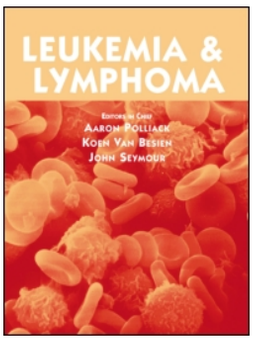

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: http://www.tandfonline.com/loi/ilal20

# Multiple myeloma in patients up to 30 years of age: a multicenter retrospective study of 52 cases

Artur Jurczyszyn, Julio Davila, K. Martin Kortüm, David S. Jayabalan, Ravi Vij, Mark Fiala, Vibor Milunovic, C.S. Chim, Katarzyna Wiśniewska-Piąty, Anna Waszczuk-Gajda, Edvan Crusoe, Roman Hajek, Paweł Robak, Małgorzata Raźny, Daria Zawirska, Max Bittrich, Hareth Nahi, Jieqi Liu, Jorge J. Castillo & David H. Vesole

**To cite this article:** Artur Jurczyszyn, Julio Davila, K. Martin Kortüm, David S. Jayabalan, Ravi Vij, Mark Fiala, Vibor Milunovic, C.S. Chim, Katarzyna Wiśniewska-Piąty, Anna Waszczuk-Gajda, Edvan Crusoe, Roman Hajek, Paweł Robak, Małgorzata Raźny, Daria Zawirska, Max Bittrich, Hareth Nahi, Jieqi Liu, Jorge J. Castillo & David H. Vesole (2018): Multiple myeloma in patients up to 30 years of age: a multicenter retrospective study of 52 cases, Leukemia & Lymphoma, DOI: 10.1080/10428194.2018.1480766

**To link to this article:** https://doi.org/10.1080/10428194.2018.1480766

Published online: 22 Jul 2018.

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2018.1480766

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE: CLINICAL



# Multiple myeloma in patients up to 30 years of age: a multicenter retrospective study of 52 cases

Artur Jurczyszyn[a], Julio Davila[b], K. Martin Kortüm[c], David S. Jayabalan[d], Ravi Vij[e], Mark Fiala[e], Vibor Milunovic[f], C.S. Chim[g], Katarzyna Wiśniewska-Piąty[h], Anna Waszczuk-Gajda[i], Edvan Crusoe[j], Roman Hajek[k], Paweł Robak[l], Małgorzata Raźny[m], Daria Zawirska[n], Max Bittrich[c], Hareth Nahi[o], Jieqi Liu[p], Jorge J. Castillo[q] and David H. Vesole[r]

[a]Department of Hematology, Jagiellonian University Medical College, Cracow, Poland; [b]Department of Hematology, Hospital Universitario de Salamanca, Salamanca, Spain; [c]Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany; [d]Weill Cornell Medical College, New York, NY, USA; [e]Washington University School of Medicine, Saint Louis, MO, USA; [f]Division of Hematology, Clinical Hospital Merkur, Zagreb, Croatia; [g]Queen Mary Hospital, University of Hong Kong, Hong Kong; [h]School of Medicine in Katowice Department of Hematology and Bone Marrow Transplantation, Silesian Medical University, Katowice, Poland; [i]Department of Hematology Oncology and Internal Medicine, Warsaw Medical University, Warsaw, Poland; [j]Hospital Universitario Professor Edgar Santos, Salvador, Brazil; [k]Department of Hematooncology University Hospital Ostrava and Faculty of Medicine University of Ostrava, Ostrava, Czech Republic; [l]Department of Hematology, Medical University of Lodz, Memorial, Hospital Lodz, Poland Copernicus; [m]Department of Hematology, State Hospital, Cracow, Poland; [n]Faculty of Medicine, Jagiellonian University Medical College, Cracow, Poland; [o]Haematology Centre Karolinska, Karolinska University Hospital, Stockholm, Sweden; [p]Rutgers New Jersey Medical School, Newark, NJ, USA; [q]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [r]John Theurer Cancer Center Hackensack University Medical Center, Hackensack, NJ, USA

**ABSTRACT**

A small proportion of patients with multiple myeloma (MM) are diagnosed at a very young age. The clinicopathological characteristics and prognosis of these patients are not well known. This analysis included 52 patients diagnosed with MM at the age of ≤30 years (range: 8–30 years). 68% of patients had International Scoring System (ISS) 1 MM; 22% presented with the light chain-only disease, and 48% with elevated serum lactate dehydrogenase (LDH). 85% of patients were treated with novel agents, and 62% received front-line autologous stem cell transplantation (ASCT). Overall response rate (ORR) to front-line treatment and ASCT were 71% and 90%, respectively. The group was followed-up for the median period of 86 months. The median overall survival (OS) was 166 months (95% CI: 53–222), with 5-year OS rate of 77% (95% CI: 61.0–87.9). This findings suggest that the prognosis in young MM patients may be as good if not better than in the general population of MM patients.

**ARTICLE HISTORY**
Received 3 January 2018
Revised 4 May 2018
Accepted 8 May 2018

**KEYWORDS**
Early-onset multiple myeloma; prognosis; treatment response; survival

## Introduction

Multiple myeloma (MM) results from neoplastic proliferation of plasma cells. The disease, representing approximately 1% of all malignancies and approximately 10% of hematological malignancies, is typically diagnosed at an older age, with a median age of 70 years [1]. The incidence of MM has been increasing over time, primarily due to population aging [1]. The implementation of novel therapies and autologous stem cell transplantation (ASCT) has likely contributed in the observed improvement in survival rates [2].

A small proportion of MMs are diagnosed at younger age, before 40 (approximately 2%) or even under 30 years of age (0.3%) [3,4]. Given the low incidence of the early-onset MM, the clinicopathological characteristics and prognosis of these patients are not well known, and available evidence originates primarily from individual case reports or small series [5–9]. Nevertheless, some previous studies, including a multicenter analysis conducted recently by our group, demonstrated that prognosis in individuals diagnosed with MM before 40 years of age may be better than in older MM patients [10–13]. It is not clear whether this survival benefit results from the lack of comorbidities and the higher proportion of younger patients being eligible for ASCT, or is also associated with more favorable prognostic factors.

In this study, we performed a retrospective analysis of the disease characteristics, treatment responses, and survival in a group of 52 newly diagnosed patients

CONTACT Artur Jurczyszyn mmjurczy@cyf-kr.edu.pl Jagiellonian University Medical College, Department of Haematology, 17 Kopernika Str., 31-501 Cracow, Poland

with MM at the age of 30 years or younger. This is the largest study reporting on patients diagnosed with MM at a very young age.

## Methods

### Case selection

Between 1989 and 2016, patients with a proven diagnosis of symptomatic MM established according to the relevant International Myeloma Working Group consensus criteria, aged 30 years or younger, were identified from the medical records at the participating institutions. The patients with asymptomatic/smoldering MM, as well as those who were too ill to receive any treatment were not included in the analysis. Pathological reports were reviewed by expert hematopathologists at the participating institutions. The study protocol was reviewed and approved by the Institutional Review Board of each participating institution.

### Data analysis

Clinical data were gathered from the medical records of patients fulfilling the inclusion criteria. The list of analyzed parameters included age at diagnosis, sex, paraprotein isotype, International Scoring System (ISS) for MM (ISS 1, 2, and 3, for cases diagnosed after 2006), presence of cytogenetic abnormalities determined by means of fluorescence *in situ* hybridization (FISH): del(17/17p), t(4;14), amp(1q21), del(13q), and t(11;14), estimated glomerular filtration rate (eGFR), plasma hemoglobin concentration, serum concentrations of calcium, albumin and beta-2 microglobulin, serum lactate dehydrogenase (LDH) level (elevated vs. normal), radiological evidence of lytic lesions, front-line anti-MM treatments and therapeutic responses, and overall survival (OS). Treatment outcomes were classified as complete response (CR), very good partial response (VGPR), partial response (PR) and no response (NR, both stable and progressive disease) [14]. Moreover, overall response rate (ORR), that is, the proportion of all responses $\geq$ PR, was calculated. OS was defined as the time in months from MM diagnosis to last follow-up or death.

### Statistical analysis

The chi-square test and Mann–Whitney U-test were used to compare categorical and continuous variables, respectively. For the survival analysis, the Kaplan–Meier method was used to generate survival curves, which were then compared using the log-rank test. The Cox proportional-hazard regression method was used to fit univariate models, the results of which are reported as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Variables with >20% of missing data were not included in the survival analysis. All reported *p* values are two-sided, and were considered significant if less than .05. Calculations and graphics were obtained using the statistical software Statistica version 10.0 (StatSoft, Tulsa, OK, USA).

## Results

In all, 52 patients with a confirmed diagnosis of MM established at the age of 30 years or younger were included in the analysis, among them one with the diagnosis established at 8 years of age. The median age at the time of MM diagnosis was 28 years (range: 8–30). There was a male predominance in the series, with a male to female ratio 2.1 to 1 (35:17). The majority of patients (32/47, 68%) diagnosed after 2006 presented with ISS 1 MM. Five patients diagnosed in 1989–2006 and lacking information about the ISS stage presented with MM with Durie-Salmon stage I ($n = 1$), IIIA ($n = 2$), and IIIB ($n = 2$). The proportions of subjects with IgG and non-IgG isotypes were 55% and 45%, respectively. At the time of MM diagnosis, 13/43 (30%) patients had hemoglobin concentrations no greater than 10 g/dL, 4/22 (18%) presented with eGFR $\leq$60 mL/min, 6/42 (14%) with serum calcium $\geq$2.65 mmol/L, 11/41 (27%) with serum albumin $\leq$3.5 g/dL, and 6/41 (15%) and 5/41 (12%) with beta-2 microglobulin 3.5–5.5 μg/mL and >5.5 μg/mL, respectively. Elevated concentrations of LDH were found in 19/40 (47.5%) patients, and lytic lesions in 36/44 (82%) patients (Table 1).

Cytogenetic profiles were available in less than 50% of the study group. The most commonly found abnormality was del(13q) (8/26, 31%) (Table 2).

Therapeutic responses and survivals were analyzed only for a subset of 37 patients diagnosed after 2006, who received front-line monotherapy or combined therapy with novel agents: proteasome inhibitors (PIs), immunomodulators (IMIDs), and/or were subjected to front-line ASCT. The largest proportion of patients (25/33, 76%) received double therapy, most often PIs combined with a conventional chemotherapy. 21/34 (62%) patients received consolidation ASCT; this subset included one patient who received allogeneic stem cell transplantation. CR, VGPR, PR, and NR rates for the 34 patients who were evaluable for response were 38%, 12%, 21%, and 29%, respectively, with ORR (CR/VGPR/PR) of 71% (Table 3).

The study group was followed-up for the median period of 86 months (95% CI: 45–121). The median OS was 166 months (95% CI: 53–222), with 5-year OS rate

**Table 1.** Clinical characteristics of 52 patients diagnosed with MM at 30 years of age or younger.

| Characteristic | Whole group ($n = 52$) | Survival analysis ($n = 37$) |
|---|---|---|
| Age at diagnosis (years) | 28 (8–30) | 28 (8–30) |
| Age at diagnosis ≥28 years | 24/52 (46%) | 18/37 (49%) |
| Male sex | 35/52 (67%) | 23/37 (62%) |
| Paraprotein isotype | | |
| IgG | 27/49 (55%) | 19/37 (51%) |
| Non-IgG | 22/49 (45%) | 18/37 (49%) |
| Light chain only | 11/49 (22%) | 8/37 (22%) |
| IgA | 9/49 (18%) | 7/37 (19%) |
| Non-secretory | 1/49 (2%) | 1/37 (3%) |
| ISS staging | | |
| ISS stage 1 | 32/47 (68%) | 20/34 (59%) |
| ISS stage 2 | 7/47 (15%) | 6/34 (18%) |
| ISS stage 3 | 8/47 (17%) | 8/34 (23%) |
| Lytic lesions | 36/44 (82%) | 30/33 (91%) |
| Hemoglobin (g/dL) | 12.0 (3.7–17.3) | 11.5 (3.7–17.3) |
| Hemoglobin ≤10 g/dL | 13/43 (30%) | 13/34 (38%) |
| eGFR (mL/min) | 91 (24–219) | 87 (24–219) |
| eGFR ≤60 mL/min | 4/22 (18%) | 3/17 (18%) |
| Calcium (mmol/L) | 2.4 (1.7–4.2) | 2.4 (1.7–4.2) |
| Calcium ≥2.65 mmol/L | 6/42 (14%) | 6/33 (18%) |
| Albumin (g/dL) | 4.1 (1.3–5.3) | 3.9 (1.3–5.1) |
| Albumin ≤3.5 g/dL | 11/41 (27%) | 10/32 (31%) |
| Beta-2 microglobulin (μg/mL) | 2.3 (1.1–15.9) | 2.4 (1.1–15.9) |
| Beta-2 microglobulin 3.5–5.5 μg/mL | 6/41 (15%) | 5/30 (17%) |
| Beta-2 microglobulin >5.5 μg/mL | 5/41 (12%) | 5/30 (17%) |
| Elevated LDH level | 19/40 (47.5%) | 18/31 (58%) |
| Europe | 36/52 (69%) | 23/37 (62%) |
| United States | 12/52 (23%) | 10/37 (27%) |
| Other* | 4/52 (8%) | 4/37 (11%) |

Results presented as medians (ranges) or numbers (percentages).
*Other includes Brazil and Hongkong.

**Table 2.** Cytogenetic characteristics of 52 patients diagnosed with MM at 30 years of age or younger.

| Cytogenetic abnormalities | Whole group ($n = 52$) | Survival analysis ($n = 37$) |
|---|---|---|
| Non-hyperdiploidy | 19/21 (90%) | 18/20 (90%) |
| del(17/17p) | 2/21 (10%) | 2/20 (10%) |
| t(4;14) | 0/20 (0%) | 0/18 (0%) |
| amp(1q21) | 2/17 (12%) | 2/15 (13%) |
| del(13q) | 8/26 (31%) | 8/23 (35%) |
| t(11;14) | 1/20 (5%) | 1/18 (6%) |

Results presented as numbers (percentages).

of 77% (95% CI: 61.0–87.9) (Figure 1). None of the analyzed variables (age ≥28 years, male sex, non-IgG isotype, ISS stage 2/3 vs. 1, presence of lytic lesions, hemoglobin ≤10 g/dL, calcium ≥2.65 mmol/L, albumin ≤3.5 g/dL, beta-2 microglobulin >5.5 μg/mL, elevated LDH level, double/triple vs. single therapy, ASCT vs. non-ASCT, and CR/VGPR to front-line treatment) were significant predictors of OS on univariate analysis (Table 4).

## Discussion

This is the largest published analysis to date in patients, including patients 30 years or younger diagnosed with MM, which included 52 patients and showed a median OS of approximately 14 years. Of note, a survey of the Surveillance, Epidemiology and End Results (SEER-18) database between 2000 and 2013 identified only 85 individuals aged 30 years or younger [15]. The vast majority of previous studies analyzing 'younger' patients with MM included persons older than 30 years; usually with age cutoff values of 40, 45, or 50 years [7,9–11,13,16,17]. Although these studies included individuals younger than 30 years, this age group constituted only a small proportion of the analyzed cohorts. The only exception was the study conducted by Blade et al. [8] that included 10 patients below 30 years of age. However, this study was conducted before the introduction of novel treatments.

To define a more contemporary cohort of individuals, we analyzed treatment responses and survivals solely in the subset of 37 patients who had been diagnosed with MM after the implementation of novel therapies in 2006. In all, 21 patients from this subset received induction therapy with PIs, alone, or in combination with IMIDs and/or conventional chemotherapy; others were treated with IMIDs with/without conventional chemotherapy. Additionally, 21 patients were subjected to front-line ASCT. ORR to induction therapy plus ASCT amounted to 90%, with 43% CR. These results are similar to those obtained in our previous study of 173 MM patients aged 21–40 years [13], also treated exclusively with novel agents, and consistent with the findings reported Cheema et al. [9] for a group of 38 MM patients between 29 and 40 years of age. Post-ASCT ORRs obtained in these two studies amounted to 82% and 79%, respectively.

The 5-year OS rate (77%, 95% CI: 61.0–87.9%) observed in our current study is higher than a 5-year survival rate reported for 15- to 29-year-old MM patients recorded in the SEER-18 database (5-year OS: 64%, 95% CI: 49.9–74.4). Even higher 5-year OS rate (83%) was also documented in our recent study of patients diagnosed with MM at 21–40 years of age [13]. In contrast, 5-year OS rates recorded in previous studies of patients with early-onset MM treated with conventional chemotherapy did not exceed 50% [7,8,10,11]. Analysis of the SEER-18 data implies that 5-year OS rates in patients younger than 30 years are substantially higher than in persons aged 60 years or older, the age group with the highest incidence of MM (64% vs. 30%) [15]. Also, the majority of previous studies demonstrated that survival in younger patients with MM is better than in older persons [10–13].

While most reports indicate that the clinical and laboratory characteristics of younger persons with MM resemble those found in a general population of MM patients, there seem to be some exceptions. For

**Table 3.** Front-line treatment for MM with responses in 34 patients diagnosed at 30 years of age or younger, who received novel agents and/or ASCT, and were evaluable for response.

| Treatment | Number (%) | CR (%) | VGPR (%) | PR (%) | NR (%) |
|---|---|---|---|---|---|
| Chemo only | 4 (12%) | 2 (50%) | 1 (25%) | 1 (25%) | 0 (0%) |
| PI only | 1 (3%) | 0 (0%) | 1 (100%) | 0 (0%) | 0 (0%) |
| IMID only | 2 (6%) | 1 (50%) | 0 (0%) | 0 (0%) | 1 (50%) |
| Chemo-PI | 13 (38%) | 5 (38%) | 1 (8%) | 2 (15%) | 5 (38%) |
| Chemo-IMID | 6 (18%) | 2 (33%) | 1 (17%) | 2 (33%) | 1 (17%) |
| PI-IMID | 6 (18%) | 3 (50%) | 0 (0%) | 0 (0%) | 3 (50%) |
| Chemo-PI-IMID | 1 (3%) | 0 (0%) | 0 (0%) | 1 (100%) | 0 (0%) |
| Chemo + ASCT | 1 (3%) | 0 (0%) | 0 (0%) | 1 (100%) | 0 (0%) |
| Single therapy | 8 (23.5%) | 3 (37.5%) | 2 (25%) | 2 (25%) | 1 (12.5%) |
| Double therapy | 25 (73.5%) | 10 (40%) | 2 (8%) | 4 (16%) | 9 (36%) |
| Triple therapy | 1 (3%) | 0 (0%) | 0 (0%) | 1 (100%) | 0 (0%) |
| Double or triple therapy | 26 (79%) | 10 (38%) | 2 (8%) | 5 (19%) | 9 (35%) |
| Front-line ASCT | 21 (62%) | 9 (43%) | 4 (19%) | 6 (29%) | 2 (10%) |
| W/o front-line ASCT | 13 (38%) | 4 (31%) | 0 (0%) | 1 (8%) | 8 (62%) |

CR: complete response; VGPR: very good partial response; PR: partial response; ORR: overall response rate; NR: no response; PI: proteasome inhibitor; IMID: immunomodulator; MA: monoclonal antibody; ASCT: autologous stem cell transplantation.
Chemo: cyclophosphamide, bendamistine, adriamycin, vincristine, cisplatin, carmustine, used as the following regimens: VAD, VBCMP-VBAD, VMBCP and VDL-PACE.

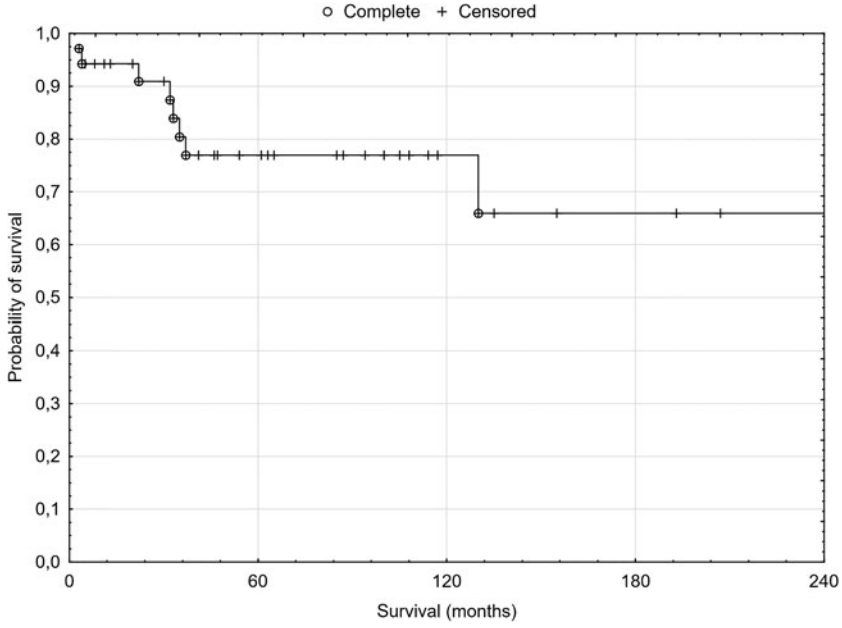


**Figure 1.** OS estimates in 35 patients diagnosed with MM at 30 years of age or younger.

**Table 4.** Univariate analysis for OS in 35 patients diagnosed with MM at 30 years of age or younger.

| | Univariate analysis | |
|---|---|---|
| Variable | HR (95% CI) | *p* value |
| Age ≥28 years | 1.16 (0.29–4.64) | .84 |
| Male sex | 0.32 (0.08–1.32) | .12 |
| Non-IgG isotype | 1.01 (0.25–4.06) | .99 |
| ISS stage 2 or 3 vs. 1 | 3.19 (0.74–13.76) | .12 |
| Lytic lesions | 0.66 (0.08–5.55) | .70 |
| Hemoglobin ≤10 g/dl | 2.00 (0.49–8.18) | .33 |
| Calcium ≥2.65 mmol/L | 0.37 (0.04–3.22) | .37 |
| Albumin ≤3.5 g/dL | 0.85 (0.18–4.11) | .84 |
| Beta-2 microglobulin >5.5 μg/mL | 0.00 | 1.00 |
| Elevated LDH level | 1.67 (0.33–8.38) | .53 |

example, our series included twice as much men as women (male to female ratio: 2.1 to 1); male to female ratio in general population of MM patients approximates 1.5 to 1, but some published evidence suggests that the proportion of male patients may decrease significantly with the age of MM diagnosis [7–9,11,13]. Furthermore, our group included at least 60% of patients diagnosed with ISS 1 MMs. Higher incidence of the ISS 1 disease in younger patients with MM was also previously reported by Cheema et al. [9] and Ludwig et al. [12]. In the studies conducted by these authors, the proportion of ISS 1 MMs diagnosed in

individuals younger than 40 years corresponded to 41% and >50%, respectively. Meanwhile, general population of MM patients typically includes 25% diagnosed with ISS 1 disease, along with 35% and 40% with ISS 2 and ISS 3 MMs, respectively.

Our series included 22% of patients with light chain MM. Similar prevalence of the light chain MM (21%) was also reported previously by Cheema et al. [9] in a group of MM patients younger than 40 years. Even larger proportions of the light chain MM cases were documented by Blade et al. [7,8] among patients who had been diagnosed with MM under 30 (50%) and 40 years of age (32%). In turn, Corso et al. [10] and Ludwig et al. [11] demonstrated that the prevalence of the light chain MM in patients diagnosed before 50 years of age was significantly higher than in older persons (12% vs. 8% and 13% vs. 10%, respectively).

Nearly half (49%) of MM patients included in our series presented with elevated serum concentrations of LDH. This proportion was markedly higher than in previous studies of patients younger than 40 years (21%–32%) [11–13]. However, it is still unclear if the elevated level of LDH can be considered a specific feature of early-age MM. In our previous study, elevated concentrations of this enzyme were more common in patients older than 40 years, and Ludwig et al. [11] did not find any age-specific differences in the prevalence of elevated LDH levels of MM patients. Nevertheless, another study conducted by the same group demonstrated an inverse correlation between the age of MM diagnosis and the serum concentration of LDH [12].

The incidence of hypercalcemia and renal failure was documented in 15% and 19% of MM patients, respectively. These proportions were similar to those documented in our previous study of patients diagnosed with MM at 21–40 years of age (16% and 25%, respectively) [13]. Two large retrospective analyses did not confirm that younger age at the diagnosis predisposed to hypercalcemia and renal failure in MM patients [10–12].

Analyzing the results of this study, one should consider its potential limitations, related to its retrospective character and lack of protocol standardization. This refers primarily to the incompleteness of some clinical and laboratory data, especially cytogenetic characteristics of MM, as well as to the heterogeneity of treatment protocols. As a result, we were unable to identify any significant predictors of OS in our series. Another important inherent weakness of a retrospective study is selection bias. Our series included only patients who received therapy, and all individuals who were too sick to be treated (11 patients, among them 5 diagnosed after 2006) were not subjected to the analysis. Interpreting our findings, one should remember that inclusion of untreated patients would likely drastically change the overall prognosis. Furthermore, although probably the largest examined to date, our sample was still too small for any definitive conclusions regarding prognosis in early-onset MM.

This study showed that prognosis in patients diagnosed with MM before 30 years of age may be at least as good as in the general population of MM patients, probably due to implementation of novel agents and ASCT in the majority of cases.

***Potential conflict of interest:*** Disclosure forms provided by the authors are available with the full text of this article online at https://doi.org/10.1080/10428194.2018.1480766.

## ORCID

Anna Waszczuk-Gajda http://orcid.org/0000-0001-5626-1750
Jorge J. Castillo http://orcid.org/0000-0001-9490-7532
David H. Vesole http://orcid.org/0000-0001-7711-4127

## References

[1] Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78:21–33.
[2] Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28:1122–1128.
[3] Blade J, Kyle RA. Multiple myeloma in young patients: clinical presentation and treatment approach. Leuk Lymphoma. 1998;30:493–501.
[4] Waxman AJ, Mink PJ, Devesa SS, et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. Blood. 2010;116:5501–5506.
[5] Hewell GM, Alexanian R. Multiple myeloma in young persons. Ann Intern Med. 1976;84:441–443.
[6] Lazarus HM, Kellermeyer RW, Aikawa M, et al. Multiple myeloma in young men. Clinical course and electron microscopic studies of bone marrow plasma cells. Cancer. 1980;46:1397–1400.
[7] Blade J, Kyle RA, Greipp PR. Presenting features and prognosis in 72 patients with multiple myeloma who were younger than 40 years. Br J Haematol. 1996;93:345–351.
[8] Blade J, Kyle RA, Greipp PR. Multiple myeloma in patients younger than 30 years. Report of 10 cases and review of the literature. Arch Intern Med. 1996;156:1463–1468.
[9] Cheema PK, Zadeh S, Kukreti V, et al. Age 40 years and under does not confer superior prognosis in patients with multiple myeloma undergoing upfront autologous stem cell transplant. Biol Blood Marrow Transplant. 2009;15:686–693.

[10] Corso A, Klersy C, Lazzarino M, et al. Multiple myeloma in younger patients: the role of age as prognostic factor. Ann Hematol. 1998;76:67–72.
[11] Ludwig H, Durie BG, Bolejack V, et al. Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: an analysis of 10 549 patients from the International Myeloma Working Group. Blood 2008;111:4039–4047.
[12] Ludwig H, Bolejack V, Crowley J, et al. Survival and years of life lost in different age cohorts of patients with multiple myeloma. J Clin Oncol. 2010;28:1599–1605.
[13] 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;175:884–891.
[14] Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–1473.
[15] Surveillance, Epidemiology and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 9 Regs Research Data, Nov 2016 Sub (1973–2014) <Katrina/Rita Population Adjustment> - Linked to County Attributes – Total U.S., 1969–2015 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Released April 2017, Based On the November 2016 Submission.
[16] Nilsson T, Lenhoff S, Turesson I, et al. Cytogenetic features of multiple myeloma: impact of gender, age, disease phase, culture time, and cytokine stimulation. Eur J Haematol. 2002;68:345–353.
[17] Sagaster V, Kaufmann H, Odelga V, et al. Chromosomal abnormalities of young multiple myeloma patients (<45 years) are not different from those of other age groups and are independent of stage according to the International Staging System. Eur J Haematol. 2007;78:227–234.