Prognostic factors and clinical characteristics of patients with newly diagnosed non-secretory multiple myeloma in the era of new drugs in "real-world" study: Experiences of the Polish Myeloma Group

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Abstract

Background. Non-secretory multiple myeloma (NSMM) accounts for approx. 2–3% of multiple myeloma (MM) cases. Due to the rare occurrence and ineligibility of patients with NSMM to participate in clinical trials, we have limited data on treatment efficacy and the clinical course in these patients. Most of the literature consists of case reports and small retrospective studies.

Objectives. The study aimed to analyze patient characteristics, prognostic factors and treatment outcomes in newly diagnosed (ND) NSMM.

Materials and methods. This is a multicenter, retrospective analysis of 43 patients with NSMM diagnosed between June 2010 and September 2021, conducted in 8 Polish hematology centers.

Results. The median overall survival (OS) was 103 months (95% confidence interval (95% CI): 20–72). The most common cause of death was MM disease progression. The overall response rate (ORR) was 84.6%; complete response (CR), very good partial response (VGPR), partial response (PR), and no response (NR) rates were 20.5%, 46.2%, 17.9%, and 15.4%, respectively. In multivariable analysis, factors contributing to worse OS included International Staging System stage 3 (ISS-3) ($p = 0.0277$), anemia (Hb <10 g/dL or >2 below upper limit of normal value (ULN), $p = 0.0270$), renal insufficiency (RI, serum creatinine >2 mg/dL, $p = 0.0476$), and serum albumin <5.5 mg/L (0.0408).

Conclusions. Non-secretory multiple myeloma is a rare subtype of MM. This small study demonstrates that outcomes are comparable to secretory MM. However, the inclusion of this subset of patients in clinical trials is essential to assess prognosis, treatment efficacy and clinical outcomes.

Key words: clinical characteristics, non-secretory multiple myeloma, prognostic factors

Background

Multiple myeloma (MM) is a bone marrow (BM) cancer characterized by uncontrolled proliferation of clonal plasmocytes (CP) in the BM, which, in most cases, produces a monoclonal (M) protein found in the serum and/or urine.[1] Approximately 2,600 new MM cases are diagnosed annually in Poland.[2] The criteria for the diagnosis of MM include the presence of CP producing an M-protein and the presence of at least 1 indicator of organ damage defined by the acronym SLiM-CRAB (≥60% CPBM, serum free light chain (sFLC) ratio ≥100 or <0.01, presence of 1 or more bone lesions on magnetic resonance imaging (MRI), hypercalcemia, renal insufficiency (RI), anemia, and bone lesions).[3] In approx. 97–98% of patients with MM, an M-protein can be detected in the serum and urine using electrophoresis and immunofixation.[3]

On the other hand, in free light chain (FLC) MM, CP produce an M-protein consisting solely of the light chains of immunoglobulins.[4] In the remaining 2–3% of MM, there is no detectable M-protein in the serum and/or Bence–Jones proteins in the urine using electrophoresis or immunofixation assays.[5,6] This type of MM is generally defined as non-secretory (NS) MM.[7,8]

The introduction of nephelometric testing to detect and measure sFLC concentrations in clinical practice has changed the definition. About 3/4 of MMs identified as NSMM have elevated clonal FLC levels and an abnormal FLC ratio; these cases are called oligosecretory MM (M-protein <10 g/L, Bence–Jones protein <200 mg/24 h and sFLC <100 mg/L).[9] True NSMM, i.e., lack of M-protein synthesis, is found in approx. 2% of MM patients.[10] The pathophysiology of NSMM includes reduced M-protein synthesis, impaired secretion and rapid degradation of the M-protein intra- or extracellularly.[7]

Virtually all clinical trials exclude patients with NSMM from participation since the trials require measurable parameters to determine therapy efficacy. Thus, we have limited data on the treatment efficacy and clinical course of NSMM.[11–13] Most of the literature consists of case reports and small retrospective studies.[14–25]

Objectives

Our study aimed to analyze patient characteristics, prognostic factors and treatment of newly diagnosed (ND) NSMM.

Materials and methods

A multicenter retrospective study was conducted in 8 Polish hematology centers. Patients were identified through database searches at each study center. Each center's institutional review board approved the study following the ethical guidelines of the Declaration of Helsinki. Patients with ND NSMM between June 2010 and September 2021 were included in the analysis. Non-secretory multiple myeloma was defined by the International Myeloma Working Group (IMWG) as the absence of M-protein in serum and urine using immunofixation testing. According to the updated IMWG criteria for MM, a sFLC <100 mg/L with an abnormal sFLC ratio was defined as "oligosecretory," and "non-producing" was defined by a sFLC <100 mg/L with a normal sFLC ratio.[26,27] Patients diagnosed with monoclonal gammopathy of undetermined significance (MGUS), asymptomatic MM and organ involvement with light-chain amyloidosis (AL) were excluded from our analysis. Staging and response criteria utilized the IMWG definitions.[4,28–30]

Progression-free survival (PFS) was expressed in months and was defined as the time from diagnosis to disease progression, change of treatment or death. Overall survival (OS) was described in months as the time from diagnosis until death or last follow-up.

Statistical analyses

Continuous and categorical variables are presented using descriptive statistics. The Kaplan–Meier (K–M) method was used for survival analysis, and survival curves were generated.

The log-rank test was used to compare the differences between groups. The Cox proportional hazards regression method was applied for fitting univariable survival models, expressed as hazard ratios (HR) with 95% confidence intervals (95% CI). The Cox regression model was used to examine potential prognostic factors for ND NSMM. The univariable Cox regression and group comparisons using the log-rank test were conducted as separate analyses and do not constitute a family of hypotheses. Tests based on the Schoenfeld residuals were used to test the proportional hazards assumptions in Cox regression assumptions (cox.zph function in survival package). The Cox regression assumptions were also verified by confirming the absence of correlation between predictors based on a correlation matrix. To assess the quality of the obtained regression models, parameters such as p-value and Nagelkerke R^2 were used. All reported p-values were 2-sided and considered significant if they were less than 0.05. Variable selection for the multivariable Cox proportional hazards regression model was based on Akaike's information criterion (AIC).

The following steps were applied to construct the multiple Cox regression model using AIC criteria:

- a model that includes all considerable variables was created;
- the dredge function in the MuMIn package was used to conduct a comprehensive analysis, considering all possible combinations of variables;
- for each combination, the AIC criterion was calculated; and
- the variables from models that achieved the lowest AIC values were selected for the multivariable model.

Finally, a multivariable Cox regression model was built, and the results were interpreted, focusing on the statistical significance of independent variables, interpretability of parameters, and the sensibility of predictions in the context of the research problem and practical application of the model. The sFLC ratio variable was excluded from the analysis because the survival curves (normal compared to abnormal sFLC ratio) crossed. Such a case suggests complexity in interpreting the impact of that variable, and excluding it reduces the complexity of the required statistical analysis. The data used in the statistical analysis were complete, and there were no missing data in the dataset, except for cytogenetic studies performed in only 56% of patients. This variable was not included in the selection variable procedures.

Statistical analysis and graphics were obtained using the software PQStat v. 1.8.4.140 (PQStat Software, Poznań, Poland) and a package dedicated to survival analysis. The software R-studio v. 1.3.959 (http://www.R-exams.org) with dedicated packages was used for variable selection for the multivariable analysis.

Results

Patient characteristics

Forty-three patients with an established diagnosis of ND NSMM were included in the analysis. The median follow-up was 24 months (range: 1–137). The median age at NSMM diagnosis was 62 years (range: 41–80). Sixteen patients (37.2%) were ≥65 years old and 4 patients (9.3%) were older than 75 years. The study included 25 men (58.1%). At diagnosis, the sFLC in 25 patients (58.1%) had a ratio <0.25 or >1.65, but all patients had an absolute sFLC <100 mg/L.

All patients were monitored using laboratory tests, sFLC assays, BM aspiration, and imaging.

Laboratory tests and sFLC determinations were performed before the start of each chemotherapy cycle and every 2 months (median; range: 1–3) after the end of treatment. Depending on the hematological center, BM aspiration in the assessment of CP (multiparameter flow cytometry – MPF) was repeated every 3–6 months during and every 6 months after treatment. At the initial diagnosis, positron emission tomography/computed tomography (PET/CT) imaging was performed in 28 patients (65.1%), MRI in 6 patients (13.9%), whole-body low-dose computed tomography (WBLD-CT) in 5 patients (11.6%), and radiological imaging of the skeletal system in 4 patients (9.4%). After treatment ended, imaging studies were repeated every 6 months (median).

Using the International Staging System (ISS), 11 patients (25.6%), 10 patients (23.2%) and 22 patients (51.2%) were diagnosed with stages ISS-1, ISS-2 and ISS-3 MM, respectively. Baseline cytogenetics by fluorescent in situ hybridization (FISH) was available in 24 patients (55.8%) with NSMM. High-risk cytogenetic abnormalities were found in 11 patients (45.8%) and the t(11;14) in 2 (8.3%) of the tested patients. Patient characteristics and clinical features are listed in Table 1.

Table 1. Baseline clinical characteristics of the patients with non-secretory multiple myeloma

Variable	Value (n = 43)
Median age (min, max) [Q1, Q3]	62 (41, 80) [54.5, 66]
Age ≥65 years, n (%)	16 (37.2)
Male sex, n (%)	25 (58.1)
ISS stage, n (%)	
ISS-1	11 (25.6)
ISS-2	10 (23.2)
ISS-3	22 (51.2)
Cytogenetics	24 (55.8)
High-risk cytogenetics[a], n (%)	11 (45.8)
t(11;14), n (%)	2 (8.3)
First-line chemotherapy, n (%)	
Bort + IMiD-based	23 (53.5)
Bort-based	11 (25.6)
Thal-based	9 (20.9)
Autologous stem cell transplantation, n (%)	16 (37.2)
Dialysis, n (%)	4 (9.3)
Response after 1st-line therapy[b], n (%)	
ORR (≥PR)	33 (84.6)
≥VGPR	26 (66.7)
CR	8 (20.5)
VGPR	18 (46.2)
PR	7 (17.9)
SD	2 (5.1)
PD	4 (10.3)
Laboratory tests	
CPBM ≥ 60%, n (%)	11 (25.6)
Abnormal sFLC ratio, n (%)	25 (58.1)
Serum Hb <10 g/dL or >2 below ULN, n (%)	21 (48.8)
Serum albumin <3.5 g/dL, n (%)	11 (25.6)
Serum creatinine >2.0 mg/dL, n (%)	9 (20.9)
Serum β2-microglobulin ≥5.5 mg/L, n (%)	18 (41.9)
Serum calcium >2.75 mmol/L, n (%)	10 (23.2)
Serum LDH >ULN, n (%)	32 (74.4)
Bone lesions presence, n (%)	39 (90.7)

Q1, Q3 – 1st and 3rd quartile; max – maximum; min – minimum; ASCT – autologous stem cell transplantation; Bort – bortezomib; CPBM – clonal plasmocytes infiltration in the bone marrow; IMiD – immunomodulatory drug; Hb – hemoglobin concentration; IMiD – immunomodulatory drug; ISS – International Staging System; LDH – lactate dehydrogenase; sFLC – serum free light chain; Thal – thalidomide; ULN – upper limit of normal value; VGPR – very good partial response; [a] defined as presence of t(4;14), t(14;16), t(14;20) or del17p in the absence of any trisomy; [b] response: ORR – overall response rate; CR – complete response; PR – partial response; VGPR – very good partial response; SD – stabile disease; PD – progression disease.

NSMM treatment

Thirty-four patients (79.1%) received bortezomib (Bort)-based therapy. Twenty-three (53.5%) patients received Bort in combination with an immunomodulatory drug (IMiD, thalidomide (Thal) – 21 patients, lenalidomide – 2 patients), and 11 patients (25.6%) were treated with Bort in combination with other drugs. Nine patients (20.9%) received Thal-based treatment. After induction therapy, 16 (37.2%) patients received high-dose chemotherapy followed by an autologous stem cell transplantation (ASCT). Maintenance therapy was not used after ASCT.

After 1st-line treatment, the ORR (≥PR) was 84.6%, while CR, VGPR, PR, and NR ratios were 20.5%, 46.2%, 17.9%, and 15.4%, respectively (Table 1). Complete response was achieved in 31.2% of patients treated with chemotherapy, followed by ASCT and in 11.1% of patients treated with chemotherapy only.

The median PFS was 16 months (95% CI: 9–34, Fig. 1A). Comparing patients treated with ASCT following induction therapy with patients not treated with ASCT, the median PFS was 34 months compared to 9 months, respectively (log-rank HR: 0.288, 95% CI: 0.137–0.606; p = 0.0034). Additionally, we found a trend towards longer PFS in patients who achieved a greater PR after 1st-line treatment compared to patients who did not; median PFS was 26 months compared to 4 months, respectively (log-rank HR: 0.263, 95% CI: 0.074–0.928; p = 0.0004).

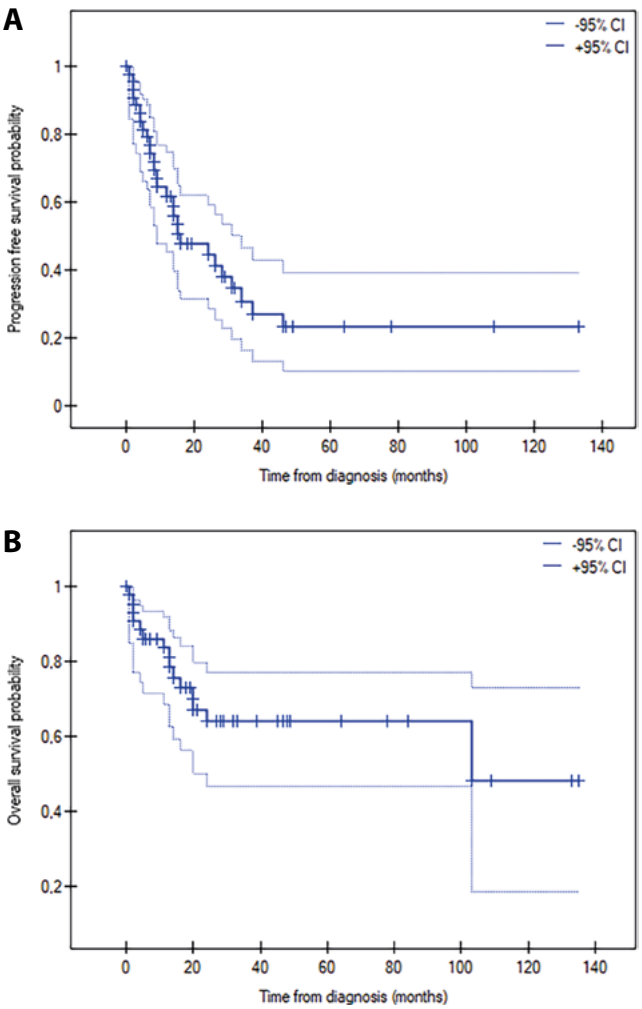

Fig. 1. The Kaplan–Meier curve for progression-free survival (A) and overall survival (B) in 43 patients with non-secretory multiple myeloma

Twenty-two patients (51.2%) received 2nd-line therapy. Ten patients received Vd-based therapy, including 3 patients with Vd in combination with daratumumab (Dara-Vd), 3 patients with doxorubicin (PAD) and 3 patients with Thal (VTd). Nine patients received Rd-based treatment, including 1 patient receiving Rd in combination with carfilzomib (KRd) and 1 patient in combination with ixazomib (Ixa-Rd). One patient was treated with Thal in combination with dex (Td), 1 patient with belantamab mafodotin and 1 patient with melflufen + dex. Six patients additionally received an ASCT. The effectiveness of treatment was assessed in 18 patients. The ORR was 77.8%, while CR, VGPR, PR, and NR rates were 22.2%, 16.7%, 38.9%, and 22.2%, respectively. The median PFS (PFS2) was 12 months (95% CI: 2–57).

Eight patients (18.6%) received 3rd-line therapy. Four patients received Vd-based therapy, including 3 who received Vd in combination with daratumumab (Dara-Vd), and 4 patients received Rd-based therapy, including 1 who received Rd in combination with carfilzomib (KRd). Due to the limited number of patients, the assessment of the effectiveness of 3rd-line treatment was not statistically analyzed.

Survival analyses and prognostic factors

The median OS for the entire group was 103 months (95% CI: 20–72, Fig. 1B). During the follow-up, 15 patients (34.9%) died. The most common cause of death was NSMM progression in 10 patients (66.7%), infection in 4 patients (26.6%), including COVID-19 disease in 1 patient, and a 2nd primary malignancy in 1 patient (6.7%).

Analyzing the effect of age on OS, a significant prolongation of OS was found in patients aged <65 years compared to ≥65 years; median OS, not achieved (NA) compared to 16 months, respectively (log-rank HR: 3.230; 95% CI: 1.089–9.583; p = 0.0171).

A significant prolongation of OS was observed in patients with stages ISS-1 and ISS-2 compared to ISS-3, and the median was NA compared to 24 months (log-rank HR: 4.394; 95% CI: 1.595–12.105; p = 0.0111). Patients with a CP infiltration of the BM (CPBM) <60% had a longer OS than patients with a CPBM ≥60%; the median OS was NA compared to 20 months (log-rank HR: 3.079; 95% CI: 0.910–10.422; p = 0.0198). Other factors identified as having a significant impact on OS were anemia (Hb <10 g/dL or >2 below the ULN, log-rank HR: 9.397; 95% CI: 3.357–26.305; p = 0.0002) and RI (serum creatinine >2 mg/dL, log-rank HR: 3.202; 95% CI: 0.838–12.230; p = 0.0180). There was a trend towards prolonged OS in patients with normal serum calcium (sCa) levels compared to hypercalcemia

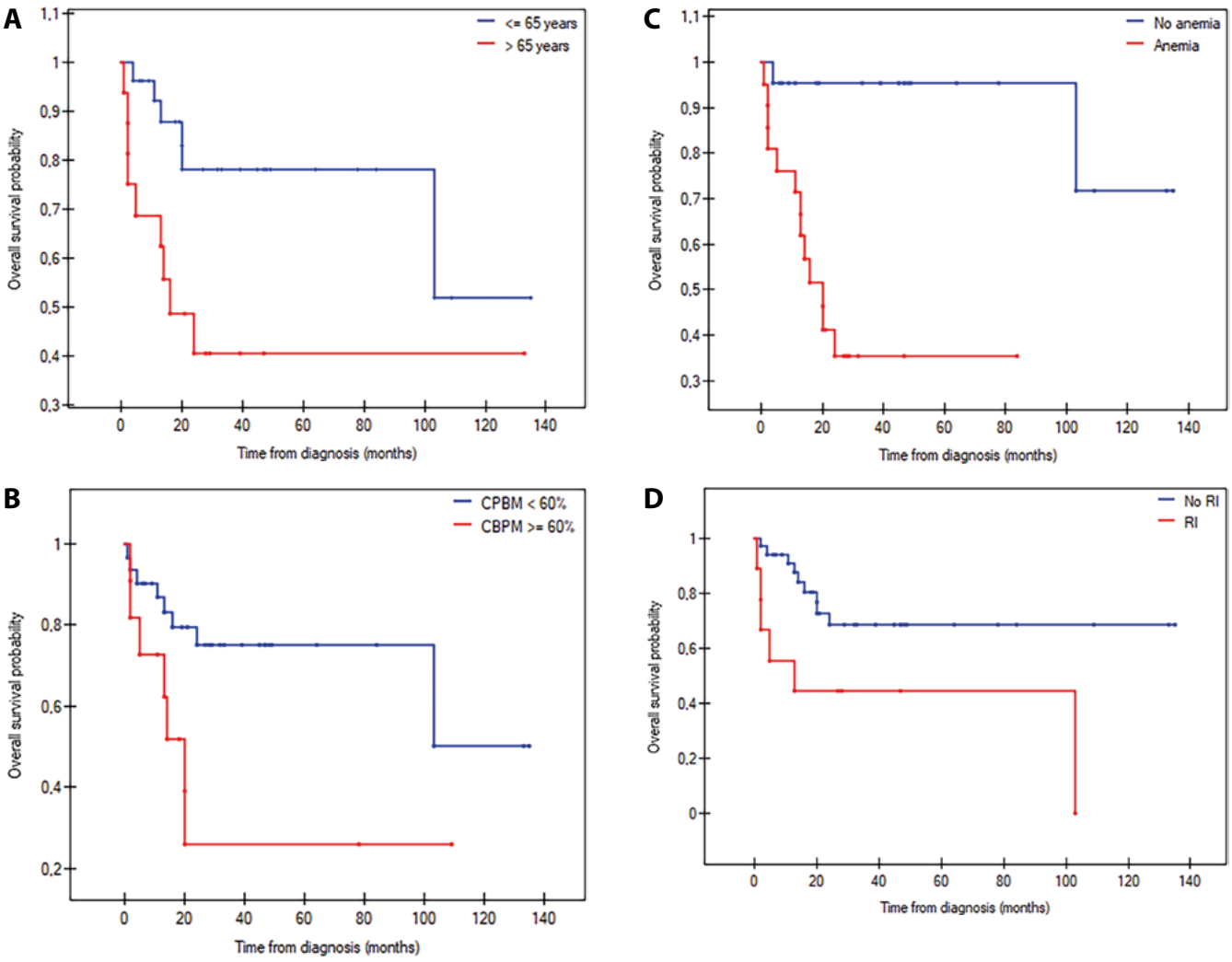

Fig. 2. The Kaplan–Meier overall survival curves in 43 patients with non-secretory multiple myeloma by age (A), clonal plasmocytes infiltration in the bone marrow (B), anemia (C), andrenal insufficieny (D)

(log-rank HR: 2.575; 95% CI: 0.653–10.145; p = 0.0647). The K–M curves of selected baseline factors related to OS (age, ISS system, CPBM, anemia, and RI) are shown in Fig. 2.

In a univariable analysis of OS, age ≥65 years, CPBM ≥60%, anemia, RI, serum albumin <3.5 g/dL, serum β2-microglobulin ≥5.5 mg/L, and bone lytic lesions contributed to a worse OS (Table 2). In a multivariable analysis, ISS-3, anemia, RI, a serum albumin <3.5 g/dL, and a serum β2-microglobulin ≥5.5 mg/L contributed to a worse OS (Table 3).

Considering 1st-line chemotherapy, we found a trend for prolonged OS in patients treated with Bort + IMiD-based compared to Bort-based and Thal-based therapy; median OS was NA compared to 24 months, respectively (log-rank HR: 2.751; 95% CI: 1.004–7.576; p = 0.0578). Furthermore, we found a significantly longer OS in patients who received ASCT after induction treatment. The median OS in the patients treated compared to untreated with ASCT groups was NA compared to 104 months (log-rank HR: 0.225; 95% CI: 0.080–0.629; p = 0.0289). We found a significantly longer OS in patients who achieved a greater PR compared to a lesser PR after 1st-line treatment with a median OS of NA compared to 4 months, respectively (log-rank HR: 0.184; 95% CI: 0.043–0.796; p = 0.0002). The K–M curves of selected factors related to 1st-line treatment (type of 1st-line treatment, ASCT, the response after 1st-line treatment) are presented in Fig. 3.

Discussion

Non-secretory multiple myeloma is a rare subtype of MM. Due to patients' low incidence and ineligibility for clinical trials, this type of MM is not fully understood. The lack of measurable M-protein probably delays the diagnosis of NSMM and makes it difficult to assess the effectiveness of treatment and disease recurrence.[22] Disease assessment requires either BM analysis and/or radiographic imaging. Our multicenter retrospective study evaluated the clinical characteristics, prognostic factors, clinical outcomes, and OS in patients with NSMM. Due to the inability to compare our results with the results

Table 2. Univariable analyses for overall survival in patients with non-secretory multiple myeloma

Variable		Univariable analysis							
		variable β	lower 95% CI	upper 95% CI	HR	lower 95% CI	upper 95% CI	Nagelkerke R^2	p-value
Age [years]	≥65	1.181	0.144	2.217	3.265	1.155	9.181	0.2883	0.0256
	<65								
Gender	male	0.059	–0.976	1.094	1.061	0.376	2.987	0.0008	0.9112
	female								
Cytogenetic risk	high-risk	0.646	–0.855	2.146	1.907	0.425	8.551	0.0982	0.3989
	standard-risk								
CPBM [%]	≥60	1.146	0.119	2.172	3.144	1.126	8.776	0.2578	0.0287
	<60								
Hb [g/dL]	<10 or >2 below ULN	2.833	0.796	4.870	17.005	2.218	130.388	0.6458	0.0064
	>10 or <2 below ULN								
Serum albumin [g/dL]	<3.5	1.539	0.501	2.577	4.660	1.650	13.158	0.4133	0.0037
	≥3.5								
Serum creatinine [mg/dL]	>2.0	1.173	0.135	2.210	3.231	1.145	9.121	0.2519	0.0267
	≤2.0								
Serum β2-microglobulin [mg/L]	≥5.5	1.144	0.065	2.224	3.141	1.067	9.248	0.2670	0.0378
	<5.5								
Serum calcium [mmol/L]	>2.75	1.003	–0.116	2.121	2.726	0.891	8.341	0.1681	0.0789
	≤2.75								
LDH	>ULN	1.049	–0.519	2.618	2.856	0.595	13.712	0.1415	0.1897
	≤ULN								
Bone lytic lesions	yes	–1.590	–2.882	–0.298	0.204	0.056	0.742	0.2471	0.0158
	no								

95% CI – 95% confidence interval; CPBM – clonal plasmocytes infiltration in the bone marrow; Hb – hemoglobin concentration; HR – hazard ratio; LDH – lactate dehydrogenase; ULN – upper limit of normal value.

Table 3. Multivariable analyses for overall survival in patients with non-secretory multiple myeloma

Variable	Multivariable analysis						
	variable β	lower 95% CI	upper 95% CI	HR	lower 95% CI	upper 95% CI	p-value
ISS-3	0.830	0.091	1.569	2.293	1.095	4.801	0.0277
CPBM ≥60%	1.246	–0.401	2.893	3.476	0.669	18.050	0.1382
Hb <10 g/dL or >2 below ULN	2.395	0.272	4.518	10.965	1.312	91.635	0.0270
Serum albumin <3.5 g/dL	1.560	0.192	2.928	4.758	1.211	18.691	0.0254
Serum creatinine >2.0 mg/dL	1.516	0.016	3.016	0.048	1.016	20.417	0.0476
Serum β2-microglobulin ≥5.5 mg/L	–2.152	–4.215	–0.090	0.116	0.015	0.914	0.0408
Serum calcium >2.75 mmol/L	–0.388	–2.006	1.230	0.678	0.134	3.423	0.6384

Nagelkerke $R^2 = 0.244$; p = 0.0003; 95% CI – 95% confidence interval; CPBM – clonal plasmocytes infiltration in the bone marrow; Hb – hemoglobin concentration; HR – hazard ratio; ISS – International Staging System; ULN – upper limit of normal value.

of clinical trials, we compared our results to available observational studies.

The median age at diagnosis in the general population of MM patients is 69 years.[31] In comparison, the median age of Polish patients with NSMM was 62 years and was comparable to the results of other observational studies of patients with NSMM and with the results of an observational study of patients with MM from Central Europe, where the median age was 64 years old.[8,20,32] At the time of MM diagnosis, 2/5 of patients were >65 years and 1/10 were over 75 years old. Although an age >65 affected OS in the univariable analysis, we did not find such a relationship in the multivariable analysis.

New drugs (Thal, lenalidomide and Bort) were used as 1st-line therapy in all Polish patients. However, in studies by Chawla et al.,[8] Sun et al.[20] and Wålinder et al.,[21]

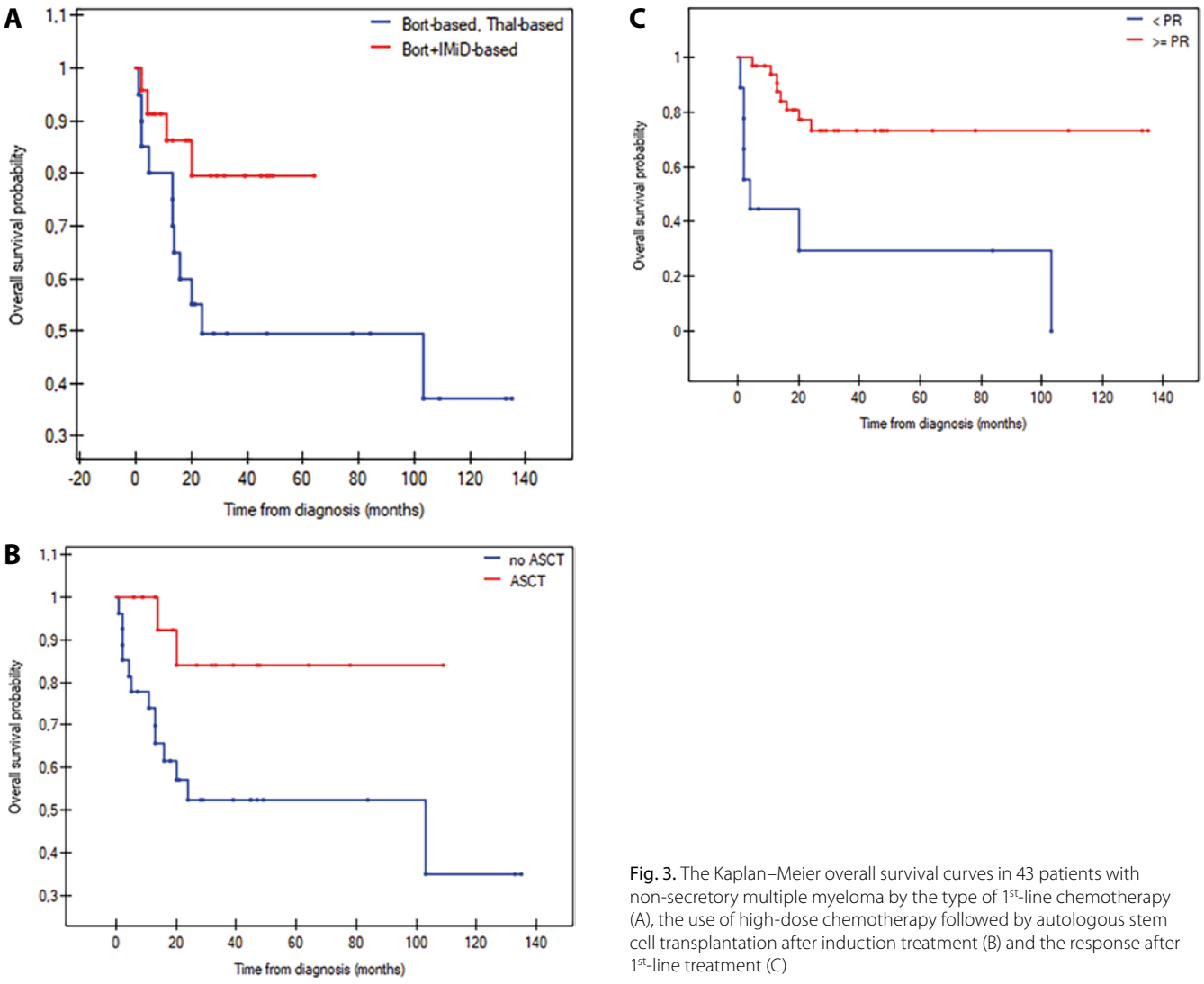

Fig. 3. The Kaplan–Meier overall survival curves in 43 patients with non-secretory multiple myeloma by the type of 1st-line chemotherapy (A), the use of high-dose chemotherapy followed by autologous stem cell transplantation after induction treatment (B) and the response after 1st-line treatment (C)

treatment based on new drugs (Thal, lenalidomide and Bort) was used in 22%, 54% and 94% of patients, respectively. In our population, 20.5% of patients achieved CR after 1st-line treatment, which is comparable to the report by Wålinder et al.[21] (26% of patients achieved CR) and lower than in the study by Chawla et al.[8] and Sun et al.,[20] where CR was achieved in 44% (patients treated with new drugs) and 65.8% of patients, respectively. In a Chinese study,[20] a higher CR rate did not improve survival, unlike the American[8] and Swedish[21] studies, which showed a trend toward better survival in patients who achieved CR.

The use of new drugs as 1st-line therapy, followed by ASCT, and the achievement of CR significantly prolonged the OS of patients with NSMM, similar to the trend observed in the general population of MM patients.[24] We found a significant difference in OS in the group of patients who received ASCT compared to those who did not receive ASCT as 1st-line therapy. This result may be because all patients in the induction treatment were treated with new drugs. However, this requires further research.

In our group, the percentage of patients with ASCT after induction treatment was 37%, comparable to the Swedish study[21] and higher than in American[8] and Chinese studies,[20] where ASCT was used in 18% and 27% of patients, respectively. In our study group, CR was achieved in 31.2% of patients with NSMM treated with ASCT. The Center for International Blood and Marrow Transplant Research showed that ASCT results are comparable in patients with NSMM and secretory MM.[14] Comparing the effectiveness of ASCT treatment in patients with NSMM and secretory MM, Kumar et al. found similar 3-year OS and PFS rates of 66% compared to 61% ($p = 0.26$) and 40% compared to 33% ($p = 0.05$), respectively.[14] Beneficial effects of ASCT in NSMM were also reported by Terpos et al.[24] Therefore, it seems that patients with NSMM should receive an ASCT as the standard of care.

We found that 41.9% of patients had an average baseline sFLC ratio, and the median OS in this subgroup of patients was comparable to that of patients with an abnormal sFLC ratio. Our results are similar to those obtained by Sun et al.[20] and Wålinder et al.,[21] and opposite to those obtained

by Chawla et al.[8] In addition, we found that an abnormal baseline sFLC ratio was not an adverse prognostic factor and median OS was comparable in both subgroups.

At the time of diagnosis, we found anemia in 49% of patients, which is comparable to the results obtained by Sun et al.[20] but higher than those reported by Wålinder et al.[21] and Migkou et al.,[22] which were 35%, 21%, and 15% respectively. We found that anemia at diagnosis is one of the essential laboratory predictors of OS in both univariable and multivariable analyses. Anemia at diagnosis is one of the most important prognostic factors affecting OS in the univariable and multivariable analyses. This may be explained by the finding that we found CPBM > 60% in a quarter of patients, indicative of a higher disease burden.

Since sFLC levels were low in our study group by definition, RI (sCr >2 mg/dL) was found in only 21% of patients and probably was not associated with FLC-associated renal pathology. Wålinder et al.[21] found RI in the unmeasurable, oligosecretory and NSMM groups to be 11%, 13% and 6% of patients, respectively. A similar incidence of RI (eGFR <30 mL/min) was found in the study by Migkou et al., 11% and 7%, respectively, in patients with oligosecretory and SMM.[22] The incidence of RI in the cited studies may be due to the definition of RI adopted in these studies and the coexistence of hypercalcemia.

Bone changes and hypercalcemia were found in 91% and 23% of Polish patients with NSMM, respectively. Wålinder et al. found bone lesions in 90% of patients, while hypercalcemia was found in only 10–12%.[21] A similar incidence of bone lesions was observed in a study by Migkou et al., where bone lesions were found in 85% of patients with NSMM and 81% of patients with oligosecretory MM, and their incidence was comparable to that of SMM (75%).[22] The same study found hypercalcemia in 5% of patients with oligosecretory MM, 16% with NSMM and 17% with SMM.[14] The slightly higher incidence of bone lesions and hypercalcemia in our study may be due to the severity of NSMM (51% of patients were diagnosed with NSMM at a clinical stage of ISS-3), more extensive infiltration of CPBM and perhaps a difference in NSMM biology.

Monitoring the effectiveness of NSMM treatment remains a challenge for hematologists. Serial histopathological examinations combined with imaging are currently considered the "gold standard" for monitoring patients with NSMM.[25] Bone marrow biopsies increase costs and patient discomfort. It should be remembered that cytological and histopathological examination of the BM reveals heterogeneous involvement of CPBM. For this reason, it is recommended that MPF be performed to assess CPBM. This study is justified because minimal residual disease (MRD) is now recognized as an important prognostic factor influencing the OS of MM patients. Further development of MPF techniques assessing circulating CP in the peripheral blood may contribute to further progress in the monitoring of NSMM. Mass spectrometry (MS) is another method that can be used to assess the effectiveness of treatment in patients with NSMM. Detection of M-proteins using matrix-assisted laser desorption/ionization-time-of-light (MALDI-TOF) MS may be an alternative to conventional immunofixation, especially in patients with NSMM. Further clinical studies using this method are undoubtedly needed.[33]

Due to the limited use of serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP) and FLC assays in patients with NSMM, it has a minimal application; for this reason, the use of MPF together with MRI and/or PET/CT is currently the optimal way to assess the response to treatment in patients with NSMM.[34,35] Although MRI is a susceptible method for detecting bone changes at the time of diagnosis of NSMM, due to the static image of bone changes in patients who have achieved MM remission, it is an insufficient method for detecting pathological changes.[36,37] However, patients with NSMM whose lesions were detected on PET/CT at diagnosis should have the examination repeated at intervals depending on the duration of treatment cycles and clinical conditions. In aggressive forms of NSMM or lack of clinical indicators indicating response to treatment, more frequent PET/CT follow-up examinations are recommended. However, the slow course of NSMM and the reduction/resolution of clinical symptoms allow for fewer routine check-ups. In patients achieving long-term remission, the frequency of PET/CT depends on the depth of response obtained and the characteristics of the patients before treatment. In patients in whom PET/CT cannot be performed, disease monitoring is based on serial BM aspirations and biopsies of extramedullary lesions.

Due to the lack of guidelines for monitoring patients with NSMM, which may cause a delay in the diagnosis of disease relapse/progression, we propose introducing guidelines as part of the recommendations of the Polish Myeloma Group. Analyzing the results obtained during NSMM treatment, we suggest performing laboratory tests assessing organ performance, known as CRAB, before each cycle of chemotherapy and BM biopsy with MPF evaluation every 3–6 months. We recommend repeating a WBLD-CT, MRI or PET/CT (depending on the test performed at the time of diagnosis) of the entire body every 3–6 months or more often, depending on the clinical situation. In patients who have achieved remission after treatment or are undergoing maintenance treatment, we suggest repeating laboratory tests assessing organ function (CRAB) every 2 months and BM biopsy with cytometric assessment and a WBLD-CT every 3–6 months or more often, depending on the clinical situation.[38] In patients with oligosecretory MM, we suggest performing the sFLC assay repeatedly during treatment every 2 months or more often, depending on the clinical situation.

Limitations

Certain limitations of our study should be considered. First, it is a retrospective study with a small number of patients analyzed. Second, the chemotherapy protocols used for 1st-line therapy were heterogeneous. In addition, cytogenetic studies were available on only a few patients. For this reason, we could not draw firm conclusions regarding the cytogenetic profile of NSMM. Another weakness of our study is selection bias, which we minimized by enrolling consecutive patients at each participating center. The relatively long median OS in our population is probably due to the long follow-up period of the analyzed patients, the relatively young age (median 62 years) of the patients, the high percentage of ASCT recipients (37%), and biological factors, such as a lower risk of renal complications. Moreover, all patients, both in the 1st and subsequent lines of treatment, were treated with chemotherapy protocols based on new drugs (Bort, Thal and lenalidomide). Additionally, in the treatment of relapsed/refractory NSMM, 45.5% of patients received chemotherapy based on daratumumab (27.3% of patients) and 2nd-generation proteasome inhibitors (carfilzomib and ixazomib – 9.1% of patients), as well as with belantamab mafodotin and melphalan flufenamide (9.1% of patients).

Conclusions

Our study showed that the most important prognostic factors with the most significant impact on OS in patients with NSMM, identified using multivariate Cox analysis, are ISS clinical stage, anemia and RI.

Non-secretory multiple myeloma makes up a small subset of MM patients. Extrapolating the statistical data to the number of reported cases of MM in Poland, approx. 50 new cases of NSMM should be expected annually. Undoubtedly, further research is needed to understand the disease's biology better and qualify patients with NSMM for randomized clinical trials to assess the effectiveness of treatment using modern diagnostic methods (MS, MPF of CPBM, and CP circulating in the peripheral blood) and to determine prognostic factors affecting OS.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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