Age and organ damage correlate with poor survival in myeloma patients: meta-analysis of 1435 individual patient data from 4 randomized trials

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ABSTRACT

Thalidomide and bortezomib are extensively used to treat elderly myeloma patients. In these patients, treatment-related side effects are frequent and full drug doses difficult to tolerate. We retrospectively analyzed data from 1435 elderly patients enrolled in 4 European phase III trials including thalidomide and/or bortezomib. After a median follow up of 33 months (95%CI: 10-56 months), 513 of 1435 patients (36%) died; median overall survival was 50 months (95%CI: 46-60 months). The risk of death was increased in patients aged 75 years or over (HR 1.44, 95%CI: 1.20-1.72; $P<0.001$), in patients with renal failure (HR 2.02, 95%CI: 1.51-2.70; $P<0.001$), in those who experienced grade 3-4 infections, cardiac or gastrointestinal adverse events during treatment (HR 2.53, 95%CI: 1.75-3.64; $P<0.001$) and in those who required drug discontinuation due to adverse events (HR 1.67, 95%CI; 1.12-2.51; $P=0.01$). This increased risk was restricted to the first six months after occurrence of adverse events or drug discontinuation and declined over time. More intensive approaches, such as the combination of bortezomib-thalidomide, negatively affected outcome. Bortezomib-based combinations may overcome the negative impact of renal failure. Age 75 years or over or renal failure at presentation, occurrence of infections, cardiac or gastrointestinal adverse events negatively affected survival. A detailed geriatric assessment, organ evaluation and less intense individualized approaches are suggested in elderly unfit subjects.

Introduction

Multiple myeloma (MM) is the second most common hematologic cancer, with a higher incidence in elderly subjects: 26% are aged 65-74 years, and 37% are older than 75 years.[1] In the future, the prevalence of myeloma is likely to increase due to the extended survival and the growing life expectancy of the general population. Until the late 1990s, the combination melphalan-prednisone (MP) had been the reference treatment for patients aged 65 years or over, and was associated with a median survival of 29-37 months.[2] The introduction of novel agents, such as the proteasome inhibitor bortezomib and the immunomodulatory drugs (IMIDs) thalidomide and lenalidomide, has changed the treatment paradigm of patients aged 65 years or over. In 6 randomized trials, MP plus thalidomide (MPT) showed a progression-free survival (PFS) advantage in comparison with MP,[3-9] while overall survival (OS) benefit has not been consistently reported. However, a recent meta-analysis has shown a significant improvement in PFS and OS.[10] The incidence of

any grade 3-4 non-hematologic adverse events (AEs) was approximately 50% and thalidomide discontinuation rate due to AEs varied from 33% to 45%, with higher incidence in patients aged 75 years or over. MP plus bortezomib (VMP) showed both a PFS and OS advantage in comparison with MP.[11,12] In patients aged 75 years or over, the efficacy of VMP was less evident: the 3-year OS was shorter in comparison with patients aged under 75 years (55% *vs.* 74%). The incidence of any grade 3-4 AEs was 91% and bortezomib discontinuation rate due to AEs was 34%. Both VMP and MPT are now considered the new standards of care for newly diagnosed MM patients aged 65 years or over. Recently, the combination of bortezomib and thalidomide with or without alkylating agents has shown to be highly effective.[13,14] The weekly administration of bortezomib reduced the incidence of AEs, especially peripheral neuropathy and gastrointestinal toxicity, without affecting efficacy.[13,14] Nevertheless, outcome was mainly improved for patients aged under 75 years, while limited advantage was reported in patients aged 75 years or over.[14] These data lead to the question as to whether less toxicity may translate into more efficacy, especially in unfit elderly patients.

In this meta-analysis of individual patient data from 4 randomized trials, we assessed the influence of age, organ damage, development of treatment-related AEs and drug discontinuation as predictive factors of outcome in elderly newly diagnosed MM patients receiving MP, MPT, VMP, or bortezomib and thalidomide combination (bortezomib, thalidomide and prednisone [VTP] or bortezomib, melphalan, prednisone and thalidomide [VMPT]).

Design and Methods

Study design and treatments

Patients with newly diagnosed MM, not eligible for high-dose therapy and autologous transplantation due to age (≥65 years) or co-existing co-morbidities, enrolled in the GISMM-2001 MP *versus* MPT, the HOVON 49 MP *versus* MPT, the GEM05MAS VMP *versus* VTP and the GIMEMA MM0305 VMP *versus* VMPT-VT phase III trials were included in this meta-analysis. Details on treatment regimens and results of these studies have been reported previously.[5-7,13,14] All trials were approved by the institutional review board at each of the participating centers. All patients gave written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki. Trials were registered at ClinicalTrials.gov or controlled-trials.com (numbers NCT00232934, ISRCTN 90692740, NCT00443235 and NCT01063179).

Assessment

Individual patient data were collected for each patient enrolled in the 4 trials at each co-ordinating center. All data were sent to a central co-ordinating center, reviewed for consistency and completeness, and entered into a new database. The following data available across all studies were collected for each patient: baseline data [age, gender, creatinine value, International Staging System, (ISS)]; date of death or date the patient was last known to be alive; grade, type and date of AEs occurring during induction. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. OS was calculated from the time of symptomatic MM diagnosis until the date of death or the date the patient was last known to be alive.

Statistical analysis

Patients were analyzed on an intention-to-treat basis for all time-to-event end points. Times of observation were censored on October 31ˢᵗ 2010. For this non pre-planned analysis, outcome and AEs definitions were based on data common to all trials. Descriptive statistics were used to characterize the incidence of AEs and treatment discontinuation rate. In case of multiple grade 3-4 hematologic or grade 3-4 non-hematologic AEs, we considered only the worst and the first occurred. Cumulative incidence of AEs and treatment discontinuation were calculated considering death from any cause as competing event. The proportional hazard frailty model for the subdistribution was applied to evaluate the effect of baseline factors (age, gender, ISS, serum creatinine, treatment) on the cumulative incidence function of AEs and treatment discontinuation accounting for heterogeneity across studies.[15] OS was estimated according to the Kaplan-Meier method and analyzed by univariate and multivariate Cox proportional hazards models. The following variables were assessed for potential association with OS: age at diagnosis (≥75 *vs.* <75 years), gender, ISS stages, baseline creatinine (≥2 *vs.* <2 mg/dL), treatment regimen (MP/MPT/VMP/VTP plus VMPT). As ISS stage and baseline creatinine data was not available for some patients, the category data missing were created, and all patients were included in the analysis. Grade 3-4 hematologic or grade 3-4 non-hematologic AEs during induction or drug discontinuation were included in the Cox regression models as time varying covariates. The inspection of Schoenfeld residuals suggested a violation of proportional hazard assumption for the hematologic AE, non-hematologic AE, and drug discontinuation variables. Thus, the Cox models were fitted dividing the post-event (hematologic AE, non-hematologic AE, drug discontinuation) period into two periods: the first six months after an event or after the start of follow up (for patients who did not experience an event), and after the six months to the final follow up. In order to account for clustering of patients within trials, Cox shared frailty models were estimated. Statistical analysis was performed by using STATA 11.0 (StataCorp LP, College Station, TX, USA).

Results

Patients

A total of 1435 patients were analyzed: 332 did not receive novel agents (MP), 332 received MP plus thalidomide (MPT), 387 MP plus bortezomib (VMP), 384 MP plus thalidomide and bortezomib (VTP/ VMPT). Baseline demographics and disease characteristics are listed in Table 1. Patients aged 75 years or over accounted for 36% of the entire study population, and were equally distributed in the 4 groups. Distribution of patients according to ISS staging was well balanced in all groups, except for a lower frequency of ISS III in the MP group. The proportion of patients with renal failure was higher in the MP and MPT groups due to less stringent inclusion/exclusion criteria of these protocols.

Outcome, adverse events and drug discontinuation

After a median follow up of 33 months (IQR 26-41 months), the median OS was 50 months (IQR 24-. months) and 64% of patients remained alive at three years. At the date of last follow up, 513 out of the 1435 patients (36%) died. The reasons for death were: 389 (76%) disease progression, and 124 (24%) toxic effects. The most frequent causes of toxicity-related death were infections (8%), cardiac complications (8%), second pri-

mary malignancies (2%) and venous thromboembolism (VTE) (2%). Early toxic mortality rate, occurring within the first three months from the start of treatment, was 2% (34 patients). The incidence of any grade 3-4 hematologic AEs was 563 of 1435 (39%) in the entire study population, with a lower incidence in patients receiving MPT (33%) compared with those receiving VMP (44%; *P*=0.002) or VTP/VMPT (43%; *P*=0.009). The most frequent hematologic AEs were neutropenia (27%), thrombocytopenia (10%) and anemia (3%).

The incidence of any grade 3-4 non-hematologic AEs was 412 of 1435 (29%) in the entire study population with a higher incidence in patients receiving MPT (43%) compared with those receiving VMP (24%) or VTP/VMPT (32%). The most frequent non-hematologic AEs were infections (10%), peripheral neuropathy (8%), cardiac (6%) and gastro-intestinal complications (5%). Rate of VTE was 3%. The cumulative incidences of all non-hematologic AEs and of relevant AEs (infections, cardiac and gastrointestinal AEs) increased over time reaching a plateau after six months of therapy in all treatment groups (Figure 1A and B). At six months, the cumulative incidence of all non-hematologic AEs was 6.4% (95%CI: 3.7-9.0) in the MP group, 23.8% (95%CI: 19.2-28.4) in the MPT group, 19.5% (95%CI: 15.5-23.5) in the VMP group and 25.2% (95%CI: 20.8-29.6) in the VTP/VMPT group. Similarly, the cumulative incidence of infections, cardiac and gastrointestinal AEs was 4.8% (95%CI: 2.5-7.2) in the MP group, 16.2% (95%CI: 12.2-20.2) in the MPT group, 12.1% (95%CI: 8.8-15.4) in the VMP group and 14.5% (95%CI: 11.0-18.1) in the VTP/VMPT group.

Among patients not receiving novel agents (MP), drug discontinuation for toxicity was reported in 4 of 332 patients (1%), mainly due to hematologic toxicity. Among patients receiving novel agents, drug discontinuation for toxicity was reported in 294 of 1103 patients (27%), with a higher incidence in patients receiving MPT (35%) compared with those receiving VMP (16%) or VTP/VMPT (29%). The main reasons for thalidomide discontinuation were peripheral neuropathy (9%), infections (4%), cardiac (4%) and hematologic toxicities (4%). The main reasons for bortezomib discontinuation were peripheral neuropathy (6%), hematologic AEs (4%), infections (2%) and cardiac AEs (3%). The cumulative incidences of drug discontinuation increased over time reaching a plateau after eight months of therapy in all treatment groups (Figure 1C). At six months, the cumulative incidence of drug discontinuation was 27.1% (95%CI: 22.3-32.0) in the MPT group, 9.0% (95%CI: 6.1-11.9) in the VMP group and 16.6% (95%CI: 12.8-20.3) in the VTP/VMPT group.

In a multivariable model, including several baseline characteristics, a higher risk to develop a grade 3-4 hematologic AE was detected for females (HR 1.32, 95%CI: 1.16-1.47; *P*<0.001), for patients with aggressive disease defined by ISS 3 (HR 1.49, 95%CI: 1.11-2.00; *P*=0.007) and for those with renal impairment (HR 1.51, 95%CI: 1.23-1.86; *P*<0.001). The risk of 3-4 non-hematologic AEs was increased by MPT treatment (HR 3.22, 95%CI: 1.20-8.64; *P*=0.02), by VTP/VMPT treatment (HR 3.03, 95%CI: 1.26-7.24; *P*=0.01) and by ISS 3 (HR 1.56, 95%CI: 1.09-2.23; *P*=0.01).

Impact of baseline patient conditions on outcome

The estimated 3-year OS was 68% in patients under 75 years and 57% in those aged 75 years or over (HR 1.44, 95%CI: 1.20-1.72; *P*<0.001). In patients aged 75 years or over the risk of death was higher in patients receiving VMP (HR 1.62, 95%CI: 1.04-2.52; *P*=0.03) and in those receiving VTP/VMPT (HR 3.02, 95%CI: 1.86-4.90; *P*<0.001) (Figure 2A).

Table 1. Baseline patients' characteristics.

Variable	ALL patients (N=1435)	MP (N=332)	MPT (N=332)	VMP (N=387)	VTP/VMPT (N=384)
Age					
Median years	72	72	72	72	72
IQR-years	69-76	69-76	69-76	69-76	69-77
≥ 75 years – n (%)	518 (36)	117 (35)	114 (34)	140 (36)	147 (38)
Sex, n (%)					
Male sex	739 (51)	185 (56)	177 (53)	188 (49)	189 (49)
Serum β2 microglobulin level, n (%)					
>3.5 mg/L	700 (49)	144 (43)	155 (47)	199 (51)	202 (53)
Data missing	229 (16)	75 (23)	61 (18)	50 (13)	43 (11)
International Staging System stage, n (%)					
I	283 (20)	51 (15)	55 (17)	92 (24)	85 (22)
II	586 (41)	157 (47)	127 (38)	143 (37)	159 (41)
III	271 (19)	14 (5)	71 (21)	94 (24)	92 (24)
Data missing	295 (20)	110 (33)	79 (24)	58 (15)	48 (13)
Creatinine level – n (%)					
≥ 2 mg/dL	89 (6)	28 (8)	34 (10)	18 (5)	9 (2)
Data missing	5 (0.3)	4 (1)	1 (0.3)	0	0
Trials – n (%)					
GISMM-2001	331 (23)	164 (49)	167 (50)	0	0
HOVON 49	333 (23)	168 (51)	165 (50)	0	0
GEM05MAS	260 (18)	0	0	130 (34)	130 (34)
GIMEMA MM0305	511 (36)	0	0	257 (66)	254 (66)

MP: melphalan and prednisone; MPT: melphalan, prednisone and thalidomide; VMP: melphalan, prednisone and bortezomib; VTP/VMPT: bortezomib, thalidomide, prednisone/bortezomib, melphalan, prednisone, thalidomide.

The 3-year OS was 66% in patients without renal failure and 38% in those with renal failure (HR 2.02, 95%CI: 1.51-2.70; *P*<0.001). Renal failure did not increase the risk of death in patients receiving VMP (HR 0.91, 95%CI: 0.22-2.58; *P*=0.86) (Figure 2B).

### Impact of treatment-related AEs and drug discontinuation on outcome

The development of grade 3-4 hematologic AEs did not increase the risk of death, both within the first six months from the occurrence of AE (HR 1.24, 95%CI: 0.88-1.73; *P*=0.21) and after this time point (HR 0.99, 95%CI: 0.80-1.23; *P*=0.94).
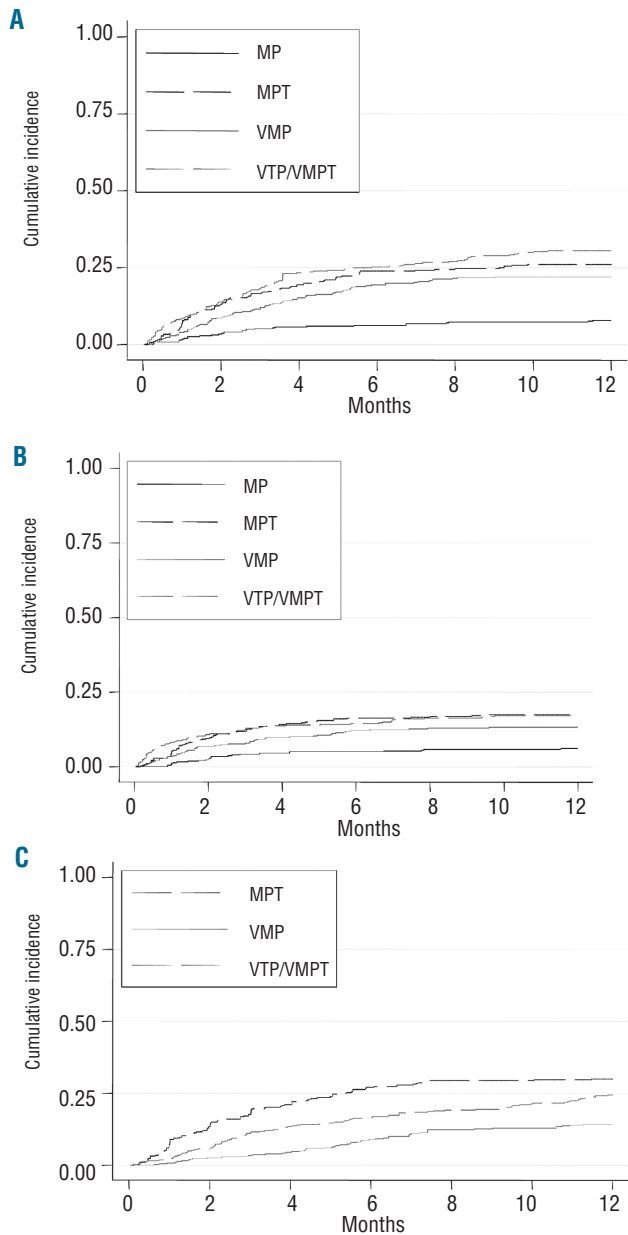
Figure 1. Cumulative incidence of grade 3-4 AEs and of drug discontinuation accounting for competing events (death and progressive disease). (A) Cumulative incidence of grade 3-4 non-hematologic toxicities. (B) Cumulative incidence of grade 3-4 infections, cardiac or gastrointestinal toxicities. (C) Cumulative incidence of drug discontinuation.
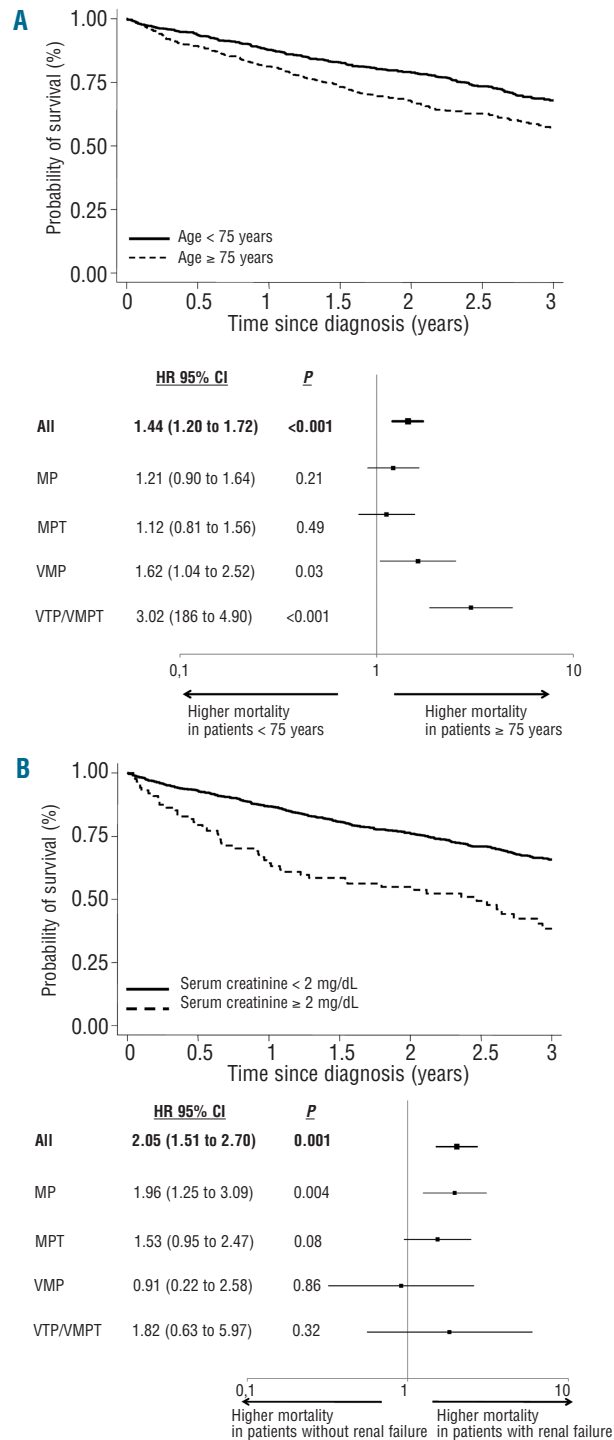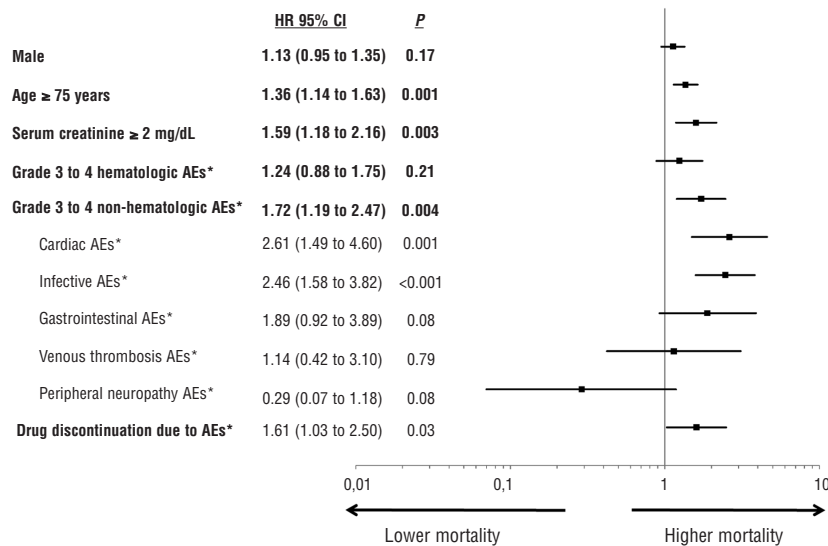

Figure 2. Overall survival according to baseline patient conditions. (A) Kaplan-Meier overall survival curves in patients younger or equal/older than 75 years in whole population and within the different treatment groups in the forest plot (results are shown, on a log10 scale, for analysis adjusted for gender, International Staging System and serum creatinine). Interaction test (heterogeneity) *P*=0.0041. (B) Overall survival in patients with or without renal failure (serum creatinine ≥ or < 2 mg/dL) in whole population and within the different treatment groups in the forest plot (results are shown, on a log10 scale, for analysis adjusted for gender, age and International Staging System. Interaction test (heterogeneity) *P*=0.65. Hazard ratios higher than 1 indicate a higher risk of death. The I bars represent 95% confidence intervals. MP: melphalan and prednisone; MPT: melphalan, prednisone and thalidomide; VMP: melphalan, prednisone and bortezomib; VTP/VMPT: bortezomib, thalidomide, prednisone/ bortezomib, melphalan, prednisone, thalidomide.

A

B

C
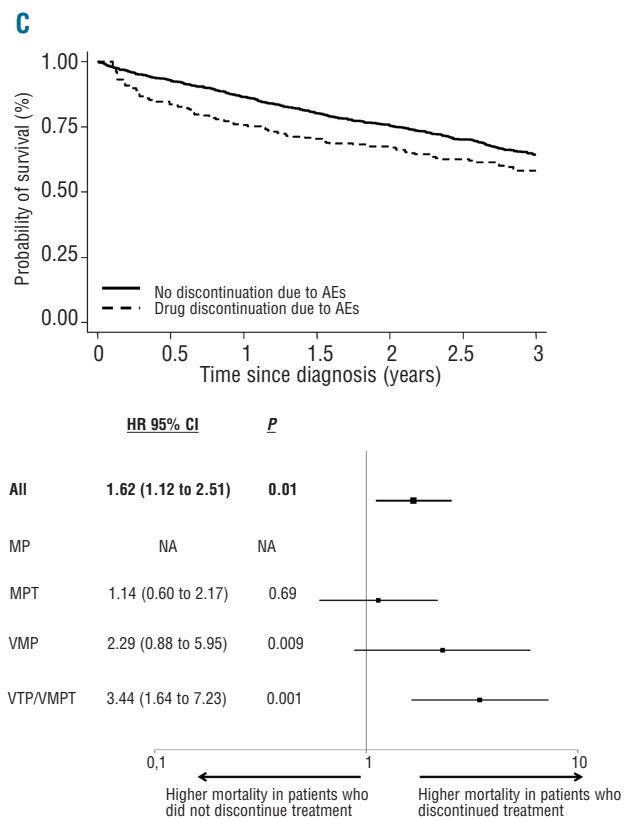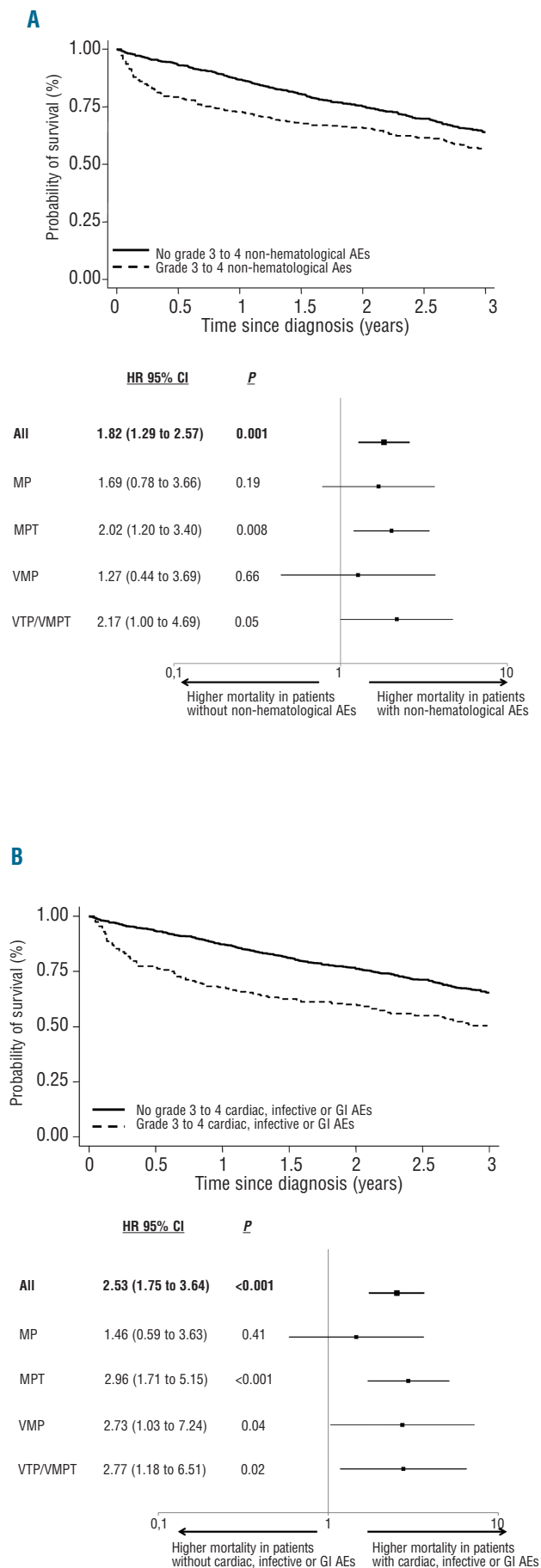
Figure 3. Impact of treatment-related complications on overall survival. (**A**) Impact of grade 3 to 4 non-hematologic toxicity in whole population and within the different treatment groups within the first 6 months after the occurrence of event in the forest plot (results are shown, on a log10 scale, for analysis adjusted for age, gender, International Staging System and serum creatinine). Interaction test (heterogeneity) *P*=0.79. (**B**) Impact of grade 3 to 4 infections, cardiac, or gastrointestinal adverse events in whole population and within the different treatment groups within the first 6 months after the occurrence of event in the forest plot (results are shown, on a log10 scale, for analysis adjusted for age, gender, International Staging System and serum creatinine). Interaction test (heterogeneity) *P*=0.52. (**C**) Impact of drug discontinuation due to grade 3-4 adverse events in whole population and within the different treatment groups within the first 6 months after the occurrence of event in the forest plot (results are shown, on a log10 scale, for analysis adjusted for age, gender, International Staging System and serum creatinine). Interaction test (heterogeneity) *P*=0.14. Hazard ratios higher than 1 indicate a higher risk of death. The I bars represent 95% confidence intervals. MP: melphalan and prednisone; MPT: melphalan, prednisone and thalidomide; VMP: melphalan, prednisone and bortezomib; VTP/VMPT: bortezomib, thalidomide, prednisone/ bortezomib, melphalan, prednisone, thalidomide.

The development of grade 3-4 non-hematologic AEs increased the risk of death within the first six months from the occurrence of AEs (HR 1.82, 95%CI: 1.29-2.57; *P*=0.001) (Figure 3A), whereas after this time point the risk of death was similar to that of patients who did not experience non-hematologic AEs (HR 0.86, 95%CI: 0.67-1.10; *P*=0.22). The occurrence of grade 3-4 cardiac AEs (HR 3.19, 95%CI: 1.79-5.71; *P*<0.001), infections (HR 2.94, 95%CI: 1.93-4.46; *P*<0.001) or gastrointestinal AEs (HR 2.30, 95%CI: 1.14-4.67; *P*=0.02) were the most significant

	HR 95% CI	*P*
Male	1.13 (0.95 to 1.35)	0.17
Age ≥ 75 years	1.36 (1.14 to 1.63)	0.001
Serum creatinine ≥ 2 mg/dL	1.59 (1.18 to 2.16)	0.003
Grade 3 to 4 hematologic AEs*	1.24 (0.88 to 1.75)	0.21
Grade 3 to 4 non-hematologic AEs*	1.72 (1.19 to 2.47)	0.004
Cardiac AEs*	2.61 (1.49 to 4.60)	0.001
Infective AEs*	2.46 (1.58 to 3.82)	<0.001
Gastrointestinal AEs*	1.89 (0.92 to 3.89)	0.08
Venous thrombosis AEs*	1.14 (0.42 to 3.10)	0.79
Peripheral neuropathy AEs*	0.29 (0.07 to 1.18)	0.08
Drug discontinuation due to AEs*	1.61 (1.03 to 2.50)	0.03

Figure 4. Hazard ratios for deaths for any cause, according to presence (*vs.* absence) of risk factors, treated as time-dependent variables. Results are shown on a log10 scale, for analysis adjusted for treatment and International Staging System (multivariate analysis). Hazard ratios higher than 1 indicate a higher risk of death. The I bars represent 95% confidence intervals. AEs: Adverse Events. *Impact on overall survival within the first 6 months after the occurrence of the event.

predictors of shorter OS. Pooled together, they increased the risk of death within the first six months (HR 2.53, 95%CI: 1.75-3.64; *P*<0.001) (Figure 3B), whereas after this time point the risk of death was similar to that of patients who did not experience this type of AEs (HR 0.86, 95%CI: 0.67-1.10; *P*=0.22). The increased risk of death associated with the development of cardiac AEs, infections and gastrointestinal AEs was similar in patients receiving MPT, VMP or VTP/VMPT. By contrast, the occurrence of VTE was not associated with shorter OS (HR 1.02, 95%CI: 0.32-3.19; *P*=0.97) and peripheral neuropathy was associated with improved OS (HR 0.27, 95%CI: 0.07-1.10; *P*=0.07).

Drug discontinuation due to AEs was correlated with increased risk of death within the first six months (HR 1.67, 95%CI: 1.12-2.51; *P*=0.01) (Figure 3C), whereas after this time point the risk of death was similar to that of patients who did not discontinue treatment (HR 0.93, 95%CI: 0.70-1.23; *P*=0.61). In patients who discontinued treatment, the risk of death was higher among patients receiving VMP (HR 2.29, 95%CI: 0.88-5.95; *P*=0.09) or VTP/VMPT (HR 3.44, 95%CI: 1.64-7.23; *P*=0.001) (Figure 3C).

Multivariate analysis

A Cox proportional hazards regression model is shown in Figure 4. Advanced age (≥75 years) (HR 1.36, 95%CI: 1.14-1.63; *P*=0.001), renal failure (creatinine level ≥ 2 mg/dL) (HR 1.59, 95%CI: 1.18-2.16; *P*=0.003), and the occurrence of grade 3-4 non-hematologic AEs (HR 1.72, 95%CI: 1.19-2.47; *P*=0.004) (especially cardiac complications: HR 2.61, 95%CI: 1.49-4.60, *P*=0.001; and infections: HR 2.46, 95%CI: 1.58-3.82, *P*<0.001) as well as drug discontinuation due to toxicity (HR 1.61, 95%CI: 1.03-2.50; *P*=0.03) were the variables associated with a shorter OS, regardless of staging and treatment administered.

Discussion

In this study, individual patient data from 1435 patients with newly diagnosed MM who received MP, either alone or in combination with thalidomide and/or bortezomib, were analyzed. In multivariate analysis, the advanced age (≥75 years), renal failure, occurrence of severe cardiac AEs, infections, gastrointestinal AEs and drug discontinuation were predictive of shorter survival. Several studies have analyzed the prognostic role of age and renal failure,[16,25] but no study has evaluated the impact of AEs and drug discontinuation on long-term outcome. The strength of this analysis lies in the size and the similarity of the patient population, derived from 4 of the largest European randomized controlled trials. Furthermore, our study focused on the two reference treatment regimens for elderly MM patients: MPT and VMP.

In 10,549 patients with newly diagnosed MM, older patients had more adverse prognostic factors and shorter survival than the younger ones.[26] In a recent meta-analysis of individual patient data from 1682 patients enrolled in 6 randomized trials comparing MP with MPT, as well as in the VISTA study comparing MP with VMP, and in the MM015 study comparing MP with MP plus lenalidomide with or without lenalidomide maintenance, survival was worse in patients aged 75 years or over.[10,12,27] Life expectancy changes as one gets older: it is about 15 years in patients under 75 years of age and ten years in those who are older.[28] Nevertheless, in our study, older patients had a higher risk of death when they were treated with a more aggressive treatment. Age 75 years or over increased the risk of death by 1.62-fold in patients receiving VMP, 3.02-fold in those receiving VTP/ VMPT, but only marginally in patients receiving MP or MPT. Combination including both bortezomib and thalidomide should be used with caution in elderly patients. Some practical issues, such as costs and intravenous injection of bortezomib, together with our results further support the use of oral combinations including immunomodulatory drugs (IMIDs) in patients with more advanced age. In the future, the availability of new oral proteasome inhibitor or subcutaneous administration could eventually modify these indications.[29,30]

Aging is associated with a reduction in cardiac, renal, and gastric functions, hepatic mass, blood flow, and bone marrow status.[31-35] All of these changes affect the pharmacokinetics and pharmacodynamics of drugs, increase toxicity, and decrease the clinical efficacy and the tolerability of treatments.

Renal failure is a common feature of MM and has been

associated with inferior survival.[35-37] Thalidomide and bortezomib pharmacokinetics are not affected by renal impairment and no dose reduction is required. In the MPT meta-analysis, the benefit of MPT was not evident in patients with renal failure.[13] By contrast, in the VISTA trial, the outcome of patients treated with VMP was not affected by renal impairment.[23] Our data showed that creatinine 2 mg/dL or over increased the risk of death by 1.53-fold in patients receiving MPT and by 1.82-fold in those receiving VMPT/VTP, while it did not increase the risk of death in patients receiving VMP. Our results should be considered with caution, due to the small number of patients with creatinine 2 mg/dL or over; on the other hand they support the recent consensus statement on behalf of the International Myeloma Working Group that recommends VMP as first-line treatment in elderly patients with renal failure.[38]

Before the introduction of novel agents, early toxic death had reached 10% in newly diagnosed MM patients receiving conventional chemotherapy.[37] Early mortality is often due to combined effect of active disease and co-morbidities. Our analysis showed that the use of novel agents decreased the early toxic death risk to 2%. This may be due to a quick reduction in tumor load. Nevertheless, the occurrence of grade 3-4 non-hematologic AEs is associated with a worse prognosis. The impact was different among the different types of toxicities. Infections, cardiac and gastrointestinal complications had the worst impact on survival, regardless of the type of therapy. Sub-clinical organ dysfunction may emerge as clinically relevant after the organ stress induced by MM treatment. These data further suggest the need for a detailed organ evaluation and geriatric assessment before starting any treatment in elderly subjects. In our study, VTE was not associated with shorter survival. Similar results were reported in a retrospective study on 668 newly diagnosed patients receiving chemotherapy with or without thalidomide[39] and in a retrospective study on 353 relapsed or refractory patients receiving lenalidomide and high-dose dexamethasone.[40] In our analysis, peripheral neuropathy was associated with improved survival. A sub-analysis of the VISTA trial showed a higher response rate and longer time-to-progression in patients who experienced peripheral neuropathy compared with those who did not.[41-43] Responding patients are likely to continue therapy for a longer period of time than non-responding patients. They receive higher cumulative doses which may explain the higher frequency of peripheral neuropathy. Recently, an interaction between myeloma-related factors and the patient's genet-ic background in the development of treatment-induced peripheral neuropathy has been shown.[44]

Drug discontinuation due to AEs was associated with a shorter survival, probably because of lower cumulative delivered-dose. The cumulative delivered-dose may be one of the factors affecting outcome. The outcome of patients aged 75 years or over receiving melphalan, prednisone and lenalidomide was worse than younger patients, due to the higher discontinuation rate and subsequent lower cumulative dose-intensity of both melphalan and lenalidomide.[27] The once-weekly schedule of bortezomib significantly reduced the incidence of grade 3-4 hematologic and non-hematologic AEs and the rate of drug discontinuation without having a negative impact on outcome.[13,45] Indeed, the cumulative delivered-dose of bortezomib was similar for both twice- and once-weekly schedules of bortezomib. This finding may underline the need to deliver the appropriate dose intensity in all patient sub-groups in order to avoid drug discontinuation and loss of efficacy. On the other hand, the inability to tolerate less drug may mirror a weaker resistance of the host to toxic injuries, which *per se* may be the main reason for shorter survival. In the future, a more precise definition of organ dysfunction (with appropriate co-morbidity scores) and frailty (with specific geriatric assessment) should become mandatory to immediately define a gentler, less dose-intense approach, instead of intervening later, after the occurrence of too many unacceptable toxicities. Patients with at least one risk factor such as age 75 years or over, cardiac, pulmonary, renal or hepatic organ dysfunction, frailty, or occurrence of grade 3-4 non-hematologic AEs during treatment, should be considered for a reduced dose-intensity treatment strategy.[46]

In conclusion, we showed that advanced age, renal failure, occurrence of infections, cardiac, or gastrointestinal grade 3-4 AEs have a significant negative impact on survival outcomes of elderly patients. Future trials focused on optimizing MM treatment regimens for both fit and unfit elderly adults are urgently needed to define tailored, 'personalized' therapy for this large patient population.

Authorship and Disclosures

Information on authorship, contributions, and financial and other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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