VIA MEDICA

ORIGINAL RESEARCH ARTICLE

Acta Haematologica Polonica 2022
Number 3, Volume 53, pages 201–206
DOI: 10.5603/AHP.a2022.0024
ISSN 0001–5814
e-ISSN 2300–7117

Survival in multiple myeloma: a real-life single-center study

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Abstract

Introduction: The development of novel drugs with a different mechanism of action has led to considerable progress in multiple myeloma (MM) treatment. However, the exact associations between overall survival (OS) and different treatment types, response to treatment, as well as clinical and laboratory parameters, have not been fully elucidated.

We aimed to determine the effect of clinical and laboratory parameters, type of induction therapy, and high-dose chemotherapy with autologous hematopoietic stem-cell transplant (auto-HSCT) on OS in patients with MM.

Material and methods: This retrospective study included 413 patients with MM treated between 2006 to 2017. Correlations between selected clinical and laboratory parameters and OS were assessed. The severity of MM was evaluated using the Durie-Salmon classification.

Results: The median OS was 4.08 years. The overall response rate to chemotherapy was 76%. The complete remission (CR) rates were higher in patients receiving bortezomib-based therapy than in those receiving thalidomide-based therapy or standard chemotherapy (p <0.001). The CR rate was positively correlated with OS. The use of auto-HSCT with bortezomib-based therapy was associated with longer OS. Renal failure and elevated urinary protein levels were inversely correlated with OS. The severity of MM at diagnosis was also associated with OS. The percentage of bone marrow plasma cell infiltration did not correlate with OS.

Conclusions: MM is still diagnosed too late, by which time patients have developed almost irreversible complications. However, we confirmed that novel treatments improve OS in these patients, especially when used in addition to auto-HSCT. These findings may facilitate clinical therapeutic decision making.

Key words: autologous hematopoietic stem-cell transplant, bortezomib, chemotherapy, multiple myeloma, overall survival

Acta Haematologica Polonica 2022; 53, 3: 201–206

Introduction

The approach to the care and management of patients with multiple myeloma (MM) is been evolving rapidly. Today, the greatest challenge is the choice of individualized therapy in this highly diverse population. Historically, the median overall survival (OS) in patients with MM was about three years. However, in the era of novel highly active treatment options, a marked improvement in patient outcomes has been observed, with median OS reaching 5–7 years

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Received: 24.10.2021 Accepted: 21.03.2022

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[1]. Even so, progress in MM treatment has complicated clinical decision making. The development of a treatment plan should include individual patient evaluation, defining treatment goals, as well as the assessment of therapy- and disease-related risk factors. Undoubtedly, for newly diagnosed patients, first-line treatment choice has the most important effect on overall response and survival rates.

Real-world registry studies have concluded that c.40% of patients with MM do not meet the inclusion criteria for clinical trials [2]. Patients who are ineligible for enrolment due to poor performance status, high comorbidity index, or organ dysfunction are thus commonly overlooked, and so the outcomes of this population are underreported in the literature.

One of the largest prospective studies to describe real-life treatment of MM patients has revealed a great diversity of treatment modalities, the availability of novel agents, and ever-evolving treatment recommendations [3].

The aim of our study was to assess the effect of selected clinical and laboratory parameters, the type of induction therapy, and response to therapy on OS in patients with MM. Moreover, we aimed to evaluate the role of high-dose chemotherapy with autologous hematopoietic stem cell transplant (auto-HSCT) in the treatment of patients with MM, and to identify patients with short OS despite the use of auto-HSCT as well as patients with long OS who did not receive auto-HSCT.

Material and methods

This retrospective study included 413 patients with MM [234 women (56.7%) and 179 men (43.3%); mean age, 66.9 years (range: 27–89)] treated at the Department of Hematology at the Rydygier Hospital in Kraków, Poland, from 2006 to 2017.

Data on the following clinical and laboratory parameters was collected and included in a dedicated database: lactate dehydrogenase, urinary protein (<1 g/L, 1–2 g/L, and >2 g/L), and total protein levels (<100 g/L, 101–120 g/L, and >120 g/L); monoclonal antibody class; type [immunoglobulin G (IgG), IgA, IgM, light chain], form (systemic, localized), and clinical stage of MM (Durie-Salmon classification); and prognosis according to the International Staging System (ISS) and Revised ISS (R-ISS). Data regarding the number of treatment lines, regimens, outcomes, and follow-up duration was also collected. The results of cytogenetic studies were assessed. Risk factors for bone lesions and surgical treatment of bone lesions were evaluated. In the case of unselected proteinuria >0.5 g/24 hours, Bence-Jones protein was assessed. Finally, we assessed associations of OS with laboratory parameters, complete remission (CR), disease severity, ISS and R-ISS stages, the extent of bone marrow infiltration, induction therapy, as well as single and tandem transplant.

Statistical analysis

Qualitative variables such as selected laboratory parameters were presented as mean and SD, median, and minimum-maximum values. The variables were compared between subgroups divided according to risk, treatment, or selected clinical parameters (such as disease severity) using a nonparametric Mann-Whitney test for comparisons between two variables and a Wilcoxon test for comparisons between more than two variables. The rank correlation coefficient between lactate dehydrogenase (LDH) levels and selected laboratory parameters was calculated. Ranked or qualitative variables were presented as number and percentage of patients. The independent χ^2 test was used to assess outcomes for consecutive lines of chemotherapy. Survival analysis was used to compare OS depending on selected risk factors, type of treatment, treatment outcomes after each line of chemotherapy, and selected clinical parameters. Patients receiving auto-HSCT constituted a separate subgroup. The independent χ^2 test was used in this subgroup to assess OS depending on selected factors as well as to assess the effect of selected risk factors on OS shorter or longer than five years. Results with a p value of 0.05 or lower were considered significant. Statistical analysis was conducted using Statistica 13 PL (StatSoft, Kraków, Poland).

Results

Depending on the analyzed parameter, data completeness ranged from 15.2% (31 of 204 patients) for the analysis of the causes of death to 96.6% (399 of 413 patients) for the analysis of the type of MM.

At diagnosis, 95.6% of patients had symptomatic MM. The most common type of MM was immunoglobulin (Ig) G kappa, observed in 155 patients (38.8%). Most patients (n = =214; 54.7%) had stage IIIA MM according to the Durie-Salmon classification. Stage IA MM was noted in 26 patients (6.6%), stage IB in two (0.5%), stage IIA in 34 (8.7%), stage IIB in five (1.3%), and stage IIIB in 110 (28.1%).

Using the ISS, MM was classified as stage III in 55.9% of patients (n = 124) and as stage II in 30.2 % of patients (n = 67).

Cytogenetic study for both karyotype and FISH (t(4;14), t(14;16), del17p) determination was known in 43 patients (10.4%). Classical cytogenetics is not part of the R-ISS classification, but karyotype can be helpful in detecting additional cytogenetic abnormalities such as hypodiploidia.

The most common cytogenetic abnormality was t(4;14), observed in 11 patients (25.6%), while more than half of the study group had normal karyotype (n = 22; 51.1%) (Table I).

Chemotherapy regimens used in the study group allowed the achievement of an overall response rate of 76% in 202 patients. CR and stringent CR was achieved in 60 patients (22.6%; Table II). The CR rate was higher

Table I. Cytogenetic study results in study group (n = 43)

Result	N	[%]
Normal	22	51.1
t(4;14)	11	25.6
del *TP53*, t(4;14)	3	7
del 13	1	2.3
del *TP53*	3	7
Hyperdiploidy	1	2.3
Trisomy 17, 17p13	1	2.3
Trisomy 17, del *TP53*	1	2.3

Table II. First-line chemotherapy outcomes (n = 266)

Outcome	N	[%]
CR	55	20.7
sCR	5	1.9
PR	100	37.6
VGPR	42	15.8
SD	36	13.6
PD	27	10.2
Patients remaining under follow-up	1	0.4

CR — complete remission; sCR — stringent complete remission; VGPR — very good partial remission, PD — progressive disease; SD — stable disease

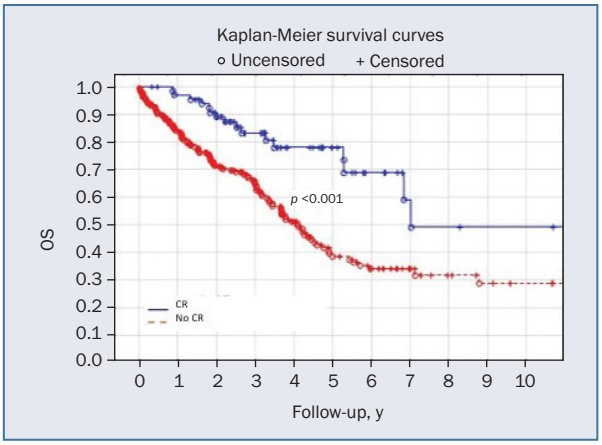

Figure 1. Kaplan-Meier survival plot showing overall survival (OS) in patients with multiple myeloma who achieved and did not achieve complete remission (CR) after first-line chemotherapy

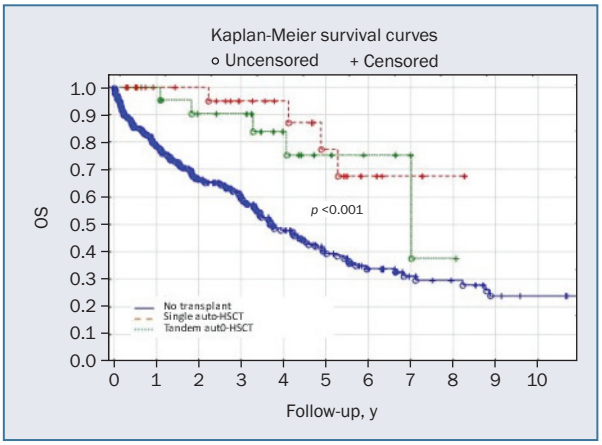

Figure 2. Kaplan-Meier survival plot showing overall survival (OS) in patients with multiple myeloma depending on use of autologous hematopoietic stem-cell transplant (auto-HSCT), single auto-HSCT, tandem auto-HSCT, or no transplant

(p <0.001) in patients treated with bortezomib-based therapy (VTD, VCD, VD, VMP, PAD) 36.1% than in those treated with thalidomide-based therapy (MPT, CTD, TD) 24.7%, and standard chemotherapy (VAD, CD, COP, CP, MD, MP, P) 10.3%. 8.2% of patients received both thalidomide and proteasome inhibitor (VTD regimen) (n = 29), and separate analysis for OS was not assessed in this group. Monoclonal antibodies were not available in Poland until July 2019 in routine practice.

Patients received a maximum of nine lines of treatment. The follow-up duration and maximum OS was 23 years. Achievement of CR after the first-line chemotherapy was associated with longer OS (median OS 7 vs. 4 years) (p <0.001) (Figure 1). Transplant treatment (both auto-HSCT and tandem transplant) was also associated with longer OS (median OS 7 vs. 3.75 years) (p <0.001) (Figure 2), regardless of age divided into two groups <60 years and 60–75 years, but this lacked statistical significance (NS, n = 50).

Elevated serum LDH levels (>248 U/L) correlated positively with leukocyte count (p = 0.037), percentage of bone marrow plasma cell infiltration (p = 0.009), and ISS stage (p = 0.025), (LDH assessment as a part of R-ISS staging was an auto-control parameter), while negatively correlated with serum IgA levels (p <0.001).

Bone lesions associated with MM were observed in 215 patients (74.4%) at diagnosis, and they were more common in men than in women (p = 0.002). The presence of bone lesions was not correlated with patient age, percentage of bone marrow plasma cell infiltration, or ISS stage. Surgical treatment such as vertebroplasty, transpedicular spondylodesis or intramedullary nailing was necessary in 50 of the 303 patients (16.5%) assessed for the presence and treatment of bone lesions. Surgical patients included 27 women (54%). 31 individuals aged 60 to 75 years (62%) were not analyzed for overall survival.

The median OS in the study group was 4.08 years. The OS for the whole study group is presented in Figure 3. Overall survival was associated with the severity of MM at diagnosis (Figure 4) and the ISS stage (Figure 5). However, no associations were shown for the R-ISS stage, probably because of a small sample size (the cytogenetic study was performed only in 43 patients). The percentage of bone

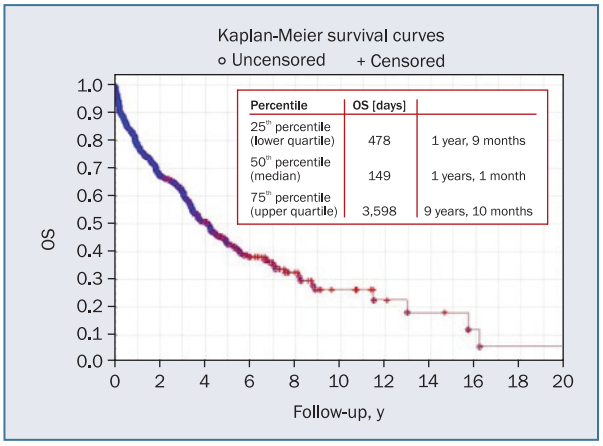

Figure 3. Overall survival (OS) for whole study group (n = 413)

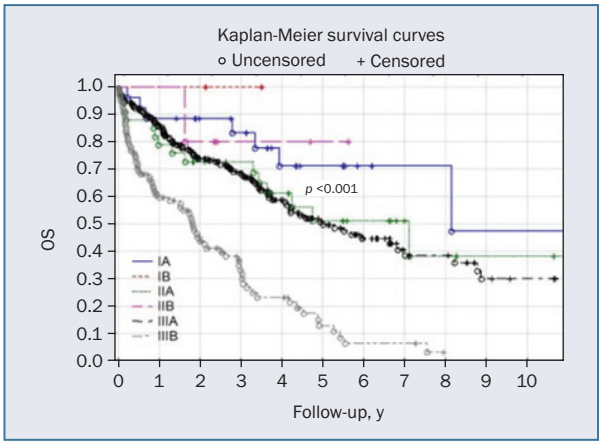

Figure 4. Kaplan-Meier survival plot showing overall survival (OS) of patients with multiple myeloma depending on disease severity according to Durie-Salmon classification (n = 391)

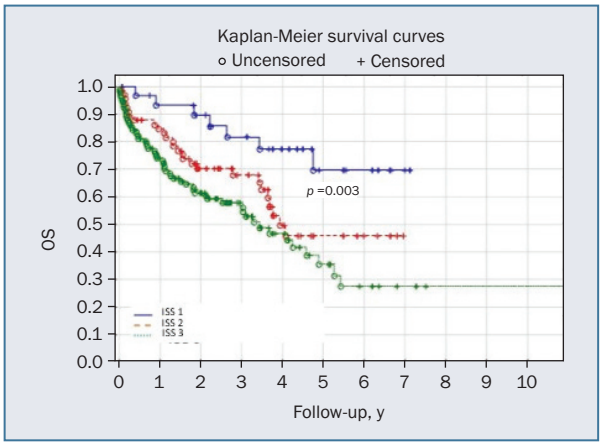

Figure 5. Kaplan-Meier survival plot showing overall survival of patients with multiple myeloma depending on International Staging System stage (n = 222)

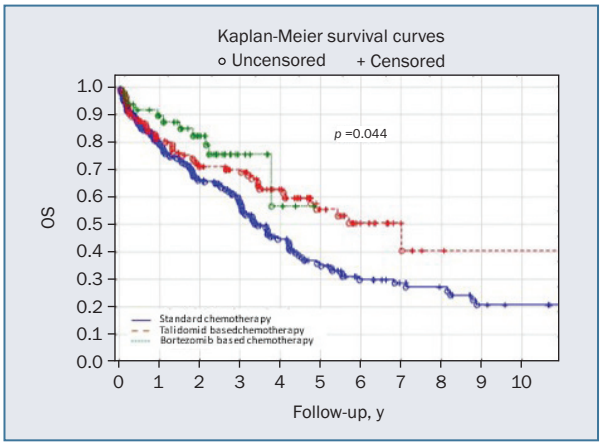

Figure 6. Kaplan-Meier survival plot showing overall survival of patients with multiple myeloma depending on type of first-line chemotherapy (n = 341)

Table III. Association between autologous hematopoietic stem-cell transplant and overall survival of less than, and more than, five years

Transplant	N	OS <5 years	OS >5 years	Censored observations <5 years	*p* value
No transplant	256	47 18.4%	124 48.4%	85 33.2%	<0.001
auto-HSCT	29*	8** 27.6%**	3** 10.3%**	18 62.0%	
Tandem auto-HSCT	21*	6** 28.6%**	4** 19.0%**	11 52.5%	

*Patients included in survival analysis; **patients included in subsequent χ^2 test analysis; auto-HSCT – autologous hematopoietic stem-cell transplant; OS – overall survival

marrow plasma cell infiltration did not correlate with OS, although the survival curves may imply a potential relationship (data not shown). Finally, induction therapy with the proteasome inhibitor bortezomib was significantly associated with longer OS (Figure 6).

A separate analysis was conducted to identify patients who do not benefit from transplant treatment. In a group of 50 transplant recipients, there were seven (three after auto-HSCT, four after tandem auto-HSCT) with a survival longer than five years. 29 patients (18 after auto-HSCT, 11 after tandem auto-HSCT) were alive at the time of the study (censored observations). The total number of patients with survival longer than five years in this group was 36 (72%) (Table III).

In patients after auto-HSCT, there were no associations between OS and sex, age, or elevated LDH levels. Moreover, no significant association between the presence of renal failure and OS was observed. There was no association between OS and urinary protein or total protein levels. No associations were noted for the ISS stage, which may suggest that these patients have a similar OS despite differences in prognostic factors (ISS, R-ISS) at baseline. However, the study group was too small (n = 43) to draw firm conclusions. Finally, OS was not significantly associated with the percentage of bone marrow plasma cell infiltration (<40%, 41%–59%, or >60%) or the achievement of CR after the first-line treatment.

Discussion

Most studies suggest that survival improvement in older adults with MM is less pronounced compared to that in younger individuals. Older adults with MM are particularly vulnerable to adverse events (AEs) associated with multidrug combinations, which can lead to dose reductions or treatment discontinuation, both of which are associated with poorer outcomes. The goals of care for older adults may differ from those in younger adults; older adults facing serious illness are more likely to prioritize symptom control and the maintenance of independence rather than prolonged survival [1].

Thus, although the effectiveness of ASCT in older patients in the era of novel agents remains an important area for investigation, ASCT can be a feasible and efficacious component of therapy for selected older patients with MM. Exactly which older adults are eligible for ASCT remains poorly defined [1].

Multiple myeloma is still diagnosed too late when the disease stage is advanced [most patients (n = 214; 54.7%) had stage IIIA according to the Durie-Salmon classification], when the tumor mass is large, and complications are almost irreversible.

Our study showed that OS, the most important survival indicator, is associated with Durie-Salmon and ISS stages at diagnosis. We also observed a positive effect of achieving CR on OS. Moreover, the CR rate was significantly higher in patients receiving chemotherapy with the proteasome inhibitor bortezomib than in those receiving thalidomide and standard chemotherapy. Longer OS was also related to auto-HSCT, both single and tandem transplant.

In recent years, there has been considerable progress in the treatment of MM due to the introduction of novel drugs and their subsequent generations, including immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, ixazomib) [1, 3–6], anti-CD38 monoclonal antibodies (daratumumab), anti-SLAMF7 antibody (elotuzumab), signaling pathway inhibitors (panobinostat) [7], and immunotherapy with chimeric antigen receptor (CAR) T cells, namely, genetically engineered autologous T-cells (anti-BCMA CAR T-cells) [8].

The use of drugs with an alternative mechanism of action in the treatment of MM has improved survival of these patients, with an increase in median OS from 3/4 years to 5–7 years over the last 20 years. It is estimated that survival since diagnosis is still less than two years in 25% of patients. In 50–70% of patients, survival is five years or longer, depending on response to therapy, treatment tolerance, use of immunomodulatory drugs, and eligibility for auto-HSCT [9].

Our study had a retrospective design and a relatively long follow-up (2006–2017). Considering the study duration and the Polish setting, the treatment outcomes and OS in the study group seem to be relatively good compared to other national and international centers. However, since the completion of our study, new generations of drugs such as carfilzomib, lenalidomide, and pomalidomide and drugs with new mechanisms of action such as monoclonal antibodies daratumumab and belantamab mafodotin have been developed, although they are not available as first-line regimens in clinical practice in Poland. This may be considered a limitation of the study.

Our study has important implications for therapeutic decision making. In the Polish setting, patients with MM should receive induction therapy based on bortezomib and should be more often referred for auto-HSCT. Bortezomib-based regimens in individuals eligible for auto-HSCT include VRD (bortezomib, lenalidomide, dexamethasone), VTD (bortezomib, thalidomide, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone), PAD (bortezomib, doxorubicin, dexamethasone), or, in exceptional cases, CTD (cyclophosphamide, thalidomide, dexamethasone) [7].

Authors' contributions

MRo — study conception and desing, manuscript writing. AMK — data collection and analysis. MRa — revision of mauscript. BJ — revision of manuscript et paper design.

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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