AFMN BIOMEDICINE

ORIGINAL ARTICLE

Check for updates

ASSESSMENT OF TREATMENT OUTCOMES IN MULTIPLE MYELOMA ACCORDING TO PROGNOSTIC FACTORS AND THERAPEUTIC APPROACH

Dragana Drašković[1] **Goran Marjanović**[1,2] **Miodrag Vučić**[1,2] **Irena Ćojbašić**[1,2]

[1]Clinic of Hematology, Allergology and Clinical Immunology, University Clinical Center Niš, Serbia [2]Department of Internal Medicine, University of Niš Faculty of Medicine, Niš, Serbia

Multiple myeloma is a malignant plasma cell disorder characterized by clonal proliferation of abnormal plasma cells. Global five-year survival rates range from 60% to 70%, largely due to novel therapeutic strategies. In our country, conventional therapies remain standard, with monoclonal antibodies recently introduced for relapsed/refractory cases. This study aimed to assess treatment outcomes in relation to therapy type and prognostic factors.

A retrospective-prospective analysis was conducted on 200 patients with multiple myeloma. The relationship between treatment modality, disease biology, clinical status, and therapeutic response was evaluated, including progression-free survival (PFS), overall survival (OS), and protocol efficacy across prognostic subgroups.

Best treatment responses were achieved in patients with good performance status and low comorbidity, particularly those receiving first-line VTD (bortezomib, thalidomide, dexamethasone). Among patients under 65, the CTD (cyclophosphamide, thalidomide, dexamethasone) protocol showed the longest average OS. In second-line therapy, PAD (bortezomib, doxorubicin, dexamethasone) yielded the highest response rates and best survival outcomes. Elderly patients with high Charlson Comorbidity Index (CCI) benefited most from the MPT regimen (melphalan, prednisone, thalidomide). In contrast, Vel-Dex (bortezomib, dexamethasone) was linked to the highest progression rates.

Therapeutic outcome in myeloma strongly correlates with prognostic factors and treatment selection. Proper risk stratification enables personalized therapy and improves outcome.

Keywords: multiple myeloma, prognostic factors, risk stratification, therapeutic protocols, treatment outcome

Submitted: August 13, 2025 **Revised:** September 14, 2025
Accepted: September 20, 2025
Published online: October 31, 2025

Correspondence to:
Dragana Drašković
Clinic of Hematology, Allergology and Clinical Immunology
University Clinical Center Niš
Bulevar dr Zorana Đinđića 48, Niš, Serbia
E-mail: draskovic.gaga@gmail.com

INTRODUCTION

Multiple myeloma is a malignant lymphoproliferative disorder, primarily characterized by the clonal proliferation and accumulation of pathologically altered plasma cells. The clinical manifestations result from the suppression of normal hematopoiesis in the bone marrow by plasma cells that produce a homogeneous monoclonal immunoglobulin, known as the M component. This disease is considered the prototype of neoplasms involving well-differentiated, mature, and typically slow-proliferating B lymphocytes–plasma cells (1). Clinically, multiple myeloma is defined by a characteristic pentad: anemia, detection of monoclonal (M) protein in serum and/or urine, skeletal lesions (mostly osteolytic), renal impairment, and hypercalcemia (2). After the diagnosis is established according to the criteria of the International Myeloma Working Group (IMWG), it is essential to assess the patient's prognostic profile. This patient-centered approach has significantly improved five-year survival rates over the past 15 years, now reaching 60%–70%, with curative potential observed in approximately 15% of cases. Prognostic factors influencing disease course and final outcome are based on the patient's clinical characteristics, the biological features of the disease, and nature of the therapeutic response, which are critical for defining a patient–tailored therapeutic approach (3).

Key clinical characteristics of patients are reflected through various comorbidity indices and patient age, while biological features are assessed using the Durie-Salmon classification, International Staging System (ISS), revised ISS (R-ISS), R2-ISS, and mSMART (Mayo Stratification for Myeloma and Risk-Adapted Therapy) classification (4). The depth and duration of therapeutic response significantly impact progression-free survival and overall survival. Achieving complete remission (CR) is considered one of the strongest prognostic markers (5).

The aim of this study was to evaluate the impact of different treatment modalities on therapeutic response, time to disease progression, and overall survival, with the identification of the most effective therapeutic combination in relation to patients' performance status and risk profile.

METHODS

This retrospective–prospective study included 200 patients with multiple myeloma, treated at the Clinic for Hematology, Allergology, and Clinical Immunology, University Clinical Center Nis, between 2016 and March 2023. The treatment outcomes of surviving patients are still being actively monitored. The diagnosis was established according to the criteria of the International Myeloma Working Group. The cohort comprised 105 men and 95 women, with a mean age of 62.49 ± 9.30 years(range 38–80 years). During the study, the following clinical and laboratory parameters were monitored: age, sex, performance status, clinical stage according to Durie-Salmon criteria, International Staging System (ISS), revised ISS for patients who underwent genetic analysis by FISH (Fluorescence In Situ Hybridization), Charlson Comorbidity Index, type of monoclonal (M) protein, serum albumin, B2-microglobulin, lactate dehydrogenase (LDH), serum calcium level, presence of osteolytic bone lesions, renal function, extramedullary disease, hemoglobin level, and platelet count. Treatment protocols were provided according to the Serbian Myeloma Group guidelines, following ESMO (European Society for Medical Oncology) and NCCN (National Comprehensive Cancer Network) recommendations. First-line regimens included VTD, CTD, VCD, PAD, TAD, MPV, MPT. Second-line regimens included PAD, Vel-Dexa, VTD, VCD, TCED, VTD-PACE, etc. (V/P–Velcade; T–thalidomide; D– dexamethasone; C–cyclophosphamide; A–Adriamycin; M–melphalan; P–prednisolone; E– etoposide). We assessed therapeutic response after first, second, and subsequent lines: complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), progression (PD) and relapse, as well as progression-free survival and overall survival in different prognostic groups. During the follow-up, 127 patients died and 73 were alive at study closure. Data are presented in the form of arithmetic mean and standard deviation, minimum and maximum values, and as absolute and relative frequencies. Comparisons of numerical variables between two groups were performed using the t-test or the Mann-Whitney test. Categorical variables were compared using the Chi-square test. Survival analysis was performed using the Kaplan-Meier survival curve and the log-rank test. The null hypothesis was tested at a significance level of $p < 0.05$. Statistical analyses were performed using the SPSS software package, version 16.0.

The study was approved by the Ethics Committee of the University Clinical Center Niš on June 19, 2024 (Approval No. 17351/9).

RESULTS

In the studied population, all patients diagnosed with multiple myeloma received first-line therapy (100.0%). Second-line treatment was administered to 52.0% of patients, third-line therapy to 24.0%, fourth-line therapy to 12.0%, and fifth-line therapy to 4.5% (Figure 1).

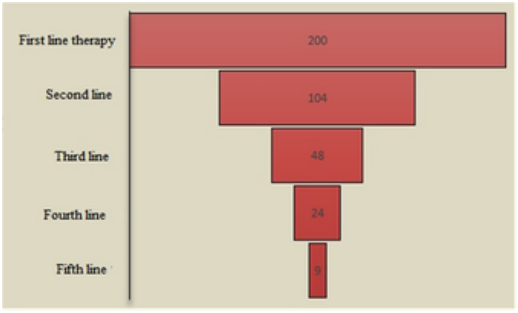

Figure 1. *Number of patients by treatment line*

The initiation and choice of therapeutic protocol were in accordance with the relevant clinical guidelines applicable at the time of treatment, which underwent changes over the study period (6). In the first-line therapy, the most frequently administered regimens were CTD (40.5%), followed by MPT (20.5%) and VTD (12.5%) (Figure 2). Among patients under the age of 65, the most commonly used therapeutic protocols were CTD (47.7%) and VTD (20.6%), whereas in older patients, MPT (37.6%) and CTD (32.3%) were predominantly used.

Following first-line therapy, complete remission (CR) was achieved in 2.1% of patients, very good partial remission (VGPR) in 48.9%, partial remission (PR) in 19.5%, stable disease (SD) in 8.4%, disease progression (PD) occurred in 18.9%, and in 2.1% of patients' treatment-related adverse effects prevented response assessment. No statistically significant difference in first-line response rates was observed between different age groups (p = 0.239) (Table 1).

Analysis of therapeutic response according to the first-line therapy showed that VGPR was achieved in 55.0% of patients treated with CTD and 50.0% of those treated with VTD. The highest rate of disease progression (53.3%) was observed in the group treated with Vel-Dex protocol as first-line therapy (Table 2). In second-line therapy, younger patients most frequently received PAD (33.9%), Vel-Dex (19.4%), and VTD (12.9%). Among patients over 65 years of age, Vel-Dex was the most frequently administred regimen (45.2%).

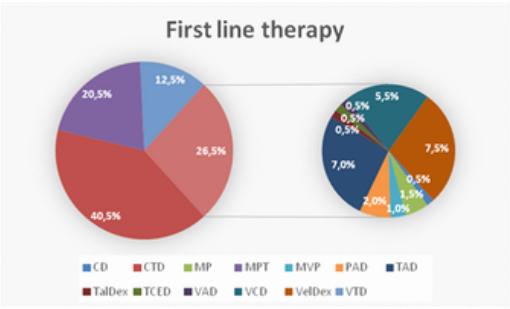

Figure 2. *First-line therapy in the studied population*

Table 1. *First-line therapy response by age group*

Response		Age (years)		Total
		≤65 years	>65 years	
CR	N	3	1	4
	%	2,9	1,1	2,1%
VGPR	N	46	47	93
	%	44,7	54,0	48,9%
PR	N	19	18	37
	%	18,4	20,7	19,5%
SD	N	12	4	16
	%	11,7	4,6	8,4%
PD	N	22	14	36
	%	21,4	16,1	18,9%
Tox eff	N	1	3	4
	%	1,0	3,4	2,1%

CR – complete remission; VGPR – very good partial remission; PR – partial remission; SD – stable disease; PD – disease progression; tox eff – toxic effects

When used as second–line therapy, PAD protocol was associated with the highest response rate (34.3% of patients achieved VGPR). In the studied population, 127 patients (63.5%) died. A statistically significant difference in mortality was observed across age groups (p = 0.014) and Charlson Comorbidity Index (CCI) categories (p < 0.001).

Sex, performance status (PS), clinical stage, ISS stage, and type of M-protein were not found to be statistically significant predictors of mortality. In our study population, the mean overall survival (OS) was 32.96 months (SE 1.92; 95% CI: 21.19–36.72 months), while the median overall survival was 36.00 months (range 12.00–48.00 months) (Figure 3). Overall survival significantly differed according to ISS stage (p=0.008). Median survival among patients with ISS stage I was 48.0 months (95% CI 36.1–59.9), for ISS stage II it was 30.0 months (95% CI 22.0–38.0), and for ISS stage III it was 24.0 months (95% CI 17.1–30.9) (Figure 4). In patients aged over 65 years, overall survival differed significantly according to Charlson Comorbidity Index (CCI) score (p = 0.012). Patients with CCI score 1 had a median overall survival of 48.5 months, compared to 29.5 months in those with a CCI score ≥ 2 (Figure 5).

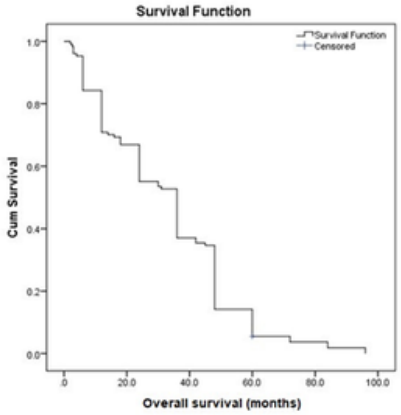

Figure 3. *Kaplan-Meier survival curve in the studied population*

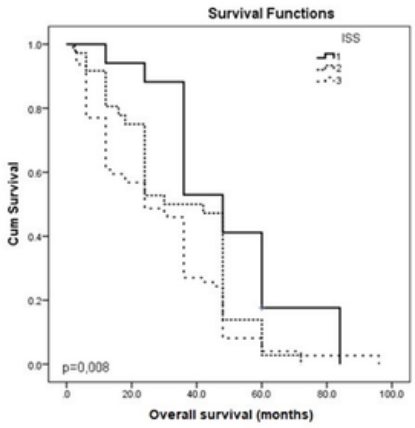

Figure 4. *Kaplan-Meier survival curve according to International Staging System (ISS) stage*

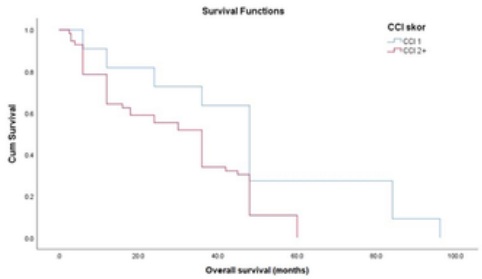

Figure 5. *Overall survival by Charlson Comorbidity Index (CCI) score in patients > 65 years*

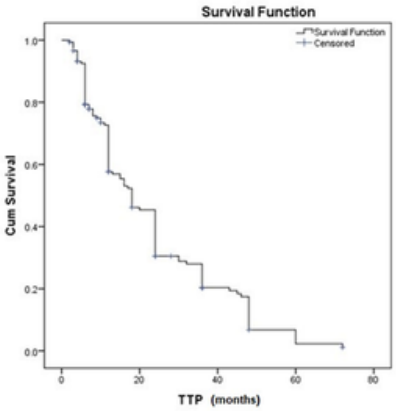

Figure 6. *Kaplan-Meier curve for time to progression (TTP) in the studied population*

Table 2. *Therapeutic response after first-line treatment*

		First line response						Total
		CR	VGPR	PR	SD	PD	Tox eff	
CD	Nbr	0	1	0	0	0	0	1
	%	0,0%	100,0%	0,0%	0,0%	0,0%	0,0%	100,0%
CTD	Nbr	0	44	16	9	9	2	80
	%	0,0%	55,0%	20,0%	11,3%	11,3%	2,5%	100,0%
MP	Nbr	0	2	1	0	0	0	3
	%	0,0%	66,7%	33,3%	0,0%	0,0%	0,0%	100,0%
MPT	Nbr	0	15	15	1	4	1	36
	%	0,0%	41,7%	41,7%	2,8%	11,1%	2,8%	100,0%
MVP	Nbr	0	1	0	0	0	0	1
	%	0,0%	100,0%	0,0%	0,0%	0,0%	0,0%	100,0%
PAD	Nbr	0	4	0	0	0	0	4
	%	0,0%	100,0%	0,0%	0,0%	0,0%	0,0%	100,0%
TAD	Nbr	0	5	2	1	5	1	14
	%	0,0%	35,7%	14,3%	7,1%	35,7%	7,1%	100,0%
TalDex	Nbr	0	0	0	0	1	0	1
	%	0,0%	0,0%	0,0%	0,0%	100,0%	0,0%	100,0%
TCED	Nbr	0	0	1	0	0	0	1
	%	0,0%	0,0%	100,0%	0,0%	0,0%	0,0%	100,0%
VAD	Nbr	0	1	0	0	0	0	1
	%	0,0%	100,0%	0,0%	0,0%	0,0%	0,0%	100,0%
VCD	Nbr	0	4	0	2	5	0	11
	%	0,0%	36,4%	0,0%	18,2%	45,5%	0,0%	100,0%
VelDex	Nbr	0	5	0	2	8	0	15
	%	0,0%	33,3%	0,0%	13,3%	53,3%	0,0%	100,0%
VTD	Nbr	4	11	2	1	4	0	22
	%	18,2%	50,0%	9,1%	4,5%	18,2%	0,0%	100,0%
Total	Nbr	4	93	37	16	36	4	190
	%	2,1%	48,9%	19,5%	8,4%	18,9%	2,1%	100,0%

C – cyclophosphamide; D – dexamethasone; T – thalidomide; M – melphalan; P – prednisolone; V,P – Velcade; A- Adriamycin; E- etoposide; CR – complete remission; VGPR – very good partial remission; PR - partial remission; SD – stable disease; PD – disease progression, tox eff – toxic effects

Overall survival (OS) differed significantly according to performance status (PS) ($p = 0.013$). The median OS for patients with PS 0–1 was 36.0 months (95% CI 32.0–40.0 months), whereas for those with PS ≥ 2 it was 31.0 months (95% CI, 19.7–42.4 months). In both younger and older patient subgroups, a statistically significant difference in OS was observed in relation to first-line therapy ($p = 0.034$ and $p = 0.004$, respectively). Among younger patients, the longest mean OS was achieved with CTD (40.0 months) and VTD (30.0 months), while the shortest was observed with VCD (16.0 months). Among older patients, the longest mean OS was achieved with MPT (36.5 months) and CTD (35.7 months), while the shortest was observed with VTD (4.5 months). Following second-line therapy, patients receiving PAD achieved the longest OS–48 months (95% CI, 44.76–51.24 months).

Time to progression (TTP) in the study population was 23.36 months (SE 1.55; 95% CI, 20.33–26.40), with a median TTP of 18.00 months (9.00–36.00 months) (Figure 6). Mean TTP did not vary significantly by sex, age, International Staging System (ISS) stage, Charlson Comorbidity Index (CCI) score, clinical stage, serum lactate dehydrogenase (LDH) > 460 U/L, or Eastern Cooperative Oncology Group (ECOG) performance status. A statistically significant difference in TTP was observed only concerning first-line therapy ($p < 0.001$). The longest median TTP was observed in patients treated with CTD (22.93 months), whereas the shortest was observed in those treated with Vel-Dex (9.22 months). Cox regression analysis identified statistically significant risk factors: prior autologous stem cell transplantation (HR 0.532, $p = 0.047$), CCI score 2+ (HR 1.298, $p = 0.041$), and elevated beta-2 microglobulin levels (HR 1.146, $p = 0.010$). In

the multivariate model, a failure to achieve VGPR after first-line therapy was the only statistically significant predictor (HR 3.162, p < 0.001). These patients had a 3.1-fold higher risk of mortality compared with the other patients.

DISCUSSION

Each year, more than 80.000 individuals worldwide are diagnosed with multiple myeloma, including approximately 520 cases in Serbia. In our unselected cohort of 200 patients, followed between 2016 and 2023, no substantial deviations in baseline characteristics were observed compared with those reported in the literature (7,8). The mean age at diagnosis was 62.5 years (range 38–80 years), which is notably younger than the mean age commonly reported (9, 10). The cohort comprised 105 men and 95 women. In this population, overall survival (OS) and median time to progression (TTP) did not differ statistically by sex, which is consistent with previously published findings (11).

Women more frequently presented with high-risk chromosomal aberrations; however, no significant differences in TTP or OS were observed compared with men (12, 13). Notably, women diagnosed with multiple myeloma before the age of 50 demonstrated a significantly poorer progression-free survival (PFS). It has been speculated that higher estrogen levels in younger women with multiple myeloma may contribute to an increased rate of disease progression, suggesting the potential consideration of anti-estrogen–based therapeutic strategies (14).

The Durie–Salmon staging system was used to determine the clinical stage of disease, serving as a parameter of tumor burden and classifying patients into three clinical stages, each subdivided into A and B categories according to renal function. In a 10-year prospective study of 109 patients with multiple myeloma, Spasov et al. reported no significant difference in OS between clinical stages II and III (15). However, patients with stage IIA disease had a longer mean survival compared with those in stage IIB (40 vs. 26 months), and patients in stage IIIA survived longer than those in stage IIIB (38 vs. 18 months). The authors concluded that patient survival depended more on the degree of renal impairment at diagnosis (A vs. B substages) than on tumor mass or clinical stage alone (15). In our cohort, median OS values were shorter than the averages reported in the literature: 34.8 months for CS I, 28.1 months for CS II, and 27 months for CS III.

Moreover, in the present study, the Durie–Salmon staging system did not demonstrate predictive value for time to progression, aligning with evidence that conventional clinical staging lacks sufficient prognostic accuracy and highlighting the necessity for incorporation of biological and additional prognostic factors. The mean overall survival (OS) in our cohort was 32.96 months, with a median OS of 36.00 months (range, 12.00–48.00 months). Published data demonstrate a progressive improvement in median OS over the decades: 22.4 months during 1980–1990, 37.4 months in 1991–2000, 61.8 months in 2001–2010, and 103.6 months from 2011 to 2020 (16).

This clearly reflects significant advancements in survival outcomes concomitant with the development of novel therapeutic modalities. The median overall survival of our patients, analyzed between 2016 and 2023, was 36 months, which corresponds to survival outcomes reported in the literature for patients treated between 1991 and 2000 (16). This finding is multifactorial. Therapeutic options used locally mirrored those applied worldwide, across the different time periods. Despite a mean patient age of 63.5 years, most treated patients were in their seventh or eighth decade, frequently burdened with multiple comorbidities. This influenced the choice of treatment regimens favoring reduced toxicity, albeit with potentially diminished efficacy. Survival outcomes in our population were significantly associated with ECOG performance status, International Staging System (ISS) stage, Charlson Comorbidity Index (CCI), beta-2 microglobulin levels, autologous stem cell transplantation (ASCT) status, first-line treatment protocol, and depth of response after both (first and second-line therapies). ECOG performance status 1 was predominant (36.0%), 53.0% of patients were classified as high-risk (ISS stage 3), and the majority of patients (44.5%) were at clinical stage IIIA. The most frequent M-protein subtype was IgG kappa (44.9%), and a CCI score 2 was most common (32.0%). Consistent with the existing literature, advanced age and comorbidities were linked to increased mortality risk in multiple myeloma (17). The impact of comorbidities was most pronounced during the first-year post-diagnosis in patients with CCI ≥ 3 and cardiovascular disease (18). Similarly, in our cohort, patients aged over 65 exhibited a statistically significant difference in survival stratified by CCI score. Since the mid-1990s, ASCT has been integrated into myeloma treatment and is associated with improved survival (19); however, ongoing research is required to optimize patient selection and outcomes.

The transplantation procedure must be evaluated holistically, considering patient age, disease burden, renal function, prior chemotherapy regimens, duration of disease before transplantation, stem cell dose, neutrophil engraftment kinetics, and psychosocial factors. Current evidence suggests that disease subtype, post-transplantation recovery rate, preserved renal function, and achieving complete remission prior to ASCT are the key determinants of transplant efficacy (20–22). In our center, 34 patients underwent ASCT. Median OS was significantly longer in transplanted patients (48.0 months) compared to non-transplanted patients (30.0 months). Beta-2 microglobulin remains the most robust and independent prognostic biomarker for survival in multiple myeloma, irrespective of renal function and clinical stage (23). Median OS was 48.0 months for ISS stage I, 30.0 months for ISS stage II, and 24.0 months for ISS stage III (beta-2 microglobulin > 5.5 g/L).

Within our cohort, FISH analysis was conducted in 34 patients. The limited number reflects the recent implementation of routine FISH testing, which commenced at the end of 2022. A subset of patients with double-hit myeloma exhibited rapid mortality following diagnosis, underscoring the significantly increased disease aggressiveness associated with the presence of concurrent high-risk mutations (24, 25).

First-line treatment outcomes

The majority of patients in our study received CTD as first-line therapy (40.5%), while 12.5% were treated with VTD. Treatment was administered in accordance with the current local clinical guidelines, and the lower number of patients receiving VTD protocol due to its delayed incorporation into practice. The CTD regimen as first-line therapy induced a VGPR in 55% of cases and a PR in 20%. It controlled disease symptoms, achieving stable disease in 11.3% of patients, while disease progression occurred in an equal percentage (11.3%). Overall survival (OS) was 38 months, and time to progression (TTP) was 22 months, representing the longest TTP observed in our cohort. We previously established a statistically significant difference in TTP depending on the first-line therapy (26-28), with the longest TTP observed in patients treated with CTD, and the shortest in those receiving Vel-Dex. Vasquez et al. reported that CTD therapy yielded a CR rate of 5% and VGPR of 32% (29). This protocol demonstrates good efficacy with tolerable toxicity, it is suitable for both transplant-eligible and transplant-ineligible patients, it is cost-effective, widely used in our country, and can be administered entirely orally. It can also be combined with novel agents, as described in the Cyklone study (cyclophosphamide, carfilzomib, thalidomide, and dexamethasone) (30), which showed high efficacy of this combination. Patients treated with the MPT protocol at our clinic achieved VGPR and PR in 41.7% of cases. This regimen rarely induced stable disease (2.8%) and led to progression in 11.1% of patients. The time to progression was 20 months, comparable to Hulín's study (31) (24 months) and Antonio Polumba's study (32) (21 months). In elderly patients, thalidomide is often omitted due to prior thrombotic events, resulting in the use of the MP protocol. Among patients treated with the VTD protocol, CR was achieved in 18.2%, VGPR in 50%, and progression in 18.2%. The TTP was 15 months. In the PETHEMA/GEM study (33), CR was achieved in 35% of patients treated with VTD, representing the highest complete remission rate attained with any pre-transplant regimen, even in patients with high-risk cytogenetic abnormalities. VGPR was achieved in 60%, and progression occurred in 13%. Median PFS was 56 months in patients with standard cytogenetic risk but significantly shorter (18 months) in those with high-risk abnormalities. In our cohort, VTD was the only protocol associated with CR according to International Myeloma Working Group criteria, achieved in 18.2% of patients. The highest progression rate (53.3%) was observed in patients treated with the Vel-Dex protocol. Vel-Dex induced VGPR in 33.3% and stable disease in 13.3% of patients.

When Vel-Dex induces a therapeutic response, its duration is typically short. Correspondingly, the shortest TTP in our cohort was 9 months for Vel-Dex, consistent with literature data from Huynh et al. (34) reporting TTP of 13.2 months and OS of 26.9 months. The average overall survival (OS) associated with the most commonly used first-line therapies was analyzed and found to differ significantly. Patients treated with CTD had the longest median OS of 38 months, while those receiving VMP had the shortest OS at 12.0 months. Patients on MPT achieved a median OS of 35.6 months, on VelDex 21.4 months, on VTD 17.2 months, and on VCD, the median OS was 17 months.

Second-line treatment outcomes

In our cohort, the highest overall response rate at first relapse was observed following the PAD regimen, with a

VGPR rate of 34.3% and a median overall survival (OS) of 48 months. Zhang et al. corroborated the efficacy of the PAD protocol in relapsed/refractory multiple myeloma (RRMM), demonstrating outcomes independent of conventional prognostic factors, particularly in patients exhibiting extramedullary disease. The triplet combination of bortezomib, doxorubicin, and dexamethasone reliably achieves at least a partial response (PR), even in patients with prior bortezomib exposure. This efficacy is attributed to the synergistic cytotoxic effects of bortezomib when combined with anthracyclines and alkylating agents, such as melphalan (35).

The survival of patients with multiple myeloma has markedly improved worldwide due to the availability of novel therapeutic options. Younger, transplant-eligible patients benefit from intensive regimens, including multi-drug combinations and autologous stem cell transplantation, while elderly, transplant-ineligible patients gain from agents with improved safety profiles. The introduction of anti-CD38 monoclonal antibodies (36), CAR-T cell therapies (37), bispecific antibodies (38), and antibody–drug conjugates (39) has expanded treatment possibilities, although these approaches are mostly reserved for relapsed/refractory cases. Additionally, novel therapeutic classes are expected to emerge (40); however, their clinical positioning and the development of MRD-guided treatment strategies have yet to be fully defined (41–43).

- The median overall survival (OS) of our entire patient cohort, as well as within individual disease stages, was shorter compared to internationally reported outcomes.
- The average survival of patients treated at our Clinic significantly differed based on performance status, ISS score, Charlson comorbidity index, β2-microglobulin levels, administration of ASCT regimen, first-line therapy protocol, therapeutic response after the first and second lines of treatment, identifying patients with poorer overall survival.
- The highest rate of complete remissions was observed in patients with good general condition and without significant comorbidities who were treated with the VTD protocol in the first line. The longest average survival was noted in younger patients treated with the CTD protocol.
- Elderly patients with a high Charlson comorbidity score benefited from MPT protocol, while the highest progression rate was associated with the Vel-Dex protocol.
- The combination of bortezomib, doxorubicin and dexamethasone (PAD) achieved the highest response rate and best survival outcomes in patients with multiple myeloma in the second-line treatment.
- Performing FISH analysis for every patient is essential. Patients with high-risk chromosomal aberrations or multiple concurrent high-risk genetic mutations (double or triple hit) require an individualized therapeutic approach, as they show statistically significant differences in mortality outcomes.

Acknowledgement

This study was not supported by any sponsor of funder.

Competing interest

The authors declare no relevant conflicts of interest.

REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al. Myeloma - Cancer Stat Facts. SEER Cancer Statistics Review, 1975-2014. 2017.

2. Bowcock S, Atkin C, Iqbal G, et al. Presenting symptoms in newly diagnosed myeloma, relation to organ damage, and implications for symptom-directed screening: A secondary analysis from the Tackling Early Morbidity and Mortality in Myeloma (TEAMM) Trial. Cancers 2023;15(13):3337. https://doi.org/10.3390/cancers15133337.

3. Mitrović M, Sretenović A, Bila J. The significance of prognostic profiling in the treatment of patients with multiple myeloma. Medicinski podmladak 2020;71(4):17-24. https://doi.org/10.5937/mp71-28137

4. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: A report from international myeloma working group. J Clin Oncol 2015;33(26):2863-9. https://doi.org/10.1200/JCO.2015.61.2267

5. Wang J, Li J, Zhang R, et al. Real-world prognostic significance of attaining minimal residual disease negativity in newly diagnosed multiple myeloma. Discov Oncol 2024;15(1):38. https://doi.org/10.1007/s12672-024-00891-8

6. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021;32(3):309-22. https://doi.org/10.1016/j.annonc.2020.11.014

7. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011;364(11):1046-60. https://doi.org/10.1056/NEJMra1011442

8. Fischer J, Knop S, Danhof S, et al. The influence of baseline characteristics, treatment and depression on health-related quality of life in patients with multiple myeloma: a prospective observational study. BMC Cancer2022;22(1):1032. https://doi.org/10.1186/s12885-022-10101-9

9. Caulier A, Roussel M, Morel P. Epidemiological landscape of young patients with multiple myeloma diagnosed before 40 years of age: the French experience. Blood 2021;138(25):2686-95. https://doi.org/10.1182/blood.2021011285

10. Jurczyszyn A, Nahi H, Avivi I, et al. Characteristics and outcomes of patients with multiple myeloma aged 21-40 years versus 41-60 years: a multi-institutional case-control study. Br J Haematol 2016;175(5):884-91. https://doi.org/10.1111/bjh.14328

11. Bird S, Cairns D, Menzies T, et al. Sex differences in multiple myeloma biology but not clinical outcomes: results from 3894 patients in the Myeloma XI Trial. Clin Lymphoma Myeloma Leuk 2021;21(10):667-75. https://doi.org/10.1016/j.clml.2021.04.013

12. Boyd KD, Ross FM, Chiecchio L, et al. Gender disparities in the tumor genetics and clinical outcome of multiple myeloma. Cancer Epidemiol Biomarkers Prev 2011;20(8):1703-7. https://doi.org/10.1158/1055-9965.EPI-11-0157

13. Derman BA, Langerman SS, Maric M, et al. Sex differences in outcomes in multiple myeloma. Br J Haematol 2021;192(3):e66-9. https://doi.org/10.1111/bjh.17237

14. Ozerova M, Nefedova Y. Estrogen promotes multiple myeloma through enhancing the immunosuppressive activity of MDSC. Leuk Lymphoma 2019;60(6):1557-62. https://doi.org/10.1080/10428194.2018.1538511

15. Zhang Y, Pan J, Kang H, et al. Prognosis of concurrent renal impairment at diagnosis of multiple myeloma: a systematic review. Ann Med 2024;56(1):2380301. https://doi.org/10.1080/07853890.2024.2380301

16. Puertas B, González-Calle V, Sobejano-Fuertes E, et al. Novel agents as main drivers for continued improvement in survival in multiple myeloma. Cancers 2023;15(5):1558. https://doi.org/10.3390/cancers15051558

17. Palumbo A, Bringhen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group

report. Blood 2015;125(13):2068-74.
https://doi.org/10.1182/blood-2014-12-615187

18. Yin X, Fan F, Zhang B, et al. Cardiovascular-specific mortality among multiple myeloma patients: a population-based study. Ther Adv Hematol 2022;13.
https://doi.org/10.1177/20406207221086755

19. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996;335(2):91-7.
https://doi.org/10.1056/NEJM199607113350204

20. Antlanger M, Dust T, Reiter T, et al. Impact of renal impairment on outcomes after autologous stem cell transplantation in multiple myeloma: a multi-center, retrospective cohort study. BMC Cancer 2018;18(1):1008.
https://doi.org/10.1186/s12885-018-4926-0

21. Kushwaha N, Kumar S, Sheikh MA, et al. Association of CD34 positive cell dose with engraftment kinetics in autologous peripheral blood stem cell transplant patients of multiple myeloma. Med J Armed Forces India 2021;78(3):296-301.
https://doi.org/10.1016/j.mjafi.2021.01.015

22. Kim JS, Kim K, Cheong JW, et al. Complete remission status before autologous stem cell transplantation is an important prognostic factor in patients with multiple myeloma undergoing upfront single autologous transplantation. Biol Blood Marrow Transplant 2009;15(4):463-70.
https://doi.org/10.1016/j.bbmt.2008.12.512

23. Qin X, Xu Y, An G, et al. The impact of renal function on prognostic value of β_2-microglobulin of ISS stage system in multiple myeloma patients--clinical data analysis of 666 patients in a single center. Zhonghua Xue Ye Xue Za Zhi 2015;36(5):393-7.
10.3760/cma.j.issn.0253-2727.2015.05.008

24. Walker BA, Mavrommatis K, Wardell CP, et al. A high-risk, double-hit, group of newly diagnosed myeloma identified by genomic analysis. Leukemia 2019;33(1):159-70.
https://doi.org/10.1038/s41375-018-0196-8

25. Hanamura I. Multiple myeloma with high-risk cytogenetics and its treatment approach. Int J Hematol 2022;115(6):762-77.
https://doi.org/10.1007/s12185-022-03353-5

26.San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359(9):906–17.
https://doi.org/10.1056/NEJMoa0801479

27. Benboubker L, Dimopoulos MA, Dispenzieri A. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371(10):906-17.
https://doi.org/10.1056/NEJMoa1402551

28. Durie BG, Hoering A, Abidi MH, et al. Bortezomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet 2017;389(10068):519-27.
https://doi.org/10.1016/S0140-6736(16)31594-X

29. Vasquez J, Ruiz R, Aliaga K, et al. Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with newly diagnosed multiple myeloma in a middle-income country: 7-year follow-up. JCO Glob Oncol 2021;7:1199-205.
https://doi.org/10.1200/GO.20.00665

30. Mikhael JR, Reeder CB, Libby EN, et al. Phase Ib/II trial of CYKLONE (cyclophosphamide, carfilzomib, thalidomide and dexamethasone) for newly diagnosed myeloma. Br J Haematol 2015;169(2):219-27.
https://doi.org/10.1111/bjh.13296

31. Hulin C, Belch A, Shustik C, et al. Updated outcomes and impact of age with lenalidomide and low-dose dexamethasone or melphalan, prednisone, and thalidomide in the randomized, phase III FIRST trial. J Clin Oncol 2016;34(30):3609-17.
https://doi.org/10.1200/JCO.2016.66.7295

32. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized

controlled trial. Blood 2008;112(8):3107-14. https://doi.org/10.1182/blood-2008-04-149427

33. Rosiñol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood 2012;120(8):1589-96. https://doi.org/10.1182/blood-2012-02-408922

34. Huynh L, Birsen R, Mora L, et al. Multiple myeloma in patients over 80: A real world retrospective study of first line conservative approach with bortezomib dexamethasone doublet therapy and mini-review of Literature. Cancers 2022; 14(19):4741. https://doi.org/10.3390/cancers14194741

35. Palumbo A, Gay F, Bringhen S, et al. Bortezomib, doxorubicin and dexamethasone in advanced multiple myeloma. Ann Oncol 2008;19(6):1160-5. https://doi.org/10.1093/annonc/mdn018

36. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet 2016;387(10027):1551-60. https://doi.org/10.1016/S0140-6736(15)01120-4

37. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene Vicleucel in relapsed and refractory multiple myeloma. N Engl J Med 2021;384(8):705-16. https://doi.org/10.1056/NEJMoa2024850

38. Verkleij CPM, Frerichs KA, Broekmans M, et al. T-cell redirecting bispecific antibodies targeting BCMA for the treatment of multiple myeloma. Oncotarget 2020;11(45):4076-81. https://doi.org/10.18632/oncotarget.27792

39. Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol 2020;21(2):207-21. https://doi.org/10.1016/S1470-2045(19)30788-0

40. Lu Q, Yang D, Li H, et al. Multiple myeloma: signaling pathways and targeted therapy. Mol Biomed 2024;5(1):25. https://doi.org/10.1186/s43556-024-00188-w

41. Perrot A, Lauwers-Cances V, Corre J, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. Blood 2018;132(23):2456-64. https://doi.org/10.1182/blood-2018-06-858613

42. Kostopoulos IV, Ntanasis-Stathopoulos I, Gavriatopoulou M, et al. Minimal residual disease in multiple myeloma: current landscape and future applications with immunotherapeutic approaches. Front Oncol 2020;10:860. https://doi.org/10.3389/fonc.2020.00860

43. Perrot A, Lambert J, Hulin C, et al. Measurable residual disease–guided therapy in newly diagnosed multiple myeloma. N Engl J Med 2025;393(5):425-37. https://doi.org/10.1056/NEJMoa2505133