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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

The role of initial clinical presentation, comorbidity and treatment in multiple myeloma patients on survival: a detailed population-based cohort study

B. E. Oortgiesen[1] · E.N. van Roon[1,2] · P. Joosten[3] · R. E. Kibbelaar[4] · H. Storm[5] · S. Hovenga[6] · B. van Rees[7] · G. Woolthuis[8] · N. Veeger[9] · E.G. de Waal[3] · M. Hoogendoorn[3]

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Abstract
Purpose This prospective, observational population-based cohort study was performed to determine overall survival (OS) in multiple myeloma (MM) patients in Friesland, the Netherlands, in the era of novel agents and to analyse the influence of first-line treatment, MM-related end-organ damage and comorbidities at initial presentation on OS.
Methods Detailed clinical information was obtained from the population-based registry 'HemoBase' during the period January 2005 to January 2013, with a follow-up to January 2014.
Results Overall, the symptomatic MM patients (n = 225) had a median OS of 40 months. In the age categories <65, 65–75 and ≥75 years, 99, 94 and 87% of the patients received treatment, with a median OS of 92, 42 and 31 months, respectively. OS for patients with or without treatment was 43 and 3 months, respectively. In multivariable analysis, risk factors for worse OS were increasing age (<65: reference; 65–75: $HR_{adj.}$ = 2.2 (95% CI 1.3–3.7) and ≥75: $HR_{adj.}$ = 2.8 (95% CI 1.7–4.8); P < 0.001), not receiving initial treatment ($HR_{adj.}$ = 4.0 (95% CI 2.1–7.7); P < 0.001), hypercalcaemia (P < 0.001, $HR_{adj.}$ = 1.7 (95% CI 1.2–2.6), P = 0.006) and impaired renal function ($HR_{adj.}$ = 2.6 (95% CI 1.7–4.0); P < 0.001).
Conclusions Increasing age, not receiving initial treatment, hypercalcaemia and impaired renal function at initial presentation were independent risk factors for worse OS. Comorbidity according to Charlson comorbidity index score was not an independent variable predicting OS.

Keywords Multiple myeloma · Population-based registry · Overall survival · Novel agents · Clinical parameters

Introduction

Randomised controlled trials (RCT) have shown that the introduction of the novel agents thalidomide,

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✉ B. E. Oortgiesen
Berdien.Oortgiesen@znb.nl

[1] Department of Clinical Pharmacy & Pharmacology, Medical Centre Leeuwarden, LeeuwardenPO Box 888, 8901 BR Leeuwarden, The Netherlands

[2] Unit of Pharmacotherapy, Epidemiology and Economics, Department of Pharmacy, University of Groningen, Groningen, The Netherlands

[3] Department of Haematology, Medical Centre Leeuwarden, Leeuwarden, The Netherlands

[4] Department of Pathology, Pathology Friesland, Leeuwarden, The Netherlands

[5] Department of Clinical Chemistry, Medical Centre Leeuwarden CERTE KCL, Leeuwarden, The Netherlands

[6] Department of Haematology, Nij Smellinghe, Drachten, The Netherlands

[7] Department of Haematology, Antonius Hospital, Sneek, The Netherlands

[8] Department of Haematology, Tjongerschans, Heerenveen, The Netherlands

[9] Department of Epidemiology, MCL Academy, Leeuwarden, The Netherlands

lenalidomide and bortezomib has greatly improved response rates, progression-free survival and overall survival (OS) in patients with multiple myeloma (MM) [1–6]. However, this improvement might be less pronounced in real life due to very strict exclusion criteria used in clinical trials. These often exclude the more elderly patients or those with significant comorbidity. This bias is largely overcome by conducting population-based studies, and these studies are therefore highly valued. Population-based studies routinely follow patients without any selection bias over a long period of time. Although results in clinical trials in patients with MM show improved OS, outcome data provided by population-based registries (PBR) show a less pronounced improvement, especially in the elderly [5, 7–9]. However, when the elderly are treated, the value of novel agents has been shown [9, 10].

A common disadvantage of PBR is the amount of missing data, such as information relating to individual patients or an incomplete patient population. Frequently, only a few characteristics of the patients are registered, giving little insight into the complex clinical situation of the patients. In this study, we provide a detailed overview of all patients with symptomatic MM in Friesland, a province of the Netherlands, with 650,000 inhabitants [11]. These patients were prospectively registered and monitored by their clinicians and other health-care professionals (e.g. pathologists and clinical chemists) in the electronic patient registry 'HemoBase' [12–16]. Since data are directly registered according to a fixed format, HemoBase contains up-to-date, complete and detailed information on patient characteristics, initial clinical presentation, type of treatment and follow-up, thus providing high-quality clinical data and an overview of the patients' circumstances.

Population-based studies with detailed information on clinical parameters in unselected MM patients are relatively limited. We therefore performed this prospective, observational population-based cohort study, using the PBR HemoBase, to obtain insight into the treatment and outcome of patients with MM in real life in the era of novel agents. In addition, we searched for clinical parameters at initial presentation, such as pre-existing comorbidity and MM-related end-organ damage related to outcome [17].

Methods

Patient cohort

All patients with newly diagnosed MM in Friesland during the period from January 2005 to January 2013, with a follow-up to January 2014, were retrieved from HemoBase. Patients were regarded as being symptomatic when MM-related end-organ damage (hypercalcaemia, renal impairment, anaemia and/or bone lesions) was present according to the International Working Myeloma Group (IWMG) guidelines [18, 19]. To be sure that all MM patients were enrolled in the study with an accurate diagnosis, an expert panel including the treating haematologists assessed all patients diagnosed with MM. In those patients with an aberrant number of plasma cells (≥10%) and/or a M protein of ≥3 g per 100 ml, the haematologist verified whether the correct diagnosis was established according to the 2008 WHO classification [20]. All bone marrow aspirates and biopsies were performed in Friesland and recorded in the database. Additional clinical information, including lab results and comorbidities, was obtained from the individual patient hospital records. The novel agents include the immunomodulatory agents (IMiDs) thalidomide and lenalidomide and the proteasome inhibitor bortezomib.

The patients were divided by age (<65, 65–75 and ≥75 years) to illustrate differences in survival in the three age categories. In addition, the patients were classified into different treatment groups using the first line of treatment, i.e. patients receiving novel agents, patients who were not given novel agents and patients who decided in consultation with their physician not to receive treatment. We also divided the patients into four groups based on date of diagnosis (2005–2006, 2007–2008, 2009–2010 and 2011–2012). Comorbidity status at the time of diagnosis was assessed using the Charlson comorbidity index (CCI) [21], and the patients were divided into groups with scores of 0, 1 or ≥2. As described in the IMWG guidelines [19], MM-related end-organ damage was defined as hypercalcaemia (serum calcium >2.75 mmol/l), renal impairment (creatinine >175 μmol/l), anaemia (haemoglobin <6.3 mmol/l) and patients with bone lesions (whole-body skeletal x-ray). Calcium was corrected for albumin using Payne's formula [22]. Some patients with smouldering MM received treatment from their haematologist because of a rapid rise of their M-protein levels. These patients were regarded as being symptomatic and were included in the analysis. Patients were classified in the 'no-treatment' group if they did not receive chemotherapy or if they only received radiotherapy or steroids.

Statistical analyses The primary end point was OS, defined as time of diagnosis until death by any cause. Survival curves were calculated according to Kaplan-Meier. Between-group differences were evaluated using the log-rank test for evaluating differences in OS. Cox proportional hazard modelling was used to identify significant risk indicators for OS. In this modelling, adjusted hazard ratios (HR_{adj}) for OS with 95% confidence intervals and P values were calculated.

A two-tailed P value <0.05 indicated statistical significance. All analyses were performed using commercially available computer software (Statistical Analysis System version 9.4, SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

A total of 225 patients were diagnosed with symptomatic MM in Friesland between January 1, 2005, and January 1, 2013. Three patients were excluded in the survival analysis, due to an unknown date of death. Data completeness for the clinical parameters and treatment was 100% except for International Staging System (ISS) stage (62%). The median observation period was 29 months (range 0.26–104; IQR 33), and the median age at onset was 70 years (range 32–92; IQR 15) with a male predominance (62% male). The median OS of the symptomatic patients was 40 months, and 126 of the 225 patients (56%) passed away during the study period. Tables 1 and 2 show baseline characteristics of the symptomatic patients. Due to incomplete β_2 microglobulin data, we were unable to consider ISS in our analysis.

Treatment

The median OS for patients who received treatment compared to patients who did not was 43 and 3 months ($HR_{adj.}$ = 4.0 (95% CI 2.1–7.7); $P < 0.001$), as illustrated in Fig. 1. The decision not to start treatment was either made by the patient or by the physician, or the reason was unknown. Frailty was the main reason for refraining from treatment. As shown in Table 2, 99, 94 and 87% of the patients in the age categories <65, 65–75 and ≥75 years, respectively, received treatment and 79% of the symptomatic patients received one of the novel agents as first-line treatment. Overall, patients who received a novel agent had a median OS of 42 months, compared to 49 months for patients who received 'other treatment'. Three-year OS for patients diagnosed in 2005–2006, 2007–2008, 2009–2010 or 2011–2012 was 68, 54, 59 and 59%, respectively (data not shown).

Age categories

The Kaplan-Meier estimate of the symptomatic patients (Fig. 2) demonstrates that the median OS is 92, 42 and 31 months and the 5-year OS is 61, 29 and 14%, respectively, for the three predefined age categories. In both univariable and multivariable analyses (Table 3), increasing age remained an independent risk factor compared to age <65 years (65–75: $HR_{adj.}$ = 2.2 (95% CI 1.3–3.7) and ≥75: $HR_{adj.}$ = 2.8 (95% CI 1.7–4.8); $P < 0.001$).

MM-related end-organ damage

When looking at the MM-related end-organ damage, in multivariable analysis, calcium >2.75 mmol/l and creatinine >175 μmol/l remained independent risk factors, with worse OS for patients with hypercalcaemia compared to patients without hypercalcaemia ($HR_{adj.}$ = 1.7 (95% CI 1.2–2.6); $P = 0.006$) and for patients with a serum creatinine >175 vs. ≤175 ($HR_{adj.}$ = 2.6 (95% CI 1.7–4.0); $P < 0.001$) (Table 3, Supplementary Fig. 1).

Comorbidity score

Univariate analysis showed that the CCI score is of no significant influence on OS (CCI score 1: HR = 1.3, (95% CI 0.84–2.0) and CCI score ≥2: HR = 1.6 (0.99–2.5); $P = 0.124$) (Table 3).

Table 1 Baseline characteristics of symptomatic patients. CCI: Charlson Comorbidity Score, ISS: International Staging System

Characteristics	Patients <65 years (*n* = 72)	Patients 65–75 years (*n* = 81)	Patients ≥75 years (*n* = 72)	Total (*n* = 225)
Male gender; *n* (%)	44 (61)	55 (68)	40 (56)	139 (62)
Participation in trial; *n* (%)	14 (19)	26 (32)	6 (8)	46 (20)
CCI; *n* (%)	59 (82)	37 (46)	41 (57)	137 (61)
0	12 (17)	21 (26)	17 (24)	50 (22)
1	1 (1)	23 (28)	14 (19)	38 (17)
≥2				
ISS; *n* (%)	8 (11)	8 (10)	4 (6)	20 (9)
I	27 (38)	24 (30)	19 (26)	70 (31)
II	16 (22)	18 (22)	15 (21)	49 (22)
III	21 (29)	31 (38)	34 (47)	86 (38)
Unknown				
End-organ damage; *n* (%)	21 (30)	18 (23)	28 (39)	67 (30)
Hypercalcaemia	16 (23)	19 (23)	18 (25)	53 (24)
Renal failure	40 (56)	48 (60)	47 (65)	135 (60)
Anaemia	57 (21)	59 (73)	44 (61)	160 (71)
Bone lesions				

Table 2 Treatment of symptomatic MM patients

Characteristics	Patients <65 years (n = 72)	Patients 65–75 years (n = 81)	Patients ≥75 years (n = 72)	Total (n = 225)
Mean number of treatments	2.0	2.0	1.3	1.8
Number of ASCT	44	1	0	45
Initial treatment	54 (75)	71 (88)	53 (74)	178 (79)
Novel agent (%)	33	67	49	149
IMiDS	32	61	48	141
Thalidomide	1	6	1	8
Lenalidomide	21	4	4	29
Bortezomib	17 (24)	5 (6)	9 (13)	31 (14)
Other (%)	16	2	0	18
VAD	1	3	9	13
Melfalan based	1 (1)	5 (6)	8 (11)	14 (6)
None[a] (%)				

ASCT autologous stem cell transplantation, *VAD* vincristine, adriamycin and dexamethasone

[a] Including patients receiving only radiotherapy and/or steroids

Discussion

This detailed population-based study followed all symptomatic MM patients for a maximum follow-up period of 9 years from diagnosis in Friesland, a province of the Netherlands. The median OS of the patients was 40 months. Increasing age was significantly associated with worse OS. As illustrated in our analysis, this impaired OS may be related to the fact that no treatment is offered to over 10% of the very elderly. The median OS for patients not receiving treatment was only 3 months. We further demonstrated that OS was negatively affected in symptomatic patients, who initially presented with hypercalcaemia or impaired kidney function. Comorbidity, scored by using the CCI, was not detected as an independent variable predicting OS.

Studies in unselected MM patients in the era of novel agents are relatively limited. Several population-based studies have shown that survival in patients with MM has significantly improved over time, especially in the younger patients (<65 years) after the introduction of high-dose melphalan with autologous stem cell support. However, improvement of OS in the elderly patients is relatively limited and the population-based studies are predominantly performed before the introduction of the novel agents [8, 23, 24]. Two studies were partially performed in the period of novel agents. Firstly, Pozzi et al. [7] investigated OS in myeloma patients (n = 1260) in Italy from 1989 to 2009. They found a 5-year OS of 78.3% in the period of novel agents (2006–2009) for patients younger than 65 years, compared to 20.9%

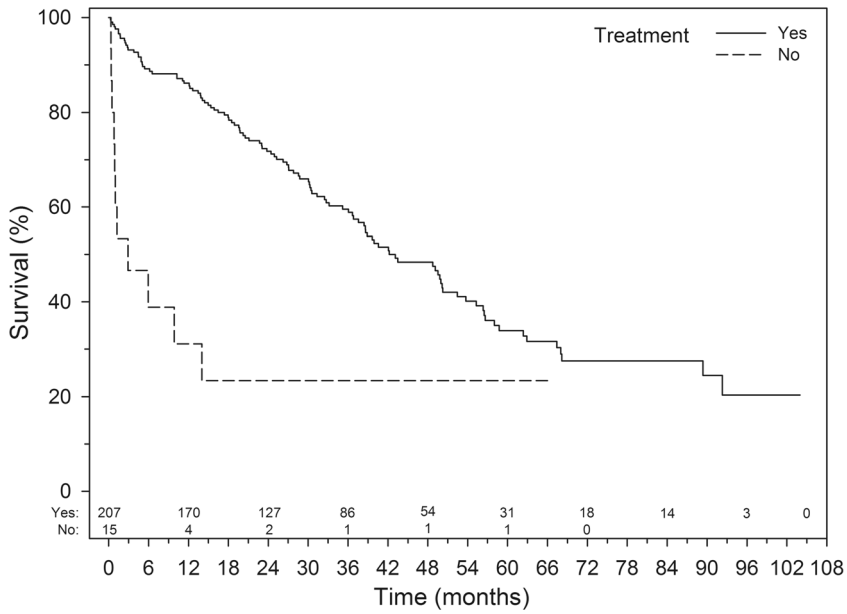

Fig. 1 Overall survival of symptomatic patients with and without treatment

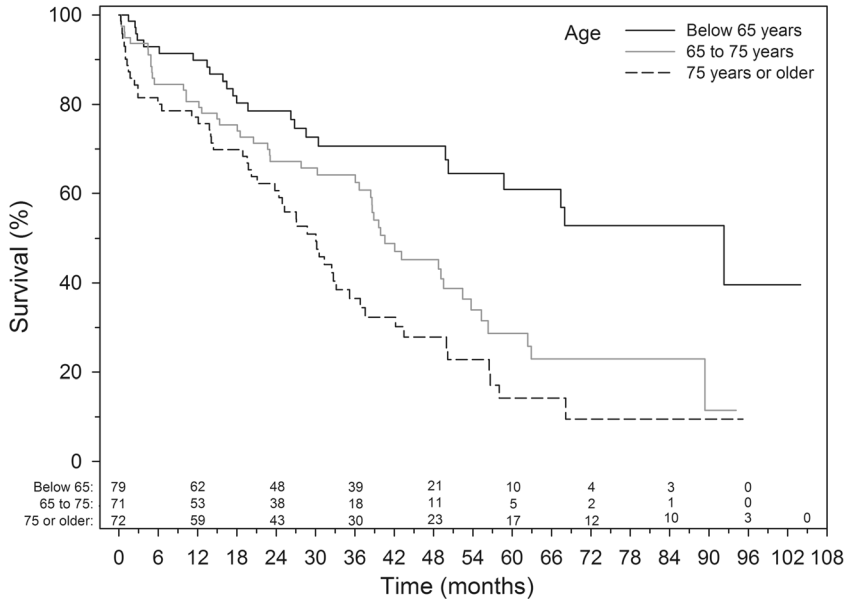

Fig. 2 Overall survival of symptomatic patients, divided by age

for patients 75 years and older. Compared to the OS before 2006, patients ≥75 years did not benefit from the novel agents. Secondly, Kristinsson et al. [9] published their results on OS among MM patients (n > 45.000) from the SEER 9 database during 1973–2009. Between 2000 and 2009, 5-year OS for patients under 65 was 63% and for patients between 66 and 79 was 41%. The OS of patients over 80 years old only improved during the first 3 months after diagnosis. These two population-based studies were relatively limited by the lack of specific clinical data regarding diagnosis and treatment, and it needs to be determined whether these population-based studies were representative for symptomatic MM patients instead of the whole MM population in that region. Furthermore, selection bias may have occurred, as some patient groups are underrepresented in the SEER database [25]. In our study, we investigated OS for MM patients in the decade of novel agents. Compared to the studies discussed earlier, our 5-year OS for the younger patients is slightly lower. In addition, our 5-year OS for MM patients 65 years and older compares unfavourably with the other population-based studies performed in the novel agent era, despite the fact that the majority of our patients received novel agents. There are several possible explanations for these differences in 5-year OS. First, in our analysis, only patients with an indication for treatment were included. The excluded patients with smouldering MM had a 5-year OS of up to 72% and a median OS >100 months (data not shown). In addition, since we prospectively registered all MM patients in our region, no selection bias occurred. Finally, we included symptomatic patients, who refused therapy or who only received radiotherapy in our analysis, thus reflecting the 'real world'. Patients treated with other treatment had a longer OS than patients treated with 'novel agents'. This difference is caused by bias between the groups; the patients in the other treatment group were mainly <65 years old and therefore received stem cell transplantation combined with vincristine, adriamycin and dexamethasone (VAD), indicating a better condition than the patients receiving novel agents as first-line treatment. Patients diagnosed in 2005–2006 showed a higher 3-year OS than the other patients. We hypothesised that this difference in OS was mainly caused by the fact that these patients were younger (although not reaching significance) and practically all patients <65 years in this cohort received treatment. In addition, the number of patients with symptomatic MM who received radiotherapy only or refused further treatment was relatively low in this group.

To our knowledge, this study is the first to show that patients who did not receive treatment have a very poor survival rate. Treatment is frequently withheld from the very elderly in particular. The question arises whether a more favourable outcome could be obtained for these patients by initiating treatment. For some patients, the reason for the treatment decision could be obtained. Frailty was the main reason for refraining from treatment.

The influence of MM-related end-organ damage on OS

Due to our detailed clinical dataset at presentation, we were able to include an analysis on prognostic clinical markers. Patients with normal calcium or creatinine serum concentrations at diagnosis had a median OS that was approximately twice as long as patients who initially presented with hypercalcaemia or impaired kidney function. Interestingly, bone lesions did not significantly influence OS of MM patients. Anaemia did not influence OS either, but this has

Table 3 Hazard ratios for OS in univariate and multivariable analyses of symptomatic patients. CCI: Charlson Comorbidity Score

Risk factors	Univariate analysis		Multivariable analysis	
	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age (years)	1	<0.001	1	<0.001
<65	2.1 (1.3–3.4)		2.2 (1.3–3.7)	
65–75	3.1 (1.9–5.1)		2.8 (1.7–4.8)	
≥75				
Treatment	1	<0.001	1	<0.001
Yes	4.1 (2.2–7.7)		4.0 (2.1–7.7)	
No				
Calcium (mmol/l)	2.2 (1.5–3.2)	<0.001	1.7 (1.2–2.6)	0.006
>2.75				
Creatinine (μmol/l)	2.9 (1.9–4.3)	<0.001	2.6 (1.7–4.0)	<0.001
>175				
Haemoglobin (mmol/l)	1.8 (1.2–2.6)	0.003	–	
<6.3				
Bone lesions	1.0 (0.69–1.47)	0.99	–	
Yes				
CCI	1	0.124	–	
0	1.3 (0.84–2.0)			
1	1.6 (0.99–2.5)			
≥2				

been expected due to the high number of confounding factors. As expected, using the multivariable analysis, patients with renal failure at diagnosis had the worst survival outcome, followed by those with hypercalcaemia. This detailed population-based study, combining MM-related end-organ damage and outcome, is unique and provides insight into associations between heterogeneity in clinical presentation and survival in myeloma. To date, the influence of MM-related end-organ damage on the survival of MM patients has hardly been examined in population-based studies. One study [26] investigated cytogenetics and determined OS on each myeloma-defining event at diagnosis of MM patients. In accordance with our study, a significantly worse outcome was observed for patients with renal failure compared to patients with bone lesions.

Comorbidity

In several types of solid tumours and non-Hodgkin lymphoma, comorbidity is an independent prognostic factor and a high CCI score correlates to a worse outcome in OS [27, 28]. We also demonstrated in diffuse large B cell lymphoma that an increased CCI induces toxicity and requires dose adjustments of the therapy [15]. However, in our analysis, CCI was not detected as an independent variable predicting OS. Limitations to this analysis might be the relatively small numbers of MM patients with significant comorbidity and the limited number of treatment lines received by the patients.

Strengths and limitations

Our study had several strengths. This population-based study in MM patients is based on a dataset rich in detail for every individual patient. All hospitals in Friesland participated by using the HemoBase database registry, therefore making this database complete and up-to-date. By prospectively gathering data on treatment and follow-up, we were able to show results reflecting real-life patients without any selection bias. Furthermore, information about patients who did not receive treatment and knowledge of the mean number of treatments per age category is unique.

Our study had several limitations when interpreting the results. The use of a real-life population might have affected the internal validity. For example, diagnostic investigations, treatment strategies and follow-up were not fully protocolised and in part depended on the clinicians' judgement. For example, due to incomplete β_2 microglobulin data, ISS classification of the complete cohort MM patients was not feasible. In addition, the calculation and interpretation of the CCI relied on the documentation of relevant comorbidities in the medical history by clinicians, with a risk of incomplete data. Finally, we only interpreted first-line treatment instead of all treatments that patients received. However, we expect this to have had little impact on the results, as patients only received a mean of nearly two lines of treatment. Finally, there may have been confounding factors not considered in our analysis that influenced OS.

Conclusions

In this detailed population-based study of a complete Dutch cohort of unselected symptomatic MM patients, a median OS of 40 months was observed. Not receiving first-line treatment, increasing age, hypercalcaemia and impaired renal function, but not the CCI score at initial presentation, were significantly associated to worse median OS.

Author's contribution ER, PJ, RK, HB, SH, BR, GW, NV, EW and MH designed the research study. BO collected the data. NV performed the statistical analysis. BO, MH, ER and NV wrote the manuscript, and all authors critically revised and approved the submitted manuscript.

Compliance with ethical standards The study was conducted in accordance with the Declaration of Helsinki, and the protocol received approval from the regional ethics committee in Leeuwarden.

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval For this type of study, formal consent is not required.

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