of lenalidomide–bortezomib–dexamethasone (RVD) followed by ASCT over RVD alone in terms of response rate and progression free survival (PFS), nevertheless of stage, presence of high-risk cytogenetics and response to induction therapy (IT) [5]. Achievement of a very good partial response (VGPR) or better after IT was associated with a superior PFS in patients receiving upfront ASCT in the Intergroupe Francophone du Myelome (IFM) 2005-01 trial

[6]. It is uncertain whether the depth of pre-transplant response has an impact on disease progression and survival outcomes. Studies have shown that post-transplant depth of response is prognostically more important than pre-transplant response in determining long-term outcomes [7]. The objective of this study was to examine the impact of pre-transplant and post-transplant remission status of patients on response, PFS and OS in newly diagnosed multiple myeloma.

Materials and Methods

Study Design, Data Collection and Supportive Care

This study has been performed in a retrospective manner. Demographic data of the patients, transplantation data and post-transplantation data were obtained from hospital database. Antiviral prophylaxis against herpes simplex and varicella zoster, and prophylaxis against *Pneumocystis jirovecii* continued through at least 6 months after ASCT. As a result of application standards of the hospitals of our tertiary care center, it has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standards of care. PFS was defined as time from ASCT to disease progression or death due to any cause. OS was defined as time from ASCT to death due to any cause. Patients who were alive and free of disease were censored at the last follow-up visit. Minimal residual disease (MRD) was not included in the analysis because most patients did not have MRD results.

Patients, Disease and Transplant Characteristics

Two hundred and four patients with newly diagnosed MM who received an ASCT in our HSCT center at our tertiary care center between the years of 2001 and 2018 were evaluated. Patients who received 4–6 courses of induction chemotherapy before ASCT were included in the study. This time period was chosen due to the routine use of VCD (bortezomib/cyclophosphamide/dexamethasone), VD (bortezomib/dexamethasone) and VAD (vincristine, doxorubicin and dexamethasone) for induction therapy. Exclusion criteria included use of more than one line of induction therapy prior to ASCT, one or more relapse prior to ASCT. Response was determined according to the current International Myeloma Working Group response criteria [8] and was evaluated at two time points: prior to ASCT and post ASCT, with the best response at any time after ASCT being captured for analysis. Peripheral blood stem cells were collected with G-CSF. The target cell dose for collection was $> 2 \times 10^6$ CD34/kg for each planned autograft.

Conditioning Regimen

Patients being conditioned with Melfelan 200 mg/m^2 in a single dose on day 2 or in 2 divided doses on days 3 and 2. Melphalan was given either as full-dose (200 mg/m^2) or reduced-dose (140 mg/m^2), at physician discretion, depending on patient's frailty and renal function [9]. All patients received standard supportive care measures, including growth factor support, blood transfusions, and prophylactic or therapeutic antibiotics according to local departmental guidelines at the time.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 25. The variables were investigated using visual (histograms, probabilty plots) and analytical methods (Kolmogorow–Simirnov/Shapiro–Wilk's test) to determine whether they are normally distributed or not. Statistical comparisons were made using Chi-square for categorical data. Student t-test (for two independent samples) was used for comparison of continuous numerical data. Survival analyses were made using Kaplan–Meier test. Multivariate analysis of predictors of survival were performed using Cox regression test. Parameters with p values ≤ 0.10 in univariate tests were included in the multivariate analysis. p values < 0.05 were considered to indicate statistical significance.

Results

Patient Characteristics

A total of 204 patients were included. One hundred and seventy patients (83.4%) were alive at the time of analyses. The median age was 58 (35–76) years at the time of transplantation. The most of the patients were male (60.7%). There was no statistically significant difference between the patients who had CR/VGPR and PR/less in pre-transplantation period in terms of international staging system (ISS) ($p = 0.21$). The baseline clinical and demographic characteristics of patients are listed in Table 1.

Overall Outcomes

The median follow-up period was 35.9 months (range 4.2–206.4) for the entire group. The 3-year OS was 93% in pre-transplant remission status CR/VGPR patients when compared to pre-transplant remission status PR or less

Table 1 Baseline clinical and demographic characteristics of patients

Baseline characteristics	CR/VGPR (pre-transplantation)	PR or less (pre-transplantation)	*p*
N	47 (23%)	157 (77%)	
Male/female (%)	27/20 (57.4%/42.6%)	97/60 (61.8%/38.2%)	0.59
Median age at transplantation (range) (years)	57 (39–76)	57 (35–74)	0.51
Karnofsky performance status			0.56
100	14 (29.8%)	38 (24.2%)	
90	19 (40.4%)	77 (49%)	
80	14 (29.8%)	42 (26.8%)	
ISS			0.21
ISS-I (%)	12 (25.5%)	25 (15.9%)	
ISS-II (%)	16 (34.0%)	49 (31.2%)	
ISS-III (%)	19 (40.5%)	83 (52.9%)	
Durie Salmon stage at diagnosis (%)			0.59
Stage I (%)	12 (25.5%)	28 (17.8%)	
Stage II (%)	11 (23.4%)	46 (29.3%)	
Stage IIIA (%)	19 (40.4%)	61 (38.9%)	
Stage IIIB (%)	5 (10.6%)	22 (14%)	
LDH > UNL at transplant (%)	27 (57.4%)	104 (66.2%)	0.27
Induction regimen (%)			0.27
VCD (%)	7 (14.9%)	29 (18.5%)	
VD (%)	20 (42.6%)	47 (29.9%)	
VAD (%)	20 (42.6%)	81 (51.6%)	
Disease status post-transplantation			**0.05**
CR/VGPR (%)	45 (95.7%)	134 (85.4%)	
PR or less (%)	2 (4.3%)	23 (14.6%)	
Mortality (%)	4 (8.5%)	30 (19.1%)	0.08

Statistically significant results were written in bold

LDH lactate dehydrogenase, *UNL* upper normal limit, *CR* complete response, *VGPR* very good partial response, *PR* partial response, *ASCT* autologous stem cell transplantation, *ISS* International Staging System

patients as 84% with no statistically significant difference. The 5-year OS for pre-transplant remission status CR/VGPR patients and pre-transplant remission status PR or less patients were 79% and 68%, respectively ($p = 0.09$) (Fig. 1).

The 3-year the PFS in pre-transplant remission status CR/VGPR patients and pre-transplant remission status PR or less patients were 69% and 70%. The pre-transplant remission status did not influence the 3-year disease free survival. The 5-year PFS in pre-transplant remission status CR/VGPR patients and pre-transplant remission status PR or less patients were 62% and 45%, respectively ($p = 0.23$) (Fig. 2).

The 3-year OS in post-transplant remission status CR/VGPR patients was 89% and for post-transplant remission status PR or less patients was 72%. The 5-year OS for post-transplant remission status CR/VGPR patients was 72% and for post-transplant remission status PR or less patients was 60% ($p = 0.02$) (Fig. 3).

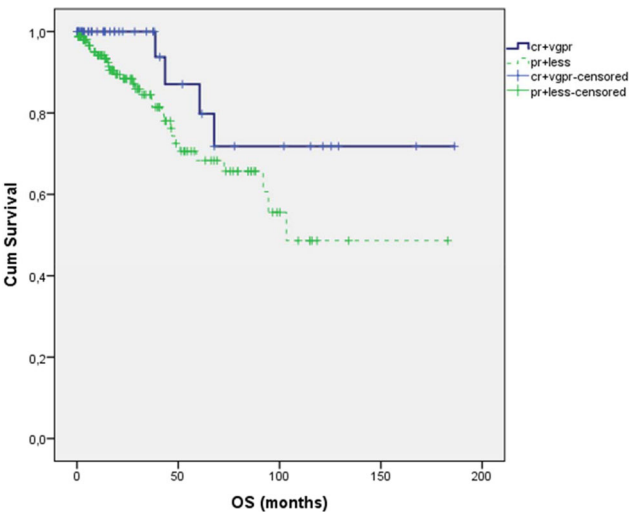

Fig. 1 Overall survival according to pre-transplant remission status ($p = 0.09$)

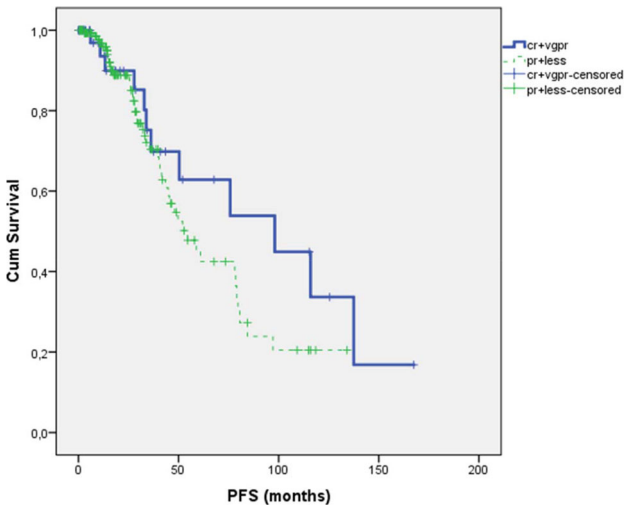

Fig. 2 Progression free survival according to pre-transplant remission status ($p = 0.23$)

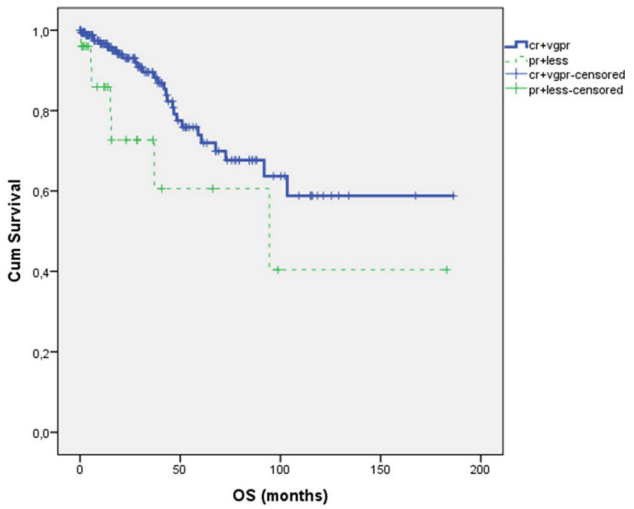

Fig. 3 Overall survival according to post-transplant remission status ($p = 0.02$)

The 3-year the PFS in post-transplant remission status CR/VGPR patients and post-transplant remission status PR or less patients were 73% and 54%. The 5-year PFS in post-transplant remission status CR/VGPR patients was 48% and post-transplant remission status PR or less patients was 36% ($p = 0.03$) (Fig. 4).

In subgroup analyses, OS (5-year OS; 92% vs 75% $p = 0.65$) and PFS (5-year PFS; 72% vs 69% $p = 0.54$) were better in patients who received VCD/VD chemotherapy than patients who received VAD chemotherapy as induction in pre-transplant CR/VGPR remission. Additionally, OS (5-year OS; 78% vs 69% $p = 0.38$) and PFS (5-year PFS; 63% vs 50% $p = 0.88$) were better in patients who received VCD/VD chemotherapy than patients who received VAD

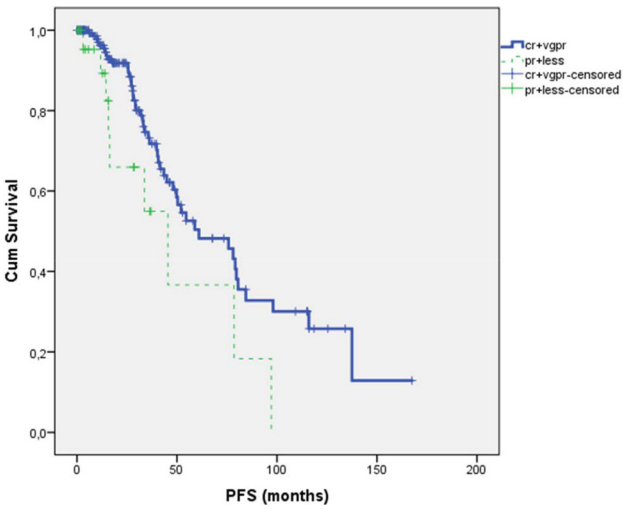

Fig. 4 Progression free survival according to post-transplant remission status ($p = 0.03$)

chemotherapy as induction in pre-transplant PR/less remission.

Cox Regression Analysis

On multivariate analysis, OS independent risk factor included pre-transplantation remission status, post-transplantation remission status and Karnofsky Performance Status of patients, PFS independent risk factors were Karnofsky Performance Status of patients and post-transplantation remission status as shown in Table 2. Karnofsky Performance Status of patients (95% CI 1.407–5.435) ($p = 0.004$) and post-transplantation remission status (95% CI 1.081–5.753) ($p = 0.03$) were associated with better OS. However pre-transplantation remission status was not associated with better OS (95% CI 0.147–1.196) ($p = 0.07$). Karnofsky Performance Status of patients (95% CI 0.243–0.987) ($p = 0.02$) and post-transplantation remission status (95% CI 1.028–4.326) ($p = 0.04$) were associated with better PFS.

Discussion

We present the results of a retrospective analysis of patients with MM who underwent ASCT in our center between 2001 and 2018. All patients received ASCT after high-dose conditioning therapy. This study shows that pre-transplant CR/VGPR remission status is associated with longer OS than pre-transplant PR/less remission status although it was not statistically significant ($p = 0.09$). Kapoor et al. showed pre-ASCT response was significant on survival on univariate analyses. Likewise pre-transplant CR/VGPR is associated with longer PFS than PR/less.

Table 2 Univariate and multivariate analyses (Cox model) of overall survival and progression free survival

Parameter	Overall survival			Progression free survival		
	Univariate	Multivariate		Univariate	Multivariate	
	p	95% CI	*p*	*p*	95% CI	*p*
Remission status pre-transplantation (CR/VGPR vs PR or less)	0.09	0.147–1.196	0.07	0.23		
Remission status post-transplantation (CR/VGPR vs PR or less)	0.02	1.081–5.753	**0.03**	0.03	1.028–4.326	**0.04**
Karnofsky performance status 100–90 versus 80	0.005	1.407–5.435	**0.004**	0.02	1.090–3.293	**0.02**
Induction chemotherapy regimen	0.91			0.29		

Statistically significant results were written in bold

CR complete response, *VGPR* very good partial response, *PR* partial response

However it was not statistically significant ($p = 0.23$), either. As a possibility, if the median follow up was longer, pre-transplant response might have reached statistically significant longer OS and PFS.

Post-transplant CR/VGPR is associated with better OS and PFS. This study validates post-transplantation CR/VGPR status was associated with improved survival. Multivariable analysis confirmed the independent high prognostic impact of post transplant response for both OS and PFS. Our data confirm the results of other studies showing that achieving CR and VGPR post autologous transplant has an important influence on both PFS and OS and that this subset of patients may obtain the greatest benefit from the procedure [10].

While MM remains largely an incurable disease, first suggested in patients who had sustained CR beyond 10 years after high–dose therapy with stem-cell support, is increasingly gaining ground [11, 12]. Although the benefit from ASCT is mainly seen in a subgroup of patients with favourable initial characteristics who achieve CR post-ASCT, it is also of advantage in patients with resistant disease [13]. Stem-cell rescue in subsequent studies permitted use of higher doses of melphalan, leading to CR in up to 40% to 60% of the patients [14]. However, several matters have to be clarified, such as defining the patient subsets that will benefit most from this procedure, the best timing of ASCT in the course of disease, the optimal conditioning regimen, the role of induction treatment in post-ASCT outcome and finally the management of patients with unfavourable characteristics [15]. There was no significant difference on survival among patients achieving CR/VGPR and PR/less before transplantation. But there was significant difference on survival among patients achieving CR/VGPR and PR/less after transplantation in this study. In this study, we found no differences on survival between patients who received VAD as initial chemotherapy compared with patients who received VCD or VD regimen in univariate and multivariate analyses. According to the results of univariate and multivariate analysis, OS and PFS was better in patients who received VD or VCD than patients who received VAD as induction chemotherapy. However, it was not statistically significant. In subgroup analyses OS and PFS was better in patients who received VD/VCD than patients who received VAD as induction chemotherapy. When we analyze each group separately according to their remission status in pre-transplantation and post-transplantation period, we found that the results were similar. Most of patients (until 2016) we could use bortezomib based regimens only after VAD regimen in less than 65 years old patients due to the social security reimbursement policies in our country. Therefore, patients who were previously diagnosed with MM received mostly VAD as induction chemotherapy and the patients diagnosed with MM later were receiving bortezomib-based induction chemotherapy. We think that this situation does not cause a statistically significant difference between the chemotherapy regimens. This situation is one of the limitation of our study. A low number of previous chemotherapy regimens before ASCT has been associated with longer survival in a number of studies [16, 17].

A retrospective analysis of patients enrolled in IFM 2005-01 (evaluating VD versus VAD) trial has shown that achievement of VGPR post-induction in patients undergoing subsequent ASCT is associated with superior PFS, especially in patients with poor-risk cytogenetics and with ISS stage 2/3 [6]. Kim et al. showed CR before ASCT to be associated with superior OS compared to PR. In their study 197 MM patients who were treated with induction chemotherapy were treated with ASCT. All patients received peripheral blood stem cell support after conditioning with melphalan similar to our study. Eighty one percent of the patients included in the study received VAD as induction chemotherapy [18]. In the study of Kim et al. there was a significant effect of pre-transplantation remission status on survival in contrast to our study. The number of patients who received bortezomib-based chemotherapy as induction was lower than the number of patients who received bortezomib-based chemotherapy as induction in

our study. The numbers and median age of the patients were similar in both studies [18]. In the study of Kim et al. the mean count of induction chemotherapy courses was less than the mean count of induction chemotherapy courses which our patients received. In conclusion, Kim et al. showed that patients who were in CR before ASCT have a statistically significant better OS than those in PR before ASCT. Nadal et al. recently showed that the pre-transplant levels of paraprotein and the plasma cell infiltration of the bone marrow were strongly associated with the achievement of CR post-ASCT [19].

On the other hand, some studies in the pre-novel agent era showed no impact of disease status at transplant on PFS and OS [20, 21]. It is possible to say that MM patients should not be deprivated from an ASCT upon lack of response to induction chemotherapy with these studies. A registry-based retrospective study had shown no impact of pre-transplant salvage chemotherapy on the relapse risk, treatment related mortality, PFS or OS, despite increasing the depth of response prior to ASCT [22]. However, salvage therapy led to a CR in only 8% of patients in that study, with 92% achieving PR or less. Furthermore, 49.7% of patients had received a PI based therapy as salvage in this study. Another issue is that the optimal timing of high-dose therapy and ASCT remains uncertain. In patients treated with planned tandem autografts, studies have shown that the timing of ASCT had a strong correlation with prolonged PFS and patients who were autografted within a year from initial chemotherapy had a longer PFS [23].

In conclusion, our analysis focuses on determination of survival outcome based on the best response obtained after ASCT and particularly highlights the significance of reaching CR and VGPR. Althought not statistically significant pre transplant response status had a positive effect on OS and PFS so we prefer obtaining a good response as possible before ASCT. Our study had a few limitations. First, this study was retrospective. Second all patients were not received the same chemotherapy before ASCT. In the era of highly active anti-myeloma therapy with an increasing proportion of patients achieving CR after transplant, further trials are needed to determine the impact of improving the depth of response prior to transplantation, preferably with higher patient numbers and longer follow up.

Compliance with Ethical Standards

Conflict of interest The authors of this paper have no conflict of interests, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included. The authors declare that they have no conflict of interest.

Ethical approval All of the ethical considerations had been strictly followed in accordance with the 1964 Helsinki declaration. As a standard care/action of the hospitals of the our tertiary care center, it has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standard of care.

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