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Treatment outcome in transplant ineligible patients with multiple myeloma: A single center real-life experience

Ayse Uysal[a,*], Mustafa Merter[a], Askin Sen[b]

[a] *Firat University, Faculty of Medicine, Department of Hematology, Elazig, Türkiye*
[b] *Firat University, Faculty of Medicine, Department of Medical Genetics, Elazig, Türkiye*

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Abstract

Aim: The objective of this study is to assess the choice of first-line and other line options, treatment outcome, and survival effects in transplant-ineligible patients with multiple myeloma (MM) in the novel anti-myeloma agents' era.

Materials and Methods: Forty-five transplant-ineligible patients with MM were evaluated retrospectively. Patients' characteristics, disease score, cytogenetic, LDH, treatment lines, treatment protocol, treatment response, and survival status at the last follow-up were examined.

Results: The median age was 71 (range, 60-85) years. Thirty-nine (86.6%) patients were over 65 years old, 32 (71.1%) of them had poor performance scores and 25 (55.6%) of them had comorbidity. The most used induction regimen was bortezomib plus cyclophosphamide plus dexamethasone (n:33;73.3%). The overall response rate was detected in 30 (66.6%) patients in overall induction regimens. The maintenance treatment was applied to 14 (31.1%) patients after induction treatment and lenalidomide plus dexamethasone (Rd) was used for maintenance treatment. Twelve (85.8%) patients are still on maintenance treatment with VGPR or better response. The most used second-line regimen was Rd (n:12; 46.1%) and bortezomib plus lenalidomide plus dexamethasone (n:9;34.6%). The median follow-up period was evaluated as 36 (1-81) months. After the first-line treatment, progression-free survival was found to be 12 (0-64) months. The median overall survival (OS) was 17 (1-81) months. Twelve patients are alive without progression. The median OS was significantly shorter among patients with high LDH at the time of diagnosis than patients with normal LDH [28 (12.06–43.94) months vs 47.21 (21.23–50.77) months, respectively] (p=0.037). The median PFS was not reached in patients with maintenance treatment, in patients without maintenance treatment the median PFS was detected 23 (10-35.9) months (p=0.058).

Conclusion: An induction regimen should be well chosen to ensure a deep and prolonged response, and maintenance treatment should be preferred in suitable patients to maintain response in transplant-ineligible patients.

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by clonal proliferation of plasma cells in the bone marrow that is the second most common hematologic malignancy and accounts for about 1% of all cancers [1]. Multiple myeloma predominantly affects elderly individuals with a median age of 69 years at the time of diagnosis and two-thirds of patients over 65 years at diagnosis, with 35–40% of patients older than 75 years [1-3]. MM is an incurable malignancy and high-dose treatment followed by autologous stem cell transplantation (ASCT) is still the standard treatment for treating newly diagnosed MM in selected, fit, and young patients. It has long been known that induction treatment followed by ASCT greatly contributes to the improvement of both progression-free survival (PFS) and overall survival (OS). Most newly diagnosed MM patients are frail or elderly that have multiple several comorbidities and poor performance status, which preclude most of them from being eligible to transplant [4-6]. Although rare, transplantation cannot be performed in young myeloma patients with poor performance status and significant comorbidities. The presence of polypharmacy also creates difficulties and complications in myeloma treatment [5]. For these reasons, it caused worsening of treatment outcome and survival in

*Corresponding author:
Email address: drayseorucuysal@gmail.com (Ayse Uysal)

elderly and/or frail patients. But, with the introduction of novel agents in myeloma treatment such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs), a significant improvement was observed in both overall and progression-free survival, and the expected survival time increased approximately two times for the transplant-ineligible patients [1, 7].

The aim of this study is to evaluate the effect of the first line and further line choices on treatment outcome and survival in transplant-ineligible patients with MM in a novel anti-myeloma agents' era for real-life experience.

Materials and Methods

This was a retrospective and single-center study and was approved by the local Ethics Committee and was conducted by the principles of the Helsinki Declaration. All data were collected from the hospitals' registries and patients' clinical notes.

Patients and data

In this study, 45 transplant-ineligible patients with MM who were followed up in our clinic were evaluated between May 2014-February 2021. The presence of several/multiple comorbidities reduced performance status, patients' frailty, and/or advanced age (>65 years) was considered as a criterion for transplant ineligibility.

Patients' demographics, clinical characteristics, and information of treatments were recorded in the hospital database. For each patient, age at the time of diagnosis, gender, comorbidities, performance status, type of M protein, presence of bone disease, disease score, cytogenetic, presence of renal failure, lactate dehydrogenase (LDH) levels at the time of diagnosis, number of treatment lines, treatment protocols, treatment response, and disease/survival status at last follow-up were examined.

The diagnosis of myeloma was determined according to the International Myeloma Working Group (IMWG) criteria [8]. Disease scores were calculated by International Staging System (ISS). High LDH level was defined as values of 230 U/L and above.

Poor performance status was defined as the Eastern Cooperative Oncology Group (ECOG)≥2. All concomitant chronic diseases and the presence of a second malignancy were accepted as comorbidities. Cytogenetic risk was defined as high if del(17p), t(4;14), and/or t(14;16) were present.

Treatments were defined as PI-based regimens (*VCD*; bortezomib, cyclophosphamide, dexamethasone *VD*; bortezomib, dexamethasone *MPV*; melphalan, prednisolone, bortezomib *PAD*; bortezomib, doxorubicin, dexamethasone), IMiD based regimens (*Rd*; lenalidomide, low dose dexamethasone *Pd*; pomalidomide, dexamethasone, thalidomide monotherapy), PI/IMiD based regimens (VRD; bortezomib, lenalidomide, dexamethasone KRD; carfilzomib, lenalidomide, dexamethasone) the others regimens (VAD; vincristine, doxorubicin, dexamethasone).

Response to treatment was evaluated according to the IMWG criteria [9]. The best response, categorized as stringent complete response, complete response, very good partial response, or partial response. Overall response rate (ORR) was determined as a partial response or better.

Progression-free survival (PFS) was calculated as the time from the start of treatment to discontinuation due to disease progression or death due to any cause. Overall survival (OS) was calculated from the beginning of the first-treatment line until death due to any cause.

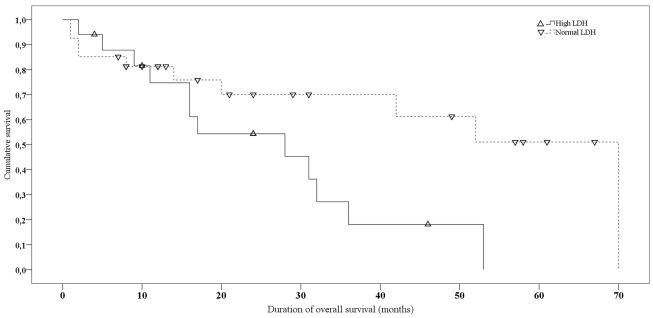
The patients were evaluated in terms of the most common grade 1-2 side effects and the side effects associated with discontinuation of treatment.

Statistical analysis

Numbers and percentages were used for categorical data in descriptive analyses. For parametric and non-parametric data mean ± standard deviation with Student's T-Test and median (min-max) values with Mann-Whitney-U Test were used respectively. The assumptions for parametric and non-parametric tests were determined with skewness–kurtosis, Kolmogorov–Smirnov test, standard deviation/mean percentages, and histogram graphics with normal distribution lines. The rates of the death in patients with and without higher LDH were compared with the Chi-square test. The probabilities of OS were demonstrated using the plots and methods of Kaplan–Meier and compared using the log-rank test. Statistically significant differences were assessed at an alpha level of $p<0.05$. All analyses were conducted using IBM SPSS Statistics version 22. The power rates of all analyses were determined with Gpower program version 3.1.

Results

The characteristics of patients and disease were given in Table 1. The median age at the time of diagnosis was 71 (range, 60-85) years. Thirty-nine (86.6%) of all patients were over 65 years old, 32 (71.1%) of them had poor performance scores and 25 (55.6%) of them had at least a comorbidity.



During the follow–up period there were 12 deaths in the High–LDH group and 10 deaths in the normal–LDH group (70.6 % vs. 37 %, Chi-Square, p=0.030). The median duration of survival was 28 (12.06–43.94) months in cases with high-LDH and 47.21 (21.23–50.77) months in cases with normal-LDH. Kaplan–Meier plot with log-rank test demonstrated that the event free overall survival was significantly shorter among patients with high LDH levels at the time of diagnosis compared to patients with normal LDH levels (Log-rank; X^2 =4.36, p=0.037)

Figure 1. Kaplan–Meier plot with log-rank test of the correlation between LDH level and overall survival.

Table 1. Baseline characteristics of patients.

Patients	n:45 (%100)
Gender	
Male	27 (60%)
Female	18 (40%)
Age (years)	
Median (min-max)	71 (60-85)
<65	6 (13.3%)
65-74	25 (55.6%)
>75	14 (31.1%)
Comorbidity	
Yes	25 (55.6%)
No	24 (45.4%)
ECOG	
1	13 (28.9%)
2	28 (62.2%)
3	4 (8.9%)
Type of multiple myeloma	
IGG	24 (53.4%)
IGA	10 (22.2%)
Light chain	10 (22.2%)
Non-secratuary	1 (2.2%)
ISS	
I	12 (26.7%)
II	10 (22.2%)
III	23 (51.1%)
Anemia	
Yes	25 (55.6%)
No	24 (44.4%)
Bone lesion	
Yes	31 (68.9%)
No	14 (31.1%)
Renal failure	
Yes	26 (57.8%)
No	19 (42.2%)
LDH	
Normal	27 (60%)
High	17 (37.8%)
Unknown	1 (2.2%)
Cytogenetic risk	
Standard	26 (57.8%)
High	2 (4.4%)
Unknown	17 (37.8%)

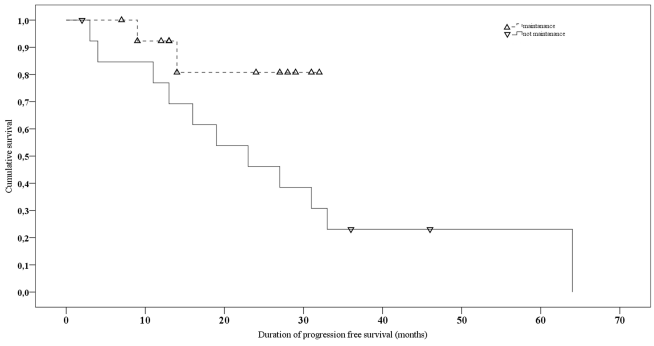
ECOG; Eastern Cooperative Oncology Group ISS; International Staging System LDH; lactate dehydrogenase.

Cytogenetic tests were performed on all patients. High-risk cytogenetic abnormalities were detected in patient 2 (4.4%) as del (17p), the standard cytogenetic risk was detected in 26 (57.8%) patients.

Table 2. Treatment regimens and results for second line therapy.

Patients	N:26 (100%)	ORR (%)
Regimens		
RD	12 (46.1%)	50
VRD	9 (34.6%)	66.6
MPV	2 (7.7%)	0
KRD	1 (3.9%)	0
Pom-dex	1 (3.9%)	100
VCD	1 (3.9%)	0

KRD; carfilzomib, lenalidomide, dexamethasone MPV; melphalan, prednisolone, bortezomib ORR; Pom-dex; pomalidomide, dexamethasone RD; lenalidomide, dexamethasone VRD; bortezomib, lenalidomide, dexamethasone.



The 18-month PFS rates; maintenance group=81% vs not-maintenance group=61.5%. (Log-rank; X^2=3.58, p=0.058).

Figure 2. Kaplan–Meier plot with log-rank test of the progression-free survival in patients with and without maintenance treatment.

The genetic test results of 17 (37.8%) patients could not be reached.

First-line treatment

The most used induction regimen was bortezomib based regimens as VCD (n:33;73.3%), followed by VD (n:5; 11%), MPV (n:3; 6.7%), PAD (n:1; 2.2%). The other induction regimens were thalidomide (n:2; 4.4%), VAD (n:1; 2.2%). In overall induction regimens, ORR (PR and better response) was detected in 30 (66.6%) patients (CR;6.7%, VGPR;43.3%, PR;50%). The ORRs according to the induction regimens were 66.6%, 60%, 100% and 100% for VCD, VD, MPV and thalidomide monotherapy respectively. ORR could not be provided with VAD and PAD regimens.

The maintenance treatment was applied to 14 (31.1%) patients after induction treatment who achieved a partial response or better. Lenalidomide plus low-dose dexamethasone was used for maintenance treatment in all patients. Only 2 (14.2%) patients who received maintenance treatment switched to second-line treatment due to progression, and the other 12 (85.8%) patients are still on maintenance treatment with VGPR or better response. The duration of maintenance therapy was 8 and 3 months, respectively in

2 patients who received maintenance treatment switched to second-line treatment due to progression.

Second-line treatment

Twenty-six (57.7%) patients received a second-line regimen. The most used second-line regimens were IMiD based regimens as Rd (n:12; 46.1%) followed by PI/IMiD based regimen as VRD (n:9;34.6%). The most common reason to take the next treatment was progressive disease (46.1%) under the treatment followed by stable disease (38.4%) and refractory to the treatment (15.5%), respectively. The ORR was determined in 13 (50%) patients (CR15.4%, VGPR46.2%, PR38.4%). The ORRs were 50% and 66.6% for RD and VRD, respectively. Other more detailed results of the second line were demonstrated in Table 2.

Third and further lines of treatment

Third line treatments were applied to 13 patients (28.8%); four and the next line applied to 7 patients (15.5%). The most used regimens in the third line were as PI/IMiD based and IMiD based regimen, ORR was 38.4% in both groups.

Survival analyses

The median follow-up time was 36 (1-81) months. After the first-line treatment, the median PFS was 12 (0-64) months. Disease-related death was observed in 23 (51.1%) patients. The median OS was 17 (1-81) months. During the 7 years follow-up period, the median OS was 20 (1-81) in patients over 65 years of age. Twelve patients are alive without progression at the time of data collection.

During the follow–up period, there were 12 deaths in the patients with high LDH level and 10 deaths in patients with normal LDH level (70.6 % vs. 37 %, Chi-Square, p=0.030). During the follow-up period, the median OS time was 28 (12.06–43.94) months in patients with high LDH level and 47.21 (21.23–50.77) months in patients with normal LDH level. Kaplan–Meier plot with log-rank test demonstrated that the OS was significantly shorter among patients with high LDH levels at the time of diagnosis compared to patients with normal LDH levels (log-rank; X^2=4.36, p=0.037) (Figure 1). Patients with partial response and better after induction treatment were evaluated for PFS according to whether or not they received maintenance treatment.

The median follow-up period was 36 (1-81) months, the median PFS was not reached in patients with maintenance treatment, and in patients without maintenance treatment, the median PFS was found to be 23 (10-35.9) months (log-rank; X^2=3.58, p=0.058) (Figure 2).

Adverse events

The most common grade 1-2 adverse events were bortezomib-related neuropathy (31.5%) and lenalidomide-related neutropenia (23.8%). Treatment was discontinued due to grade 4 thrombocytopenia/neutropenia in one patient and grade 4 neuropathy in one patient who received bortezomib. Treatment was discontinued due to diarrhea in 1 patient, skin rush in 1 patient, and acute coronary syndrome in 1 patient who received lenalidomide.

Discussion

There is an obvious need for new treatment options that provide long-term PFS, OS, and low toxicity in transplant-ineligible patients. In the last decade, a significant improvement was observed in both overall and progression-free survival with the introduction of novel agents such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs) which are quite safe treatment options [7]. In particular, after 2005, an increase was observed in the OS and PFS specifically in those aged over 65 years [5, 10]. Pulte et al. reported that 5-year relative survival reached above 50% levels for patients with MM who are below 75 years of age, probably reflecting the increased use of newer agents in myeloma treatment in the first decade of the 21stcentury [11]. At the time of diagnosis, over half of the patients with MM are considered elderly (median age 69 years) [1]. Consisted with this finding, many of our transplant-ineligible patients (86.7%) were aged ≥65 years at the time of diagnosis. In our study, most of the patients had comorbidities (55.6%) and poor performance status (ECOG≥2) (71.1%). During the median follow-up period of 36 months, the OS was found to be 20 (1-81) months in patients over 65 years of age. These results were found to be similar with the literature.

High LDH levels at the time of diagnosis negatively affect the PFS and OS in patients with MM. Gu et al. analyzed serum LDH levels in 105 elderly and newly diagnosed MM patients and reported that high LDH level was an adverse prognostic factor for elderly MM patients. Our results demonstrated compatibility with the literature. OS was significantly shorter among patients with high LDH levels at the time of diagnosis compared to patients with normal LDH levels (p<0.05) [12].

VRd and daratumumab-based regimens are recommended by both European and USA guidelines for patients who are newly diagnosed with myeloma and ineligible for ASCT [13, 14]. VRd has shown a survival benefit and was recommended for 8-12 cycles, followed by maintenance treatment. The ORR was 86% (66% VGPR or better) with VRd combination treatment in the phase 2 study with the transplant-ineligible patients [15]. However, we preferred mostly VCD treatment as the first-line treatment by the insurance reimbursement policy and ORR was found to be 66.6% (%PR or better). Zepeda et al. evaluated the impact of different bortezomib-containing regimens including VD, VCD, and VMP for the treatment of transplant-ineligible MM. VGPR was achieved in 57% of patients compared to 33% and 18% in VMP and VD groups, respectively. PFS was better in VCD than other groups. The most common side effect was neuropathy in all groups, but grade 3/4 neuropathy was the most seen in the VMP group (21%), compared to VCD (2.3%) and VD (5.2%) (p<0.05) [16]. In our study, response rates were similar to the literature.

Transplant-ineligible patients with MM may receive continuous treatment with an antimyeloma regimen or maintenance treatment after initial treatment. Proteasome inhibitors as bortezomib and immunomodulatory drugs as lenalidomide are mostly used for maintenance treatment in recent years which have demonstrated efficacy in this

setting. In the literature, continuous lenalidomide was extremely effective in increasing PFS. In the MM-015 trial, the addition of lenalidomide maintenance significantly improved PFS (median, 31 months; P < .001) [17]. In the SWOG S0777 trial, treatment with RVD induction plus Rd maintenance was compared with Rd induction plus Rd maintenance and PFS was significantly higher in the RVD induction group (Median PFS 43 months in the VRd group, 30 months in the Rd group; p = 0•0018) [15]. In the literature, maintenance with bortezomib monotherapy or bortezomib plus steroid combination improved PFS but was associated with higher hematologic or non-hematologic toxicities [18, 19]. In our study, the maintenance treatment was applied to 14 (31.1%) patients after induction treatment and lenalidomide plus low dose dexamethasone was used for maintenance treatment in all patients. Twelve (85.8%) patients are still on maintenance treatment with VGPR or better response. High hematologic toxicities as neutropenia were observed in lenalidomide treatment.

In patients who are refractory or relapsed after the first-line treatment, the choice of the second line is affected by many factors including the timing of the relapse, response to prior treatment, and performance status. PI and IMiDs combinations with or without daratumumab are recommended firstly [20]. The primary factors that affect our choice of second-line regimen are the patients' previous treatment, performance status, and insurance reimbursement policy. In our study, the most used second-line regimens were IMiD based regimens as Rd (n:12; 46.1%) and VRD (n:9;34.6%). Despite the small number of patients, the ORR was higher in the VRD group than in the RD group (66.6% vs %50). This situation was consistent with the literature. Triplet regimens provide more deep and durable responses than double regimens [13, 14, 20].

Unfortunately, the sample size was insufficient to make a comparison in terms of OS between patients who received maintenance or not. The limitations of the study are that it is retrospective, and the number of cases is small.

Conclusion

Most of newly diagnosed MM patients are frail or elderly and have multiple comorbidities and poor performance status, which preclude most of them from being transplant-eligible. Therefore, an induction regimen should be well chosen to ensure a deep and prolonged response and maintenance treatment should be preferred in suitable patients to maintain response. Our number of patients was low to compare the treatment regimens, but we found that the response rates were better in the triple regimens and maintenance regimens. But multi-drug regimens can be difficult to tolerate for frail or elderly patients and it is necessary to be very careful in terms of drug side effects.

Ethics approval

This study was approved by the Ethics Committee of Fırat University (date: 22.04.2021, decision number: 2021/06 - 10).

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