Received: 18 December 2018 | Revised: 28 January 2019 | Accepted: 29 January 2019

DOI: 10.1111/ejh.13264

ORIGINAL ARTICLE

European Journal of Haematology | WILEY

Understanding mortality in multiple myeloma: Findings of a European retrospective chart review

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Funding information
The study was funded by Amgen (Europe) GmbH.

Abstract

Objectives: This study aimed to provide real-world data on the characteristics and treatment of patients with multiple myeloma (MM) at the time of death.

Methods: The study was a retrospective patient chart review across France, Germany, Italy, Spain and the UK during 2016, and included patients who had died in the 3 months before the index date.

Results: Data from 786 patients were reviewed. At the time of death, 37% of patients were receiving active treatment, 12% were in a treatment-free interval and 51% were receiving only supportive care. Death before and during active first-line treatment was not uncommon (6% and 24% of patients, respectively) but these deaths were often not solely due to disease progression; factors such as renal failure and infection frequently played a role (in 30% and 20% of patients at first-line, respectively). Most deaths at later lines were due to progressive disease. Cox model results suggested that early deaths were associated with advanced disease stage, high-risk cytogenetics and poor response and relapse profiles.

Conclusions: These real-world data could be used to help develop strategies for improving survival in patients with MM and to support management tailored to the stage of disease.

KEYWORDS
death, Europe, mortality, multiple myeloma, risk, survival

1 | INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disorder,[1] affecting approximately 4 in every 100 000 individuals in Europe.[2] The past few decades have seen improved management of MM through multidisciplinary approaches. A European population-based study reported an increase in 5-year survival in patients with MM/plasmacytoma from 29.8% in 1997-1999 to 39.6% in 2006-2008.[3] Furthermore, data from the Swedish Myeloma Registry suggested that a later year of diagnosis was associated with improved survival between 2008 and 2015 (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.77-0.92; $P < 0.05$).[4]

Despite the positive trend in survival, response to anti-MM therapy remains variable. Although some treated patients survive progression-free for more than 10 years,[5] approximately 10% die within 1 year of diagnosis.[6,7] Furthermore, most patients will relapse and, because there is currently no effective cure, many will die of refractory disease.[8,9]

A clear understanding of why patients with MM die is still lacking. Study populations often include a mixture of surviving patients and those who have died; there are few studies that focus on deceased patients. Mortality is usually attributed to combined effects of active MM and comorbid factors, but it is also linked to cytogenetic abnormalities that drive disease aggressiveness.[10] More research is required to improve our understanding of mortality in patients with MM, particularly if it occurs soon after diagnosis. Improved understanding could help to inform clinical decision-making regarding the benefit-risk profiles of therapeutic options and guide monitoring requirements for patients with MM at different stages of the disease and treatment pathway. Improved understanding of clinical events occurring before death related to MM might facilitate interventions to extend survival and improve tailored management at this critical stage.

This study was conducted to describe the characteristics, treatment patterns and outcomes before death associated with patients with MM.

2 | METHODS

2.1 | Study design

This was a retrospective chart review to describe treatment patterns, outcomes and healthcare resource use in European patients with symptomatic MM. During the second half of 2016, data were collected from the charts of patients in five European countries (EU5: France, Germany, Italy, Spain and the UK). Ethics committee approval was received in Germany and Spain as per national regulations. The remaining countries did not have this requirement because the study was anonymous. The index date was the date on which physicians received study materials. Documentation occurred in June or July 2016 in France, Italy and the UK, and between September and November 2016 in Germany and Spain.

Herein, we report a longitudinal analysis of a subgroup of patients with MM identified as part of the full study. This subgroup of patients formed the "deceased population": those who had died in the 3 months before the index date. The primary objective of this part of the study was to describe the treatment pathway from symptomatic MM diagnosis to death for this subgroup of patients.

2.2 | Eligibility

The recruitment process for participating physicians was designed to ensure that data were representative of clinical practice. Regional quotas and practice settings quotas (hospital types, office-based for Germany) for the physicians were determined. Physicians, including oncologists, haematologists and onco-haematologists, and internists in Germany were solicited to participate in the study. The numbers of physicians and patients per physician included in the study were based on the distributions in the respective countries, reflecting the methodology of a previously conducted chart review.[11,12] Documenting physicians were required to be personally responsible for initiating anti-MM treatment in patients, and for the management of at least 15 patients with symptomatic MM per month (or 10 for office-based physicians in Germany). They were also required to have at least 3 years of clinical experience.

Patients were eligible for the "deceased patients" subgroup of the study if they had been diagnosed with symptomatic MM and had died, at the age of 18 years or over, in the 3 months prior to the index date. Such patients were included irrespective of other parameters, such as diagnosis date, profile, disease characteristics, treatment stage at death, treatment previously received, or previous participation in a clinical trial or early access programme.

2.3 | Analysis variables for the deceased population

Demographic data recorded at MM diagnosis included age, sex, height and weight. Details relating to diagnosis included diagnosis date, International Staging System (ISS) stage, circumstances of diagnosis, cytogenetic abnormalities, comorbidities (including cardiovascular disease, neuropathy and deep vein thrombosis) and history of skeletal-related events.

Details relating to end of life included time from the end of the last treatment to death, cause of death and the last line of treatment received. Patients were classified according to whether they were receiving active anti-MM treatment, were between treatment lines with further treatment planned, or were receiving supportive care with no further treatment planned. A patient was considered to be at a treatment line, for example first-line (1L), if they were receiving active treatment at that line, receiving supportive care after having received active treatment at that line (with no further treatment planned), or were in a treatment-free interval (TFI) after that treatment line with further treatment planned.

Data were analysed according to the treatment line received when patients died. It is important to appreciate that analysis of the data in this study was not intended to establish the relative risk of death at each treatment line, because the distribution of patients across lines was not reflective of the distribution observed in the overall MM population.

2.4 | Statistical analyses

The sample size was determined according to the 95% CI for describing treatment lines of patients with symptomatic MM. Based on two patients dying in the past 3 months per physician (three patients in the UK), the total anticipated sample size for the deceased population was 875 patients across the five countries. Aggregated data for the EU5 were weighted according to MM prevalence in each country.

An exploratory multivariate Cox model regression analysis was performed using backward selection with a significance threshold of $P < 0.05$ to explore factors associated with overall survival from diagnosis and from the initiation of 1L therapy. Models were developed to include baseline characteristics, and baseline characteristics and outcomes at 1L treatment. The following variables at

TABLE 1 Deceased focus population: clinical and demographic characteristics

	Treatment status at time of death					
	Before treatment (n = 50; 6%)	1L (n = 188; 24%)	2L (n = 167; 21%)	3L (n = 167; 21%)	4L (n = 121; 15%)	5L (n = 96; 12%)
Time elapsed since diagnosis (months)						
Mean	2.6	11.0	30.1	49.0	61.4	87.7
Range	0-48	0-112	1-150	2-220	13-183	9-256
Age group at diagnosis (%)						
<65 y	5	18	17	38	54	57
65-75 y	15	21	45	40	37	34
>75 y	80	61	38	22	10	9
Age at diagnosis (y)						
Mean	81.0	75.4	72.2	66.7	63.7	62.1
Median	83.0	78.0	74.0	67.0	64.0	63.0
Range	53-96	38-96	41-91	32-91	39-83	40-83
ISS stage at diagnosis (%)						
I	5	3	8	14	13	26
II	5	21	21	29	32	24
III	80	69	63	49	47	38
Unknown	10	8	9	9	9	12
Sex (%)						
Male	56	54	56	54	57	52
Female	44	46	44	46	43	48
Transplantation status (%)						
SCT	0	10	21	42	51	62
No SCT	100	90	79	58	49	38
Cytogenetic risk status (%)[a]						
High	6	21	27	30	21	18
Low	9	17	20	19	27	45
Unknown	84	62	53	52	53	37
Comorbidity (%)						
Deep vein thrombosis	42	27	18	14	10	10
Neuropathy	18	15	11	12	10	16
Significant cardiovascular disease	86	53	34	23	16	20
Skeletal-related event	20	19	25	30	32	22
ECOG score at 1L therapy initiation (%)[b]						
0-1	NA	33	61	71	81	73
2	NA	67	39	29	19	27

Note: Total patient number is reported here as 789, rather than 786, owing to weighting of the data.
Low cytogenetic risk was defined as being negative for all three cytogenetic abnormalities.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; L, treatment line; NA, not available; SCT, stem cell transplantation.
[a]High cytogenetic risk was defined as having t(4;14), t(14;16) or del(17p).
[b]ECOG score at 1L therapy initiation was measured approximately 1 mo after diagnosis.

diagnosis were tested: age (<65 vs ≥65 years), ISS stage (I or II vs III), presence of bone complications (yes vs no), renal dysfunction (yes vs no) and anaemia (yes vs no). The following variables at 1L were tested: Eastern Cooperative Oncology Group performance status at 1L initiation (0-1 vs ≥2), time to progression (TTP; ≤15 months vs >15 months, based on the median TTP), very good partial response (VGPR) or better (yes vs no) and symptomatic progression after 1L (yes vs no). Additional variables tested included prior stem cell transplantation (yes vs no) and cytogenetic risk (high vs low). Included patients had initiated at least one treatment line and

TABLE 2 Situation of death, by treatment line

	Treatment status at time of death						
	Overall (n = 789)	Prior to treatment (n = 50; 6%)	1L (n = 188; 24%)	2L (n = 167; 21%)	3L (n = 167; 21%)	4L (n = 121; 15%)	5L (n = 96; 12%)
During active treatment (%)	37	0	47	35	38	35	41
During TFI (%)	63	100	54	65	62	65	59
On supportive care (%)	51	97	34	49	52	55	55
Further treatment planned (%)	12	3	19	16	10	10	5

Note: Categorisation by treatment line includes patients who died during or following each treatment line, before moving on to the subsequent line. Total patient number is reported here as 789 rather than 786, owing to weighting of the data.
Abbreviations: L, treatment line; TFI, treatment-free interval.

progressed after 1L. Patients with missing or unknown values for these variables were excluded from the analysis. No formal hypotheses were tested. Categorical data were summarised as the number and percentage of patients in each category. Continuous data were summarised as the mean, median, minimum and maximum. Missing or incomplete data were marked as unavailable if they could not be captured even after communication with the participating physician.

3 | RESULTS

3.1 | Physician and patient characteristics

Across the countries, 391 physicians from 391 centres participated (France, 82; Germany, 91; Italy, 85; Spain, 75; UK, 58). Almost all physicians (99.5%) were oncologists or haematologists. The charts of 786 deceased patients were reviewed (France, 139; Germany, 171; Italy, 171; Spain, 138; UK, 167). The clinical and demographic characteristics of these patients at diagnosis are summarised in Table 1 (note that the distribution of patients across treatment lines does not reflect the overall population with MM).

3.2 | Treatment status at time of death

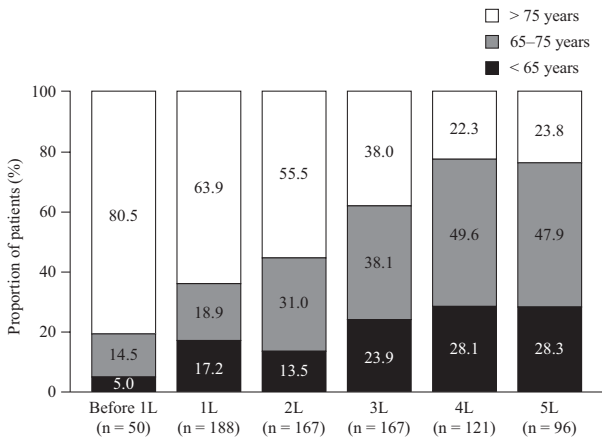
At the time of death (ie study inclusion), 37% of patients were receiving active anti-MM treatment (6% in remission, 31% not in remission). Another 12% were in a TFI, with further treatment planned (4% in remission, 9% not in remission). The remaining 51% were receiving only supportive care (ie no active anti-MM treatment; 3% in remission, 48% not in remission).

Of the 786 included patients, who died in the 3 months prior to the index date, approximately one-quarter (24%) were at 1L at the time of death (Figure S1). Similar proportions of patients were at second or third line (2L, 3L), with fewer at fourth or fifth line (4L, 5L). For those who died during a TFI, the earlier the treatment line, the more likely it was that further treatment was planned (Table 2).

At diagnosis, there were some notable differences in the characteristics of patients who subsequently died at early (ie 1L or 2L) versus later treatment lines (ie 4L or 5L) (Table 1). For example, those reaching later lines were typically younger (Figure 1) and at a lower ISS stage at diagnosis (Table 1). Patients reaching later lines also had a lower Eastern Cooperative Oncology Group score and carried a lower morbidity burden (Table 1).

3.3 | Survival

The mean duration of survival from the end of the last treatment line tended to decrease with increasing line up to and including 4L (Figure 2A), indicating that patients dying at later lines had shorter treatment-free periods leading up to death. The median overall survival was 30 months (Figure 2B). As expected, patients dying at later treatment lines survived for longer overall, although the survival curve reached a plateau for a small proportion of patients who died at 1L, indicating that a subset of patients may live for many years without requiring treatment beyond 1L.



	Before 1L (n = 50)	1L (n = 188)	2L (n = 167)	3L (n = 167)	4L (n = 121)	5L (n = 96)
Mean age at time of death (years)	81.1	76.2	74.7	70.8	68.8	69.4
Median age at time of death (years)	83.0	78.0	76.0	71.0	69.0	70.0
Mean time since diagnosis (months)	2.6	11.0	30.1	49.0	61.4	87.7

FIGURE 1 Age at time of death, by treatment line. Categorisation by treatment line includes patients who died during or following each line, before moving on to the subsequent line. Total patient number is reported here as 789, rather than 786, owing to weighting of the data. L, treatment line

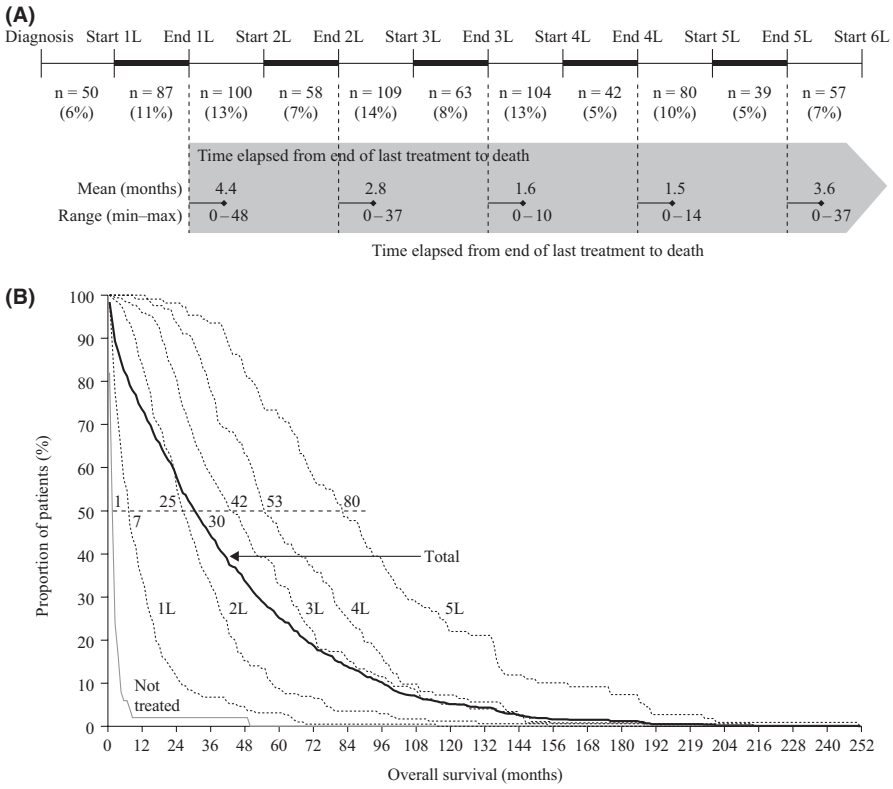


FIGURE 2 A, Patient flow through the treatment pathway. Categorisation by treatment line includes patients who died during or following each line, before moving on to the subsequent line. Total patient number is reported here as 789, rather than 786, owing to weighting of the data. L, treatment line. B, Overall survival according to treatment line at time of death. Black line and data labels show the median overall survival in months. L, treatment line

3.4 | Cause of death

For two-thirds (67%) of patients, death was primarily attributed to disease progression (which was defined as symptomatic relapse, increases in M-protein or free light chain levels) (Figure 3A). Among those whose death was attributed to disease progression, 44% also had other causes listed. These were primarily renal failure (59%) and infection (28%).

Across treatment lines, deaths were often not solely due to disease progression (Figure 3B). Factors such as renal failure and infection also played a role (in 30% and 20% of patients at 1L, respectively). The later the treatment line at which a patient died, the greater the likelihood that disease progression was the primary cause of death (Figure 3B). The proportion of patients whose death was attributed to disease progression increased from 40% of those who died before 1L, to 50% at 1L, 72% at 3L and 84% at 5L. This pattern for the contribution of disease progression to death was seen regardless of patient age group at death (data not shown).

Renal failure and infection were the next most common causes of death across all treatment lines (Figure 3B). This was true across all age groups; however, for patients in the age groups 65 years and under or 65-75 years at death, infection and renal failure became less likely to be the primary cause of death as therapy line increased, whereas the opposite trend was seen for patients aged over 75 years (data not shown).

The proportion of patients with at least one other cause of death in addition to disease progression also tended to decrease with increasing treatment line: 73%, 53%, 48%, 42%, 30% and 39%, respectively. The proportion of patients whose death was linked to disease progression was higher in those receiving supportive care (78%) than those on active treatment or in a TFI with further treatment planned (57% and 52%, respectively).

For the group of patients who died while in remission (12%), deaths were still related to factors that may be associated with MM or its treatment, including disease progression (10%), renal failure (15%) or infection (22%) (Figure 3C).

3.5 | Factors associated with death in MM

An exploratory Cox model regression analysis was conducted using data from 338 patients after excluding the following patients: patients with missing or unknown values for one or more variables; patients who had not initiated at least one treatment line; or patients who had not progressed after 1L (Figure 4). This analysis found that overall survival from diagnosis was significantly increased in patients with low cytogenetic risk (vs high risk), ISS stage I or II at diagnosis (vs stage III) and a TTP of over 15 months at 1L (vs ≤15 months). In contrast, overall survival was significantly reduced for patients whose best response was partial or worse at 1L (vs VGPR or better) and for patients with symptomatic relapse at 1L (vs non-symptomatic relapse). Similar results were obtained regarding patient survival from the initiation of 1L therapy, and when assessing baseline variables only (data not shown).

4 | DISCUSSION

Most data relating to mortality in MM come from clinical trials, in which populations are subject to eligibility criteria that often exclude

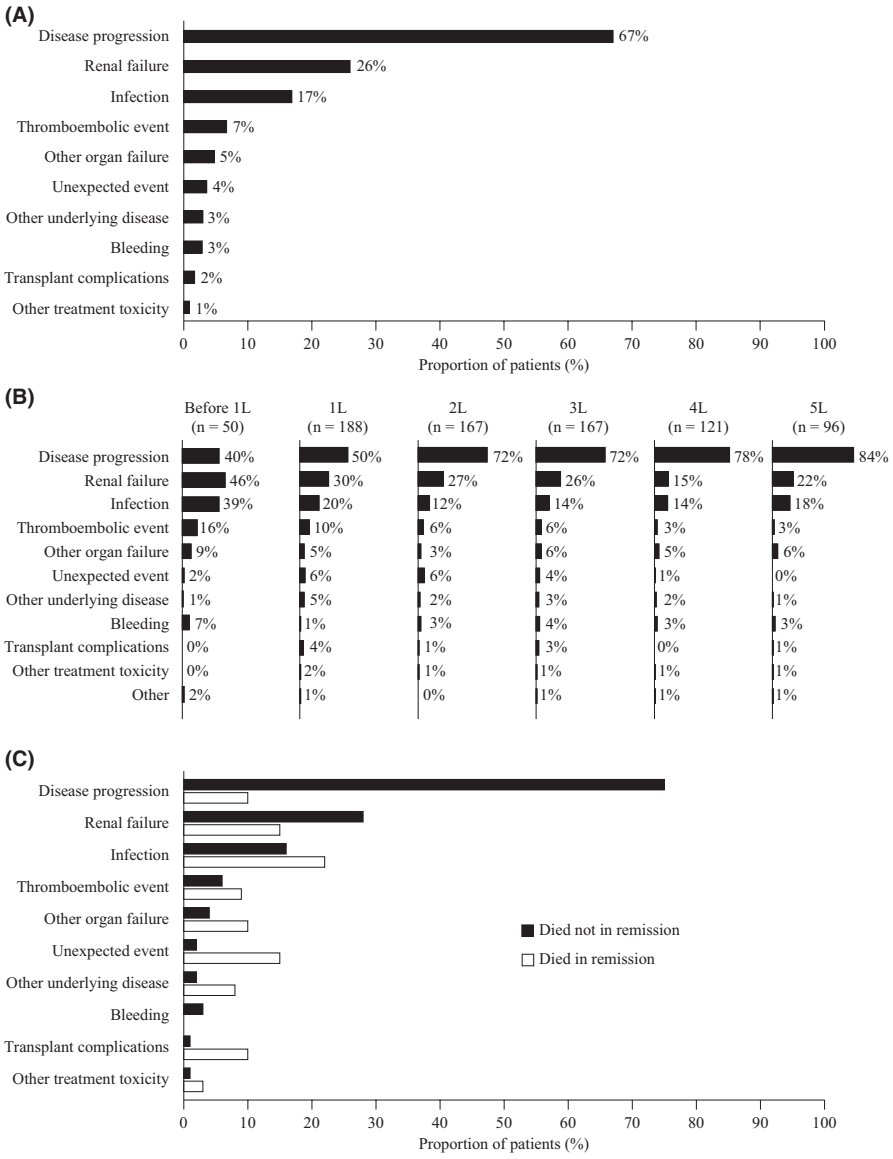


FIGURE 3 Causes of death[a] (A) overall and (B) by line, and (C) overall stratified by response status at time of death. Total patient number is reported here as 789, rather than 786, owing to weighting of the data. [a]Multiple factors may be captured as cause of death. L, treatment line

patients with major comorbidities, thus confounding analysis of circumstances of death. To the best of our knowledge, this is the first study to evaluate data from deceased patients with MM in Europe. The large size of this study, and the setting of care in oncology/haematology units, allowed us to examine both patient pathways and the association of patient and disease factors with death, in patients who died in 2016.

Despite the increasing availability of effective treatment options, relapse remains inevitable for most patients with MM, and an unmet medical need exists with regard to the unchanged prevalence of early deaths (approximately 10%).[7,9,13] Owing to the study design, it is not possible to provide mortality per treatment line because the study population is not representative of the distribution of patients across treatment lines in the overall MM population. Nevertheless, our data suggest that death during active 1L treatment remains a key issue; 47% of deaths at 1L were during active treatment. This study adds to a chart review conducted in 2014 that reported high losses of patients along the treatment pathway; in the previous review, 39% of patients did not go on to receive 2L treatment, and 62% did not receive 3L treatment.[11,12]

Death during active treatment is not only an issue at 1L; a substantial proportion of patients at each line died while on active treatment (more than one-third of patients overall). Half of deaths at 1L were due to MM progression, and the prognostic influence of depth of response to, and early relapse from, 1L treatment is borne out by the Cox model results. This underscores the considerable contribution that disease progression makes to death. Nevertheless, other causes of death that may be related to MM and associated treatment were also important, such as renal failure (30%) and infection (20%), particularly at early treatment lines. The proportion of deaths due to disease progression increased at later lines, but renal failure and infections remained significant contributors to cause of death.

The Cox model results also highlight the fact that deaths can be associated with disease-related factors not captured by the ISS, such as cytogenetic risk and time to progression. Indeed, approximately one-quarter of patients who died at 1L or 2L had an ISS stage of I

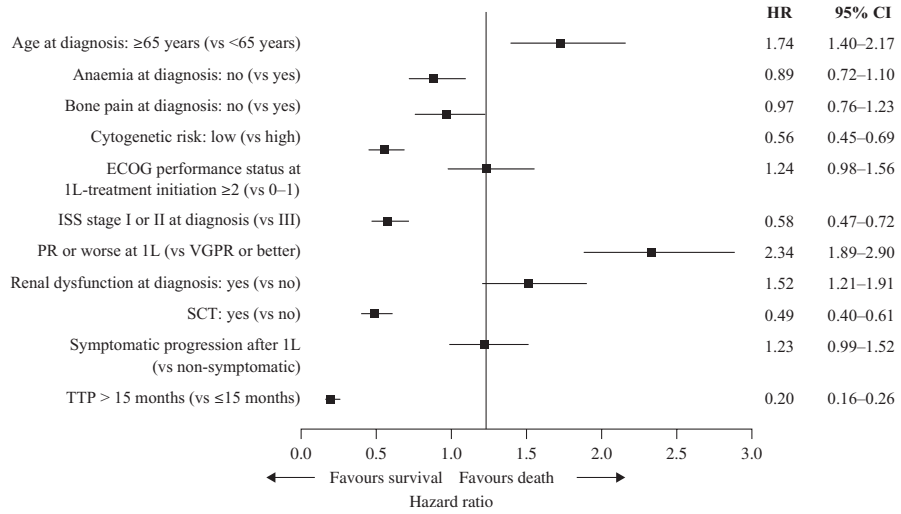


FIGURE 4 Factors associated with overall survival after MM diagnosis. Results of an exploratory multivariate Cox model regression analysis of overall survival from MM diagnosis using data from 338 patients. The analysis included variables at baseline and outcomes at 1L treatment for patients who had initiated at least one treatment line and progressed after 1L. Patients with missing or unknown values for the variables tested were excluded from the analysis. High cytogenetic risk was defined as having t(4;14), t(14;16) or del(17p). Low cytogenetic risk was defined as being negative for all three cytogenetic abnormalities. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ISS, International Staging System; L, treatment line; MM, multiple myeloma; PR, partial response; SCT, stem cell transplantation; TTP, time to progression; VGPR, very good partial response

or II. It is established that the ISS is not the strongest available predictive tool, and it has recently been revised to include serum lactate dehydrogenase and chromosomal abnormalities, which improve prognostic power.[14]

Although sparse, there are other real-world data available on factors associated with mortality in MM in Europe. A recent study found that over four-fifths of deaths in a cohort of patients with MM from Germany could be attributed to the underlying malignancy and associated complications, with approximately half of those myeloma-related deaths attributed to the malignancy itself, 15% to infections and 13% to renal disorders.[15] A study using the Connect® MM Registry identified predictors of early death (defined as death within the first 6 months after diagnosis).[9] These predictors included age over 75 years, worse performance status, adverse cytogenetics, lower mobility score, higher ISS stage, lower platelet count and previous history of hypertension.[9] A study using the Danish National MM Registry found that patients with newly diagnosed MM had increased comorbidities compared with the general population, particularly in the year preceding diagnosis; those with any registered comorbidity had increased mortality compared with those without a comorbidity (HR: 1.6).[16] In a population-based cohort study, the impact of comorbidities on early mortality was analysed over a 31-year period.[17] Comorbidities were found to have an independent impact on early mortality: at different time points, renal failure, respiratory disease, liver disease and hepatitis C infection were each associated with early mortality.[17] Similarly, a large chart review across seven European countries found that comorbidities reduced continuation to the next treatment line.[12] These studies suggest that disease-related prognostic variables, such as ISS stage and cytogenetic risk,[18] are not the only determinants of death early in the disease course. This is consistent with our data, which showed that there were fewer deaths related to disease progression at earlier treatment lines than at later treatment lines.

Many patients in this study died while their disease was considered to be in remission, and yet deaths were often related to causes that may be associated with MM and its treatment. A possible explanation for this observation is that despite exhibiting a therapeutic response to each treatment line, patients were nonetheless subject to a cumulative disease burden, contributed to by multiple relapses, drug resistance and increasingly aggressive biology. Thus, in order to maximise the benefits of increasingly effective MM therapies, a better understanding is needed of how to optimise the management of MM for patients who are in remission. Reducing the risk of renal damage, and immune and bone marrow suppression, should be given due attention in the overall care of these patients.[19,20] Additionally, sufficient guidance needs to be produced to support physicians in this aspect of treating patients with MM.

Our study also identified patients who died before 1L therapy. These individuals were typically elderly and had advanced disease at diagnosis. Nearly all (97%) of these patients did not receive active anti-MM treatment but instead received supportive care only. Further work is required to improve the prognosis of these patients; for example, if poor organ function and comorbidities are the result of MM, opportunities for effective management may include institution of anti-MM therapy with careful dose and schedule adjustment.[20]

A strength of this real-world study is that findings should be reflective of clinical practice; the five countries included in the study were selected because of their large populations, representing the majority of patients treated in Europe. These populations offer a broad and generalisable data set because of the differences in health

systems and drug access among the countries. It is, however, challenging to compare the characteristics of the study population with those from other European population-based studies owing to differences in the parameters reported.[16,21] A relatively high proportion of patients scored III using the ISS at diagnosis compared with other studies,[16,21] although high ISS stages are associated with poor survival and would be expected in a population of now deceased patients.[22] Furthermore, only one-quarter of patients had a history of skeletal-related events; this is lower than would be expected because bone disease occurs in 80% of patients with newly diagnosed MM.[23] This may be explained by the specific definition of skeletal-related events (pathologic fracture, spinal cord compression, and radiation or surgery to bone); "bone disease" is likely interpreted by physicians as a more general term.

Potential limitations of the study include the possibility of data inconsistencies resulting from site-specific management differences, such as variation in clinical interpretation of disease progression and remission. Interpretation of the data must consider the recording of multiple "causes" of death (primary, secondary; eg renal failure associated with MM progression), and the generalisability of the exploratory Cox model regression analyses may be limited by the fact that they included data from fewer than half of study patients. Only deceased patients were evaluated; hence, the characteristics reported are specific to that population. Finally, it is important to note that the characteristics of patients at each treatment line were taken from separate populations.

In conclusion, this real-world study of patients confirms that deaths at early treatment lines remain a key challenge in MM management. It also highlights that death during early treatment lines is often not due to disease progression, and death commonly occurs during active treatment, indicating a need for improvements in supportive care. As patients reach later lines, death is more typically related to progression, owing to treatment resistance.[24] Understanding factors associated with death in MM could help to increase the proportion of patients who reach later lines and inform new management approaches for improving patient survival.

ACKNOWLEDGEMENTS

Medical writing support was provided by Kim Allcott PhD of Oxford PharmaGenesis Ltd and was funded by Amgen (Europe) GmbH.

CONFLICT OF INTEREST

M Mohty has received honoraria from Amgen, BMS, Celgene, Janssen, Takeda, Novartis, Sanofi and research funding from Celgene, Janssen, Sanofi. M Cavo has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen and Takeda; L Fink is an employee of Kantar Health, which received funding from Amgen to conduct this research; S Gonzalez-McQuire is an Amgen employee and holds Amgen stock; H Leleu has received honoraria from Amgen; M Mateos has received honoraria from Janssen, Celgene, Amgen, Takeda derived from lectures and participation in advisory boards; MS Raab has received research support from Amgen, Novartis and honoraria from Amgen, Novartis, Celgene, Janssen and BMS; P Schoen is an Amgen employee and holds Amgen stock; K Yong has received honoraria from Celgene, Amgen, Takeda, Sanofi and Janssen, research funding from Janssen, Amgen and Celgene and was a consultant for Autolus.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Mohty M, Cavo M, Fink L, et al. Understanding mortality in multiple myeloma: Findings of a European retrospective chart review. *Eur J Haematol*. 2019;103:107–115. https://doi.org/10.1111/ejh.13264