bjh research paper

Characteristics and outcomes of patients with multiple myeloma aged 21–40 years versus 41–60 years: a multi-institutional case-control study

Artur Jurczyszyn,[1] Hareth Nahi,[2] Irit Avivi,[3] Alessandro Gozzetti,[4] Ruben Niesvizky,[5] Sujitha Yadlapati,[5] David S. Jayabalan,[5] Paweł Robak,[6] Tomas Pika,[7] Kristian T. Andersen,[8] Leo Rasche,[9] Krzysztof Mądry,[10] Dariusz Woszczyk,[11] Małgorzata Raźny,[12] Lidia Usnarska-Zubkiewicz,[13] Wanda Knopińska-Posłuszny,[14] Małgorzata Wojciechowska,[15] Renata Guzicka-Kazimierczak,[16] Monika Joks,[17] Sebastian Grosicki,[18] Hanna Ciepłuch,[19] Marcin Rymko,[20] David H. Vesole[21] and Jorge J. Castillo[22]

[1]Jagiellonian University Medical College Department of Haematology, Cracow, Poland, [2]Karolinska University Hospital, Stockholm, Sweden, [3]Tel Aviv Medical Centre, Tel Aviv, Israel, [4]Azienda Ospedaliera Universitaria Senese, Siena, Italy, [5]Weill Cornell Medical College, New York, NY, USA, [6]Department of Haematology, Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland, [7]University Hospital Olomouc, Olomouc, Czech Republic, [8]Department of Medicine, Vejle Hospital, Vejle, Denmark, [9]UAMS Myeloma Institute, Little Rock, AR, USA, [10]Medical University, Warsaw, [11]Department of Haematology, State Hospital, Opole, [12]Department of Haematology, State Hospital, Kraków, [13]Wroclaw Medical University, Wroclaw, [14]Ministry of the Interior Hospital in Olsztyn with Warmia and Masuria Oncology Centre, [15]Department of Haematology, State Hospital, Olsztyn, [16]Pomeranian Medical University, Szczecin, [17]Department of Haematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznan, [18]Department of Cancer Prevention, School of Public Health, Medical University of Silesia, Katowice, [19]Copernicus. Regional Oncology Centre, Gdańsk, [20]Department of Haematology, District Hospital in Torun, Toruń, Poland, [21]John Theurer Cancer Center, Hackensack University Medical

Summary

We compared the outcomes of multiple myeloma (MM) patients aged 21–40 and 41–60 years in the novel agent era. This case-control study included 1089 patients between 2000 and 2015. Cases and controls were matched for sex, International Staging System (ISS) stage and institution. There were 173 patients in the younger group and 916 patients in the older group. Younger patients presented with a higher incidence of lytic lesions (82% vs. 72%; $P = 0{\cdot}04$) and high-risk cytogenetic abnormalities (83% vs. 68%; $P = 0{\cdot}007$), but lower rate of elevated lactate dehydrogenase (21% vs. 44%; $P < 0{\cdot}001$). Five- and 10-year overall survival (OS) in younger versus older patients was 83% vs. 67% and 56% vs. 39%, respectively ($P < 0{\cdot}001$). Similar results were seen when studying the subset of 780 patients who underwent autologous transplantation. Younger patients with ISS stage 1 had a better OS than older patients ($P < 0{\cdot}001$). There was no survival difference between younger and older patients with ISS stage 2 or 3. Younger MM patients, aged 21–40 years, treated in the era of novel agents have a better OS than their counterparts aged 41–60 years, but the survival advantage observed in younger patients was lost in more advanced stages of MM.

Keywords: myeloma, young, survival, outcomes, transplantation.

First published online 29 September 2016
doi: 10.1111/bjh.14328

Center, Hackensack, NJ, and [22]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Received 3 May 2016; accepted for publication 20 July 2016
Correspondence: Artur Jurczyszyn, Jagiellonian University Medical College Department of Haematology, 17 Kopernika Str., 31-501 Krakow, Poland.
E-mail: mmjurczy@cyf-kr.edu.pl

Multiple myeloma (MM) is characterized by the neoplastic proliferation of plasma cells, particularly affecting the elderly, with a median age of 70 years (Kyle *et al*, 2003). MM comprises 1% of all neoplasms and over 10% of haematological malignancies. The incidence of MM has increased over the past few decades directly proportional to the aging of the population worldwide and increased awareness. Recent improvements in survival are most likely due to the emergence of new therapeutic options (Kumar *et al*, 2014).

Given that individuals under 40 years of age rarely suffer from myeloma (up to 2% of all cases), limited studies are focused on the incidence, outcomes and prognosis of young MM patients, with most of the available data arising from case reports or small series (Hewell & Alexanian, 1976; Lazarus *et al*, 1980; Blade *et al*, 1996; Cheema *et al*, 2009). In general, treatment outcomes in younger patients are better than those observed in older patients groups. These differences may be explained by less comorbidity in the younger patients, and the incorporation of autologous stem cell transplantation (ASCT) in younger patients. In the era of novel agents, intensive therapy shows a clear survival advantage, particularly in patients under 60 years of age (Lenhoff *et al*, 2006).

In our study, we identified 173 patients who were 40 years or younger at the time of MM diagnosis, and compared their characteristics and outcomes with matched older patients aged 41–60 years treated in the era of novel agents.

Materials and methods

Case selection

Between January 2000 and December 2015, 1089 previously untreated patients aged 21–60 years with a pathological diagnosis of MM were identified from the medical records at the participating institutions. Pathological reports were reviewed by expert haematopathologists at the participating institutions and reclassified, if necessary, according to the 2008 World Health Organization (WHO) Classification of Tumours of the Haematopoietic and Lymphoid Tissues (Campo *et al*, 2011). 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. Clinical parameters were categorized and included age (21–40 years vs. 41–60 years), sex (male vs. female), heavy chain (IgG vs. non-IgG myeloma) and light chain (kappa vs. lambda), haemoglobin (≥100 g/l vs. <100 g/l), calcium (elevated vs. normal) and lactate dehydrogenase (LDH) serum levels (elevated vs. normal), estimated glomerular filtration rate (GFR; >60 ml/min vs. ≤60 ml/min), presence vs. absence of lytic bone lesions (as assessed by skeletal surveys or magnetic resonance imaging), International Scoring System (ISS, 1, 2 and 3), cytogenetic abnormalities (high-risk vs. other) and overall survival (OS).

Overall survival was defined as the time in months from diagnosis to last follow-up or death. Non-IgG myeloma included IgA, IgD, light chain only and non-secretory myeloma. High-risk cytogenetic abnormalities included del(17p) and t(4;14) (Rajkumar, 2016). Patients were divided according to their response to first line therapy into complete response (CR), very good partial response (VGPR), partial response (PR), and no response (NR) (Durie *et al*, 2006). For this analysis, CR includes stringent and near CR, and NR includes stable and progressive disease.

The distribution of missing data appeared random, and was as follows (young vs. older group): haemoglobin (5% vs. 6%), calcium level (8% vs. 28%), LDH (46 vs. 86%), GFR (8% in both groups), presence of bone lytic lesions (22% vs. 84%), ISS stage (14% vs. 21%) and cytogenetic abnormalities (53% vs. 80%). All other data were complete.

Statistical analysis

The Chi-square and the rank-sum tests were used to compare categorical and continuous variables, respectively. OS was defined as the time in months between date of diagnosis and the date of last follow-up or death. 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 and multivariate survival models, the results of which are reported as hazard ratio (HR) with 95% confidence intervals (CIs). Due to the high rates of missing data, LDH and cytogenetic abnormalities were not included in the survival analyses. Variables with significant *P*-values in the univariate analysis were then included in the multivariate analysis. All reported *P*-values are two-sided, and were considered significant if less than 0·05. Calculations and graphics were obtained using the statistical software STATA version 13·1 (College Station, Texas, USA).

Results

A total of 1089 patients with a histologically confirmed diagnosis of MM were included in this analysis, of which 173 patients (16%) were 21–40 years of age (younger group), and 916 (84%) aged 41–60 years (older group). The median age in the younger group was 37 vs. 55 years in the older group. There was a male predominance with a male:female ratio of 1·3:1 in the entire cohort, and 1·5:1 in the younger group. Younger patients presented with a higher proportion of lytic lesions (82% vs. 74%; $P = 0·04$) and high-risk cytogenetic abnormalities (32% vs. 17%; $P = 0·007$), but lower elevated LDH (21% vs. 44%; $P < 0·001$). There were no significant differences in gender, heavy chain or light chain restriction, haemoglobin levels, estimated GFR, calcium levels or ISS stage. Selected patient characteristics are shown in Table I.

Table I. Patient characteristics ($n = 1089$).

	MM patients		
	21–40 years ($n = 173$)	41–60 years ($n = 916$)	*P*-value
Median age, years	37 (21–40)	55 (41–60)	<0·001
Sex			
Female	69 (40%)	406 (44%)	0·33
Male	104 (60%)	510 (56%)	
Heavy chain			
IgG	107 (69%)	375 (59%)	0·10
IgA	26 (17%)	127 (20%)	
IgD	1 (0·6%)	16 (3%)	
None	22 (14%)	114 (18%)	
Light chain restriction			
Kappa	110 (69%)	339 (67%)	0·70
Lambda	50 (31%)	166 (33%)	
Haemoglobin			
≥100 g/l	120 (69%)	678 (73%)	0·29
<100 g/l	53 (31%)	247 (27%)	
Estimated GFR			
>60 ml/min/1·73 m^2	120 (75%)	590 (69%)	0·13
≤60 ml/min/1·73 m^2	40 (25%)	265 (31%)	
Calcium			
Normal	134 (84%)	582 (87%)	0·26
Elevated	26 (16%)	86 (13%)	
LDH			
Normal	75 (79%)	76 (56%)	<0·001
Elevated	20 (21%)	59 (44%)	
Lytic lesions			
Absent	31 (18%)	224 (26%)	0·04
Present	139 (82%)	644 (74%)	
International Staging System			
ISS 1	71 (47%)	303 (42%)	0·40
ISS 2	50 (33%)	280 (38%)	
ISS 3	30 (20%)	146 (20%)	
Cytogenetic abnormalities			
High risk*	26 (32%)	31 (17%)	0·007
Other abnormalities	55 (68%)	150 (83%)	

GFR, glomerular filtration rate; ISS, International Scoring system; LDH, Lactate dehydrogenase; MM, multiple myeloma.
*del(17p) and t(4;14).

Of the 780 patients (72%) who underwent ASCT, 83 patients (11%) were 21–40 years old and 697 (89%) were aged older than 40 years. Similar to the entire cohort, the analysis of clinical characteristics in patients who received ASCT showed that younger patients had higher rates of lytic lesions at diagnosis (85% vs. 75%; $P = 0·04$). Otherwise, there were no differences in the characteristics between groups.

All patients were treated with novel agents. The younger group had CR, VGPR, PR and NR rates of 32%, 23%, 24% and 21%, respectively, while these were 29%, 28%, 26% and 17%, respectively, in the older group ($P = 0·51$). The overall response rate (ORR: CR/VGPR/PR) was similar in younger and older patients (79 vs. 83%). In the ASCT-only sub-analysis, the CR, VGPR, PR and NR rates in the younger group were 33%, 23%, 27% and 18%, while those in the older group were 34%, 30%, 25% and 12%, respectively ($P = 0·19$). The ORR for the younger and older group was 82% and 88%, respectively.

The median follow-up time was 51 months, and the median OS for the entire group was 95 months (7·9 years), with 5- and 10-year OS rates of 70% (95% CI 67–73%) and 42% (95% CI 37–47%), respectively (Fig 1A). The difference in 5- and 10-year OS between younger and older group was 83% vs. 67% and 56% vs. 39%, respectively ($P < 0·001$; Fig 1B). In the univariate analysis, younger age and IgG-restricted myeloma were associated with longer survival (median OS: not reached vs. 91 months, and 104 vs. 88 months, respectively), whereas haemoglobin <100 g/l (80 vs. 104 months), estimated GFR ≤60 ml/min (78 vs. 102 months), and high ISS stage (184 months for ISS 1 vs. 87 months for ISS 2 vs. 75 months for ISS 3) were associated with worse OS. Univariate and multivariate models are shown in Table II. In patients who underwent ASCT, the median OS was 107 months (8·7 years) with 5- and 10-year OS rates of 73% and 45%, respectively (Fig 1C). For the younger group, the median OS was not reached versus 101 months in the older

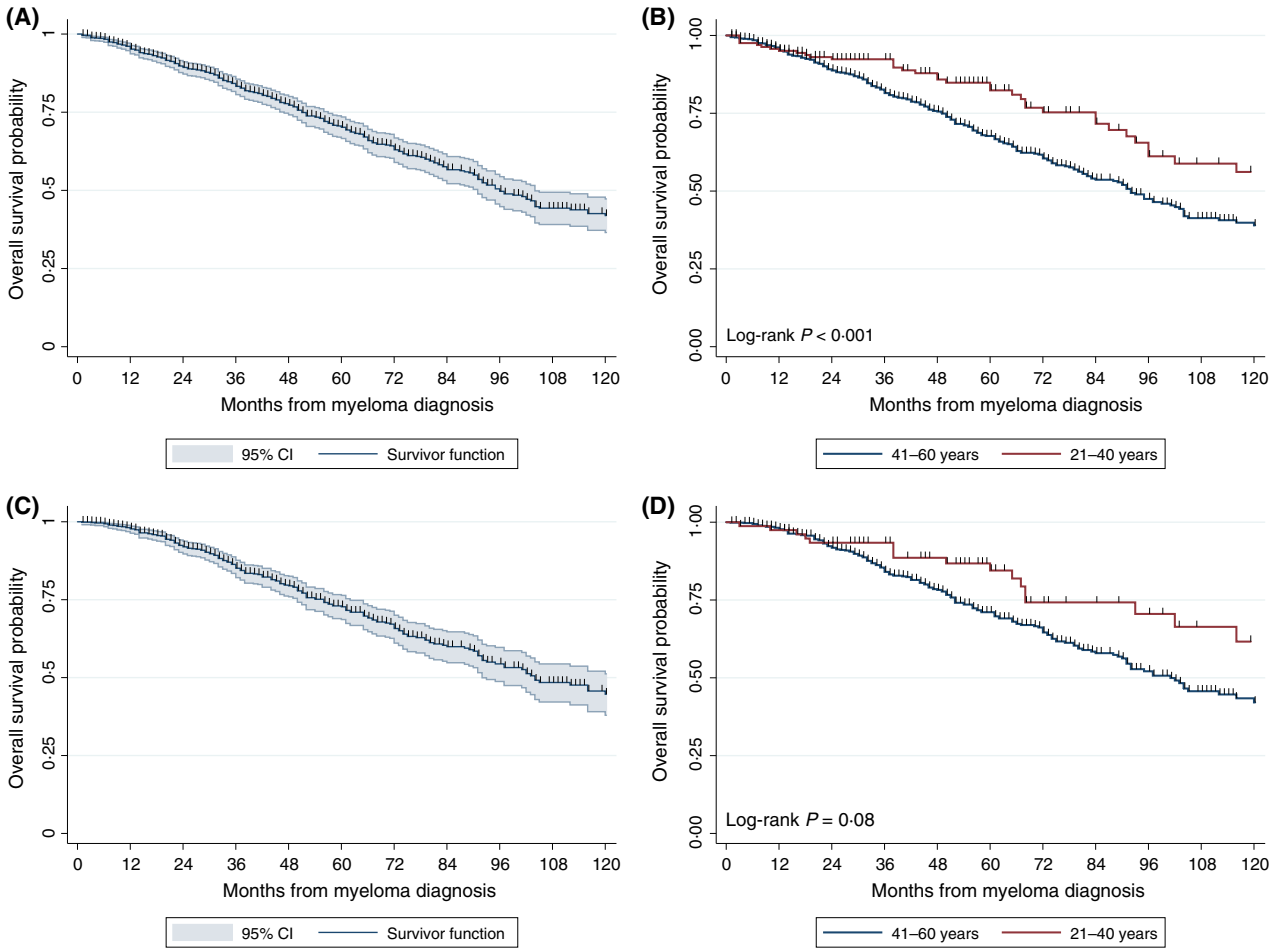

Fig 1. Overall survival estimates in 1089 myeloma patients, (A) entire cohort and (B) by age group, and in 780 myeloma patients who underwent autologous stem cell transplantation, (C) entire cohort and (D) by age group. [Colour figure can be viewed at wileyonlinelibrary.com].

Table II. Univariate and multivariate survival prognostic models.

	Univariate analysis		Multivariate analysis*	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age ≤40 vs. >40 years	0·53 (0·38–0·76)	<0·001	0·63 (0·42–0·94)	0·02
Male vs. female	1·18 (0·95–1·48)	0·14		
IgG vs. non-IgG	0·64 (0·49–0·83)	0·001	0·74 (0·54–1·02)	0·07
Kappa vs. lambda	1·22 (0·92–1·62)	0·16		
Haemoglobin <100 g/l	1·72 (1·37–2·16)	<0·001	1·22 (0·84–1·76)	0·29
Estimated GFR ≤60 ml/min	1·64 (1·30–2·06)	<0·001	0·95 (0·65–1·39)	0·79
Elevated calcium	1·31 (0·95–1·80)	0·10		
Presence of lytic lesions	1·18 (0·90–1·55)	0·22		
ISS score 2 vs. ISS score 1	1·87 (1·37–2·54)	<0·001	1·54 (1·04–2·28)	0·03
ISS score 3 vs. ISS score 1	2·74 (1·95–3·85)	<0·001	2·40 (1·47–3·89)	<0·001

HR, hazard ratio; CI, confidence interval; GFR, glomerular filtration rate; ISS, International Scoring System.
*Multivariate analysis did not include cytogenetics or LDH levels due to small sample size in these categories.

group. In the younger group, the 5- and 10-year OS rates were 84% and 62%, compared with 71% and 42% in the older group, respectively (P = 0·01; Fig 1D).

We then fitted univariate and multivariate survival models into the younger cohort only, looking for specific factors affecting OS in young patients; the results are shown in

Table III. In the univariate analysis, IgG myeloma was associated with better survival (not reached vs. 96 months in non-IgG myeloma), while haemoglobin <100 g/l (91 vs. 115 months), estimated GFR ≤60 ml/min (96 months vs. not reached), elevated calcium (96 months vs. not reached) and higher ISS stage (91 months for ISS 3 vs. not reached for ISS 1 and 2), were associated with worse OS. In the multivariate survival analysis, higher ISS stage was independently associated with worse OS. When evaluating ASCT patients, only the ISS was associated with OS (102 months for ISS 3 vs. not reached for ISS 1 and 2).

The OS in older patients presenting with ISS 1 was worse than in their younger counterparts (127 months vs. not reached, Fig 2A). There was a trend towards worse OS in ISS 2 for older patients compared with young patients (79 months vs. not reached, Fig 2B), but not for patients presenting with ISS 3 (72 vs. 84 months; Fig 2C). In ASCT patients, older patients had worse OS in ISS 1 (134 months vs. not reached; Fig 2D) and ISS 2 (89 months vs. not reached; Fig 2E), but there were no differences in ISS 3 (83 vs. 102 months; Fig 2F).

Response to first line therapy was associated with better OS. Using CR as comparator (HR 1·0), patients with VGPR, PR and NR had a HR of 1·86 (95% CI 0·98–3·52; $P = 0·06$), 2·29 (95% CI 1·20–4·40; $P = 0·01$) and 3·49 (95% CI 1·79–6·82; $P < 0·001$) for all-cause mortality, respectively. In the ASCT group, patients who did not achieve a CR had a worse outcome; VGPR, PR and NR were associated with a HR of 1·89 (95% CI 1·33–2·70; $P < 0·001$), 1·61 (95% CI 1·11–2·31; $P = 0·01$) and 1·59 (95% CI 0·93–2·69; $P = 0·09$) for all-cause mortality, respectively.

Discussion

Multiple myeloma is uncommon in individuals younger than 40 years (approximately 2%) (Waxman *et al*, 2010). Given the low incidence of MM in young people, most data on clinical presentation and outcome come from single case reports or small case series. A previous study on 72 myeloma patients younger than 40 years was published two decades ago and evaluated patients diagnosed and treated between 1956 and 1992 (Blade *et al*, 1996). A recent retrospective report reviewed 38 patients who were under 40 years of age at the time of MM diagnosis and had undergone upfront ASCT between 1990 and 2007 (Cheema *et al*, 2009). One large, recently published, multi-centre study (10 549 patients from 17 institutions), focusing on survival and years of life lost in different age cohorts, has described the presenting features and prognosis of young MM patients treated in the era of novel agents (Ludwig *et al*, 2010).

The present multi-institutional study was performed to investigate disease-specific and subject-related factors affecting the outcome of treatment of MM in different age groups. Among 1089 patients included in our study, 173 (16%) were 40 years or younger. There was a male predominance in the younger group, which was also found in previous studies (Blade *et al*, 1996). A registry-based study from Sweden, reviewing MM patients treated between 1950–1959 and 1970–1979, showed a shift towards a younger subject population, particularly males, over the three decades of observation (Turesson *et al*, 2010).

In our study, the rates of anaemia, kidney disease, and hypercalcaemia in young patients were similar to older patients, and comparable to those previously reported (Blade *et al*, 1996). Although no difference in haemoglobin levels was observed between the study groups, it should be noted that the majority of the patients (73% of the older, and 69% of the younger group) presented with haemoglobin >100 g/l. With a cut-off of hemhaemoglobin level <120 g/l applied to our study, the percentage of entire cohort, as well as younger and older patients, was around 60%. This similar finding was observed in a previous study, in which 60% of patients also had haemoglobin level <120 g/l (Blade *et al*, 1996). With regard to bone lytic lesions, a similar study published two decades ago reported a lesion rate of 68% (Blade *et al*, 1996), which is lower than the one observed in our study.

Table III. Univariate and survival analysis of 173 multiple myeloma patients aged 21–40 years.

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	0·97 (0·88–1·06)	0·45		
Male vs. female	1·12 (0·58–2·17)	0·74		
IgG vs. non-IgG	0·46 (0·24–0·90)	0·02	0·96 (0·25–3·73)	0·95
Kappa vs. lambda	0·96 (0·84–1·12)	0·67		
Haemoglobin <100 g/l	3·75 (1·90–7·40)	<0·001	1·47 (0·39–5·53)	0·57
Estimated GFR ≤60 ml/min	2·05 (1·04–4·07)	0·04	1·84 (0·43–7·82)	0·41
Elevated calcium	2·21 (1·05–4·67)	0·04	0·59 (0·16–2·22)	0·44
Presence lytic lesions	2·34 (0·82–6·62)	0·11		
ISS 2 vs. ISS 1	5·38 (1·52–19·1)	0·009	14·5 (1·52–138·8)	0·02
ISS 3 vs. ISS 1	12·7 (3·69–44·1)	<0·001	17·5 (1·63–188·2)	0·02
Poor-risk cytogenetics	3·85 (1·61–9·22)	0·003	5·00 (1·40–17·8)	0·01

HR, hazard ratio; CI, confidence interval; GFR, estimated glomerular filtration rate; ISS, International Scoring System.

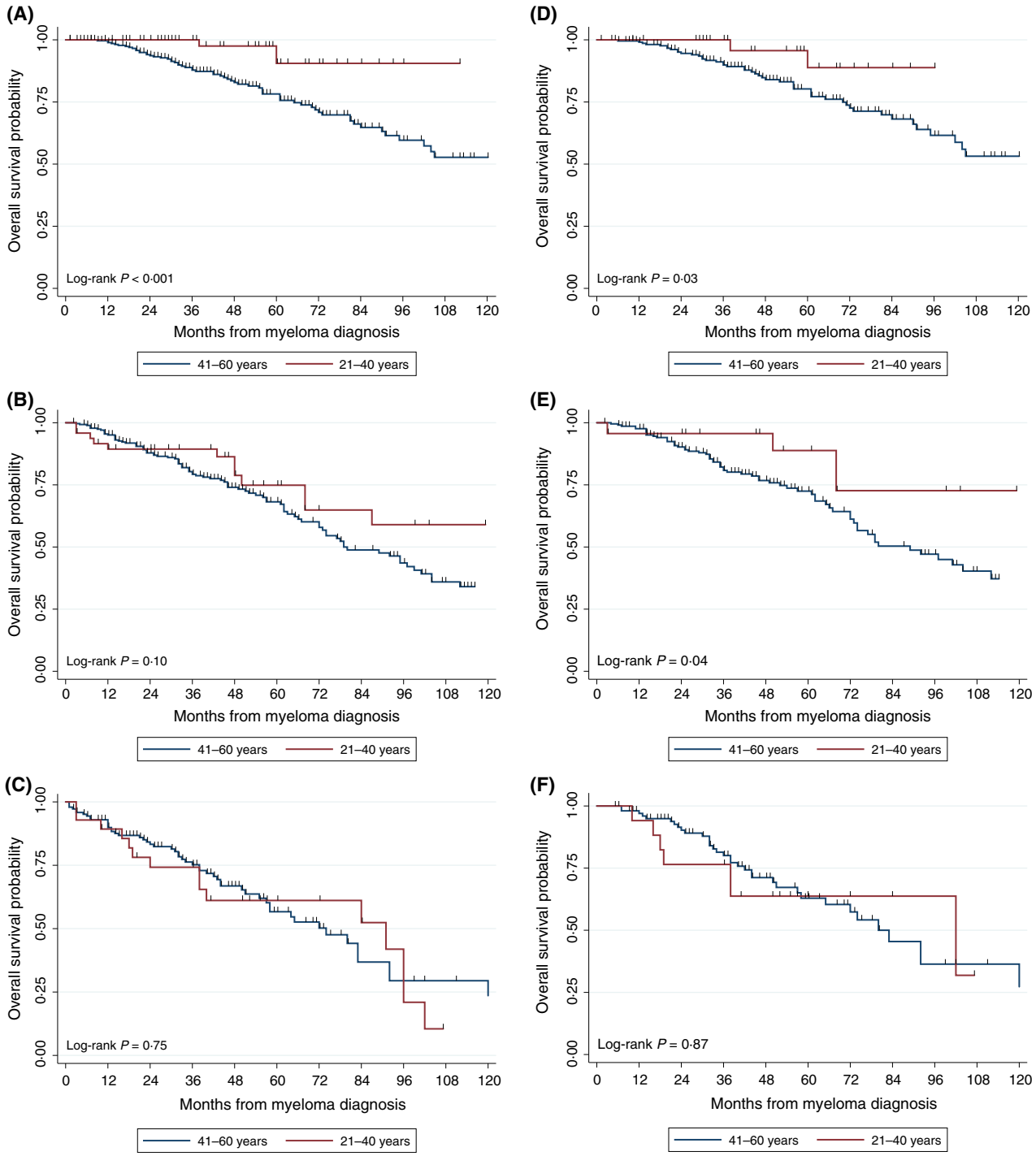

Fig 2. Overall survival estimates of younger versus older myeloma patients with (A) International Scoring System (ISS) score 1, (B) ISS 2 and (C) ISS 3, and in younger versus older myeloma patients who underwent autologous stem cell transplantation with (D) ISS1, (E) ISS 2 and (F) ISS 3. [Colour figure can be viewed at wileyonlinelibrary.com].

This discrepancy can be partly explained by the recent development of more sensitive diagnostic imaging tools, such as computed tomography, magnetic resonance imaging and positron emission tomography.

The prognosis in MM is affected by host factors (i.e. age, performance status, comorbidities), disease stage, disease biology and response to therapy. Although survival may have improved in recent years, MM is still considered an incurable disease (Kristinsson *et al*, 2007; Rajkumar, 2016). In our study, the median OS for the entire group was approximately 8 years, with 5-year OS rates of 70%, which is comparable to the results of a study on newly

diagnosed MM from 11 international trials and shows significant improvement in comparison to data published earlier (Blade *et al*, 1996; Rajkumar, 2016). These improvements in OS are probably the result of incorporation of novel therapies, increased use of haematopoietic stem cell transplantation, earlier and more accurate diagnosis of MM, advances in supportive care and improved risk-stratification (Rajkumar, 2016).

In previously published series of young MM patients, the median survival time was 4·5 years (Blade *et al*, 1996). This is interesting if one considers that such series included patients from 1956, when novel drugs for this disease were not available. Patients younger than 40 years with normal renal function had a median survival of 8 years (Blade *et al*, 1996). Although the median survival of 4·5 years in Mayo Clinic patients younger than 40 years is the longest reported so far in long-term studies of patients with MM that were conventionally treated, it was suboptimal (Kumar *et al*, 2014). In our study, the 10-year OS in young MM patients has improved remarkably. In contrast, the 10-year OS of their older (41–60 years) counterparts was 39%. The reduced survival rate observed in the older group cannot be attributed to their older age only, but is likely to reflect disease-related factors.

Younger patients showed better survival regardless of the response to first line treatment. Admittedly, our study did not focus directly on the analysis of the effectiveness of therapy and there is a need for further investigations to confirm the supposition that a younger MM population might be more likely to benefit from subsequent treatments, including autologous or allogeneic transplantation. This benefit could derive from a better tolerance to the conditioning regimens and, perhaps, better immunosurveillance that could allow long-lasting control of disease once a very low tumour burden is achieved.

Stratification for ISS stage revealed a very interesting observation for MM patients aged 40 years or younger: a significantly better OS than older patients with ISS stage 1, with only a trend towards significance for ISS stage 2, and no different outcome compared to the older patients with the highest ISS stage. These findings could represent the different disease biology of patients who present at advanced stage of disease. However, younger patients with ISS stage 3 survived 12 months longer on average than older patients. One of the most important findings of this paper is that the median OS in low ISS has not been reached in young patients, with a 10-year OS approaching 80%, compared with a 10-year OS of 59% and 10% for Stage 2 and Stage 3 in the older population, respectively.

To date, this is the largest study on the prognosis, outcomes and clinical characteristics of young MM patients treated with novel agents. Nevertheless, our study is not without limitations. Although our study was retrospective in nature the multi-centre modality has enabled a large cohort of young patients with MM diagnosed and treated in the modern era to be gathered. Missing data are common in retrospective studies. We have decided to report missing data for transparency purposes. Any analysis was only performed on those patients with a complete data set. Although it is most likely that all patients were treated with novel agents, specific data on lines of therapy were not collected. The treatment modalities at different institutions might not be uniform, however, given the era of accrual, we believe most patients were treated with a combination of alkylators, proteasome inhibitors and/or immunomodulatory drugs. Despite these shortcomings, we were able to perform a meaningful comparison of factors, which may have an effect on the outcome of younger patients with MM. Our results represent a "real-world" cohort of MM patients.

As the field of MM therapy advances with the advent of novel proteasome inhibitors (e.g. ixazomib), immunonomodulating drugs (e.g. pomalidomide) and monoclonal antibodies (i.e. daratumumab, elotuzumab), it is unclear what the role of these agents will be in the treatment of young patients with MM. Our study indirectly shows a survival benefit in patients undergoing ASCT regardless of age and ISS stage. However, the best approach to this question is through randomized controlled studies. The final results of the Intergroupe Francophone Du Myelome/Dana-Farber Cancer Institute 2009 trial (ClinicalTrials.Gov Identifier NCT01191060) are eagerly expected. Preliminary data from this study are encouraging in favour of a survival benefit with the use of ASCT in young patients with *de novo* MM (Attal *et al*, 2015). The best therapeutic approach in young MM patients should include induction therapy with novel agents followed by ASCT, whenever possible.

In conclusion, we have shown that patients with MM aged 21–40 years had better survival when compared to patients aged 41–60 years, independent of other clinical factors. Our study showed that MM patients aged 40 years or younger had a median OS time that has not been reached at 10 years. The survival advantage in younger patients is lost in more advanced stages of MM, where both younger and older groups have a poorer outcome. These data should be taken into account when designing new clinical trials enrolling young MM patients, as well as in prognostic discussions in the clinic.

Author contributions

AJ, DHV and JJC designed the study and drafted the initial manuscript. All the authors provided patient data for the study, provided critical input and approved the final manuscript.

References

Attal, M., Lauwers-Cances, V., Hulin, C., Facon, T., Caillot, D., Escoffre, M., Arnulf, B., Macro, M., Belhadj, K., Garderet, L., Roussel, M., Mathiot, C., Avet-Loiseau, H., Munshi, N.C., Richardson, P.G., Anderson, K.C., Harousseau, J.L. & Moreau, P. (2015) Autologous transplantation for multiple myeloma in the era of new drugs: a phase III study of the Intergroupe Francophone Du Myelome (IFM/DFCI 2009 Trial). *Blood*, **126**, 391–391.

Blade, J., Kyle, R.A. & Greipp, P.R. (1996) Multiple myeloma in patients younger than 30 years. Report of 10 cases and review of the literature. *Archives of Internal Medicine*, **156**, 1463–1468.

Campo, E., Swerdlow, S.H., Harris, N.L., Pileri, S., Stein, H. & Jaffe, E.S. (2011) The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood*, **117**, 5019–5032.

Cheema, P.K., Zadeh, S., Kukreti, V., Reece, D., Chen, C., Trudel, S. & Mikhael, J. (2009) Age 40 years and under does not confer superior prognosis in patients with multiple myeloma undergoing upfront autologous stem cell transmplant. *Biology of Blood and Marrow Transplantation*, **15**, 686–693.

Durie, B.G., Harousseau, J.L., Miguel, J.S., Blade, J., Barlogie, B., Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., Vesole, D., Kyle, R., Alexanian, R., Tricot, G., Attal, M., Merlini, G., Powles, R., Richardson, P., Shimizu, K., Tosi, P., Morgan, G. & Rajkumar, S.V.; International Myeloma Working G. (2006) International uniform response criteria for multiple myeloma. *Leukemia*, **20**, 1467–1473.

Hewell, G.M. & Alexanian, R. (1976) Multiple myeloma in young persons. *Annals of Internal Medicine*, **84**, 441–443.

Kristinsson, S.Y., Landgren, O., Dickman, P.W., Derolf, A.R. & Bjorkholm, M. (2007) Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. *Journal of Clinical Oncology*, **25**, 1993–1999.

Kumar, S.K., Dispenzieri, A., Lacy, M.Q., Gertz, M.A., Buadi, F.K., Pandey, S., Kapoor, P., Dingli, D., Hayman, S.R., Leung, N., Lust, J., McCurdy, A., Russell, S.J., Zeldenrust, S.R., Kyle, R.A. & Rajkumar, S.V. (2014) Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*, **28**, 1122–1128.

Kyle, R.A., Gertz, M.A., Witzig, T.E., Lust, J.A., Lacy, M.Q., Dispenzieri, A., Fonseca, R., Rajkumar, S.V., Offord, J.R., Larson, D.R., Plevak, M.E., Therneau, T.M. & Greipp, P.R. (2003) Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proceedings*, **78**, 21–33.

Lazarus, H.M., Kellermeyer, R.W., Aikawa, M. & Herzig, R.H. (1980) Multiple myeloma in young men. Clinical course and electron microscopic studies of bone marrow plasma cells. *Cancer*, **46**, 1397–1400.

Lenhoff, S., Hjorth, M., Westin, J., Brinch, L., Backstrom, B., Carlson, K., Christiansen, I., Dahl, I.M., Gimsing, P., Hammerstrom, J., Johnsen, H.E., Juliusson, G., Linder, O., Mellqvist, U.H., Nesthus, I., Nielsen, J.L., Tangen, J.M. & Turesson, I.; Nordic Myeloma Study G. (2006) Impact of age on survival after intensive therapy for multiple myeloma: a population-based study by the Nordic Myeloma Study Group. *British Journal of Haematology*, **133**, 389–396.

Ludwig, H., Bolejack, V., Crowley, J., Blade, J., Miguel, J.S., Kyle, R.A., Rajkumar, S.V., Shimizu, K., Turesson, I., Westin, J., Sonneveld, P., Cavo, M., Boccadoro, M., Palumbo, A., Tosi, P., Harousseau, J.L., Attal, M., Barlogie, B., Stewart, A.K. & Durie, B. (2010) Survival and years of life lost in different age cohorts of patients with multiple myeloma. *Journal of Clinical Oncology*, **28**, 1599–1605.

Rajkumar, S.V. (2016) Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. *American Journal of Hematology*, **91**, 719–734.

Turesson, I., Velez, R., Kristinsson, S.Y. & Landgren, O. (2010) Patterns of multiple myeloma during the past 5 decades: stable incidence rates for all age groups in the population but rapidly changing age distribution in the clinic. *Mayo Clinic Proceedings*, **85**, 225–230.

Waxman, A.J., Mink, P.J., Devesa, S.S., Anderson, W.F., Weiss, B.M., Kristinsson, S.Y., McGlynn, K.A. & Landgren, O. (2010) Racial disparities in incidence and outcome in multiple myeloma: a population-based study. *Blood*, **116**, 5501–5506.