Early mortality in myeloma patients treated with first-generation novel agents thalidomide, lenalidomide, bortezomib at diagnosis: A pooled analysis

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Running title: Toxic deaths in newly diagnosed myeloma

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ABSTRACT

Introduction. Early toxic death (≤60 days of diagnosis) in elderly multiple myeloma (MM) patients is attributable to active disease, age and co-morbidities. Rate of early toxic deaths is 10% with conventional chemotherapy mainly due to infection and renal failure. Novel agents have improved MM outcome at the expense of newer toxicity.

Methods. We analyzed 1,146 individual patient data to assess toxic deaths during induction treatment with first-generation novel agents thalidomide, lenalidomide, bortezomib.

Results. During first-line therapy, 119/1,146 patients (10%) died for any cause, and 47/1,146 (4%) due to toxicity, including 12/1,146 (1%) early deaths. The 24-month cumulative incidence was 4.1% without any difference between bortezomib (18/503 patients,4%) and lenalidomide (29/643patients,5%;p=0.31). Toxic deaths occurred in 34/1,039 (3%) patients <80 years and 13/107 (12%) patients≥80 years. Causes were cardiac events (28%), infections (26%) and vascular complications (15%). In a multivariate analysis, older age and unfavorable ISS stage increased the risk of death.

Conclusion. First-generation novel agents significantly reduced toxic deaths compared to conventional chemotherapy. One third of deaths during first-line therapy were due to cumulative drug-related toxicities, thus supportive approaches and prevention strategies should be optimized. The higher mortality rate for toxicity in octogenarians confirms the need for a careful frailty assessment.

Keywords: multiple myeloma, toxic death, early mortality, newly diagnosed, transplant-ineligible, new drugs, bortezomib, lenalidomide, thalidomide

INTRODUCTION

In patients with multiple myeloma, significant improvements in survival have been obtained following the introduction of high-dose melphalan and autologous stem-cell transplantation, as well as with bortezomib and the immunomodulatory agents thalidomide and lenalidomide (Kumar et al., 2008; Palumbo and Anderson, 2011; Pulte et al., 2011). A population-based survival of European hematological malignancies before and after the introduction of novel agents showed that the improvement in survival was primarily restricted to patients younger than 65 years, while the benefit was less evident in older patients. Furthermore, little information is available regarding the impact of these new agents on early mortality.

Studies on causes of death among elderly patients are difficult to conduct due to low compliance. Studies conducted before the introduction of novel agents found a 2-month mortality of approximately 10%. In patients treated with novel agents, this rate decreased to approximately 6% (Morgan et al., 2011). The most common causes of death were renal failure and infections, mainly pneumonia and sepsis.

Many factors may contribute to increase the risk of death due to toxicity (toxic death) in myeloma. Age is one such factor. In the study by Augustson et al, 60% of patients who died within 2 months from start of treatment were older than 65 years. In the study by Dimopoulos et al, the incidence of early death was 14% in patients older than 80 years and 3% in those younger than that (Dimopoulos et al., 2012). In addition, older people are at high risk of developing frailty, that is a state of increased vulnerability, with cumulative deficits in several physiological systems, and a diminished resistance to stressors, such as myeloma and its treatment (Clegg et al., 2013). Age and geriatric assessment are the most sensitive predictors of frailty. The cut-off age of 80 years was found to identify frail myeloma patients that are at higher risk of death, disease progression, non-hematologic toxicities, and treatment discontinuation. However, irrespective of age, the presence of either a functional decline or the presence of comorbidities, may identify frail patients. Approximately one third of elderly MM patients at diagnosis are frail (Palumbo et al., 2015, 2014b).

Active disease is a particularly important contributing factor to early mortality, because it may cause anemia, thrombocytopenia, neutropenia, skeletal disease with reduced mobility and impaired ventilation, hypercalcemia and renal impairment (Palumbo and Anderson, 2011). Therapy itself may further increase the risk of early death, by affecting renal and cardiac function and causing immunosuppression by damaging mucosal barriers and impairing both innate and specific cellular immunity. These adverse effects of therapy

occur in the early stage of induction treatment, before achieving major reduction of tumor load and MM-related organ and tissue impairment. Consequently, induction treatment is associated with a high mortality risk (Augustson et al., 2005; Murakami et al., 2001).

In the era of novel agents, limited data are available on the risk, characteristics and predictability of early death in elderly patients. To address these issues, we analyzed individual patient data from 2 large multicenter randomized phase 3 trials. All patients received upfront first-generation novel agents, thalidomide, lenalidomide, bortezomib. The objectives were to: (1) evaluate the rate of death during first-line therapy, and particularly the risk of early death, (2) analyze the documented direct cause of death and (3) analyze the associated contributing factors.

MATERIALS AND METHODS

Patient Population

A total of 1,173 patients with newly diagnosed multiple myeloma not eligible for autologous transplantation for age or co-morbidities entered into Gruppo Italiano Malattie Ematologiche dell'Adulto and European Myeloma Network trials from May 2006 to September 2012, and were included in this analysis. Details on treatment regimens and results of these studies have been previously reported (Magarotto et al., 2016; Palumbo et al., 2014a). Briefly, in the GIMEMA MM-03-05 trial 511 patients were randomly assigned to receive 9 cycles of bortezomib, melphalan and prednisone (VMP) or bortezomib, melphalan, prednisone and thalidomide (VMPT) followed by continuous VT as maintenance. In the EMN-01 trial 662 patients were randomized to lenalidomide and dexamethasone (Rd) or lenalidomide, melphalan and prednisone (MPR) or lenalidomide, cyclophosphamide and prednisone (CPR) followed by continuous R or RP as maintenance (Table 1). Trial protocols were approved by the ethics committee at each participating institution and the procedures were conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave written informed consent before enrolment.

Assessment

Patient trial clinical report forms (CRFs) and adverse event (AE) – particularly serious AE (SAE) - forms were examined to determine the documented cause of death. These forms included information about grade, type, date of AEs, as well as date and cause of death, and relation to study drugs. A comment section was also available to report any other relevant variables thought to be relevant to the patient's final illness, such as information about dehydration, transfusion, or iatrogenic complications. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 and 4.0. In case of multiple grade 3-4 AEs, only the worst and the first AE occurred was considered.

Statistical Methods

Mortality was calculated from date of diagnosis to date of death occurring during first-line therapy or within 60 days since dropout; or to the date of dropout from first-line therapy (if applicable); or to the date the patient was last known to be alive, as appropriate. We analyzed separately two categories of death: toxic death and death from other causes. *Toxic death* was defined as death due to toxicity occurring during first-line therapy or within 60 days since dropout. *Death from other causes* was defined as death due to causes other than toxicity occurring during first-line therapy or within 60 days since dropout. *Early death* was defined as death (either toxic death or death from other causes) occurring within 60 days of diagnosis. Overall survival (OS) was calculated from date of diagnosis to the date of death or the date the patient was last known to be alive. Progression-free survival (PFS) was calculated from date of diagnosis to the date of progression or death or the date the patient was last known to be in remission. The cumulative incidence function (CIF) of toxic death and its associations with patient characteristics were analyzed considering death from any cause as a competing event using the method of Gooley et al. Differences between groups were assessed using Gray's test (Gray, 1988) and the hazard ratios (HRs) were estimated using the Fine and Gray proportional-hazards model (Fine and Gray, 1999). Differences in patient and disease characteristics were investigated using Mann–Whitney U test or Kruskal-Wallis test and Pearson's chi^2 test or Fisher's exact test, as appropriate, for continuous and categorical variables, respectively. OS and PFS were analyzed

according to the Kaplan-Meier method and Cox proportional hazards models were used to estimate HRs and 95% confidence intervals (CIs). Statistical analysis was performed using STATA (version 11) and R (version 3.1.1).

RESULTS

Patient Data

The two source trials enrolled 1,173 patients with newly diagnosed multiple myeloma; 1,146 (98%) of them received treatment and were included in this analysis. Toxic deaths occurred in 47/1,146 (4%) patients, including 12 (27%) early deaths. Deaths from other causes were reported in 72/1,146 (6%) patients, including 7 (9%) early deaths and 51 (72%) disease progression.

Table 2 shows baseline characteristics of patients. A higher proportion of patients (42%) who died early (≤60 days from diagnosis) due to toxicity were older than 80 years (P<0.001). In addition, increased serum β2-microglobulin (P=0.006), higher serum creatinine (P=0.006) and a higher proportion of ISS stage III (P=0.004) were observed in patients who died early due to toxicity compared with the rest of the population.

Toxic Death Data

Table 3 shows the direct causes of toxic deaths from start of treatment. There was no difference in the incidence of toxic death between patients receiving lenalidomide-containing regimens (29/643 patients, 5%) and those receiving bortezomib-containing regimens (18/503 patients, 4%; p=0.31). Twenty-eight percent of deaths were attributable to cardiac complications (13 patients), 26% to infections (12 patients) and 15% to vascular complications (7 patients). Other causes included second primary malignancies (3 patients, 6%), bleeding (4 patients, 9%), sudden death (3 patients, 6%), pulmonary events (2 patients, 4%), gastrointestinal events (2 patients, 4%) and renal events (1 patient, 2%). By comparing causes of toxic death between the two different treatment regimens, there was no significant difference in the proportion of deaths attributable to cardiac, infective, vascular or other causes. Causes of early toxic deaths were cardiac (3 patients, 12%),

infective (3 patients, 12%), sudden death (2 patients, 17%), second primary malignancies (1 patient, 8%), pulmonary events (1 patient, 8%), gastrointestinal events (1 patient, 8%), renal events (1 patient, 8%).

In particular, toxic deaths due to cardiac events included cardiac heart failure in 8 (62%), cardiac arrest in 3 (23%) and arrhythmia in 2 (15%) patients. The median age of these patients was 77 years, 9 (69%) patients were older than 75 years and 4 (31%) were older than 80 years. These deaths were associated with vascular risk factors, such as hypertension, renal impairment, diabetes or previous vascular events in 7 (54%) cases. Sudden death without a specific identifiable cause occurred in 2 patients and all of these occurred at home.

Toxic deaths due to infections included sepsis (9 patients, 69%) pneumonia (2 patients, 15%), and gastrointestinal infection (1 patient, 8%). Two of 12 patients dying from infections had a neutrophil count less than 0.5 x 10^9/L (grade 4), 5 patients had a count between 0.5 and 1.0 x 10^9/L (grade 3) and 1 patients had a count between 1.0 and 1.5 x 10^9/L (grade 2). Six patients (50%) received antibiotic prophylaxis with co-trimoxazole (3 patients) or fluorquinolones (2 patients).

Toxic deaths due vascular events included 4 during lenalidomide treatment, 1 during bortezomib-thalidomide treatment and 2 during bortezomib treatment, and were specifically stroke (5 patients, 71%) , pulmonary embolism (1 patient, 14%) and other (1 patient, 14%). All patients treated with immunomodulatory drugs received anti-thrombotic prophylaxis. Among patients who experienced stroke, 2 received low-dose aspirin, 1 low-molecular weight heparin, 1 low-dose warfarin and 1 no prophylaxis (because treated with bortezomib-melphalan-prednisone). These deaths were associated with vascular risk factors, such as hypertension or previous vascular events in 2 (29%) cases.

Toxic deaths caused by second primary malignancies (all solid tumors) included gastrointestinal cancer (1 patient), mesothelioma cancer (1 patient), and breast cancer (1 patient).

Cumulative incidence

Cumulative incidence of toxic deaths was 1.1% at 60 days and increased linearly over time of approximately 1% every 6 months, reaching 4.1% at 24 months (Figure 1A). The median time to occurrence was 8.6 months. Overall, 77% of toxic deaths occurred during induction. In particular, 93% of cardiac deaths, 83% of vascular deaths, 67% of infective deaths occurred during induction.

Cumulative incidence of deaths from other causes was 0.6% at 60 days and increased to 7.3% at 24 months (Figure 1A). The median time to occurrence was 10.8 months. Overall, 75% of deaths occurred during induction, of them 37 patients had disease progression.

The incidence of toxic deaths was 3% (20/773) in patients aged <75 years and 5% (14/266) in patients aged 75-79 years. The incidence of toxic death was ~4 fold higher in patients older than 80 years (13/107 [12%], p<0.001). Cumulative incidence of toxic deaths at 60 days and 24 months, respectively, was 4.7% (95% CI, 0.7%-8.8%) and 10.5% (95% CI, 3.6%-17.4%) in patients older than 80 years and 0.7% (95% CI, 0.2%-1.2%) and 3.4% (95% CI, 2.2%-4.7%) in those younger than 80 years (Figure 1B).

The incidence of deaths from other causes was 5% (38/773) in patients aged <75 years, 9% (24/266) in patients aged 75-79 years, and 9% (10/107) in patients older than 80 years (p=0.022). Cumulative incidence of death from other causes at 60 days and 24 months, respectively, was 1% (95% CI, 0-3%) and 12.9% (95% CI, 4.6%-21.1%) in patients older than 80 years and 0.6% (95% CI, 0.1%-1.1%) and 6.8% (95% CI, 5%-8.6%) in those younger than 80 years (Figure 1B).

No difference in patient characteristics - β2-microglobulin, albumin, creatinine and ISS stage - were observed between patients younger and older than 80 years.

In a multivariate analysis, age increased the risk of toxic death by 13% per 1 year increase. ISS 2 and ISS 3 increased the risk of toxic death approximately 3- and 4-fold, respectively, compared to ISS 1 (table 4). The risk did not increase with poor performance status. Greater tumor burden and activity (ISS) increased the risk of death because such deaths occurred before the maximal beneficial effect of therapy in reducing tumor load: 92% of toxic deaths occurring within 60 days occurred in patients with a suboptimal response (8 not available, 3 stable disease, 1 partial response).

Grade 3-4 Adverse Events

Grade 3-4 infectious, cardiac, vascular or gastrointestinal AEs occurred in 199 patients (17%). The development of grade 3-4 AEs significantly increased the risk of death (HR 1.80, 95% CI 1.42-2.27; p<0.001) and/or progression (HR 1.44, 95% CI 1.20-1.73; p<0.001) (Fig. 2A and 2B).

This survival difference was particularly evident in the older population. In patients aged 80 years or over, the occurrence of grade 3-4 AEs significantly increased the risk of death (HR 2.43, CI 1.30-4.55; p=0.005)

and/or progression (HR 1.89, CI 1.08-3.23; p=0.027) as compared to patients who did not experience grade 3-4 toxicities.

DISCUSSION

This pooled analysis of individual participant data from 1,146 elderly patients with newly diagnosed MM treated with first-generation novel agents (bortezomib, thalidomide, lenalidomide) showed that a small portion of patients experienced early mortality – within 60 days of diagnosis - either due to toxicity (1%) or due to any other cause (0.6%). The incidence of toxic deaths was ~4-fold higher in octogenarians (12%) compared with younger patients (3.1%). No difference was observed between patients who received bortezomib-containing regimens and those who received lenalidomide-containing regimens. The most common causes of death were cardiac, infections and vascular diseases. Predictive markers for death were older age and high ISS stage. The occurrence of grade 3-4 AEs was associated with a 2-fold higher risk of death.

Before the introduction of novel agents, toxic death within the first 60 days from start of treatment was up to 10% in newly diagnosed MM patients receiving conventional chemotherapy (Augustson et al., 2005). A recent study in an unselected nationwide population showed a mortality of 22% within 6 months of diagnosis. Only one third of patients received novel agents: 15% bortezomib and corticosteroids, 7% thalidomide and corticosteroids and 7% new drugs and alkylators (Holmström et al., 2015). Our analysis showed that the use of novel agents – in our case, first-generation novel agents - decreased the risk of toxic death from 10% to 1.1% within 60 days and to 4.1% within 24 months of diagnosis. These data compared favorably with those of major randomized phase 3 trials reporting an early mortality of 3-6% (Mateos et al., 2014, 2010; Palumbo et al., 2012). This may be due to a higher efficacy of novel agents, inducing a quick reduction in tumor load.

The most likely explanation for the reduction in early mortality is the use of less toxic therapies. Indeed, the study comparing lenalidomide with high-dose dexamethasone (480 mg/cycle) to lenalidomide plus low-dose dexamethasone (160 mg/cycle) reported a survival advantage for the low-dose dexamethasone arm, which was in part linked to a reduction in early mortality from 13% to 4% (Rajkumar et al., 2010).

The higher incidence of early death in octogenarians is not surprising. In very old patients, comorbidities and impairment of functional status are often present. Approximately one-third of patients with myeloma at diagnosis are older than 75 years and 15-20% are older than 80 years. At least 30% of elderly patients with newly diagnosed MM are frail because of the presence of concomitant diseases, abnormal laboratory test results and symptoms or signs of disability that may complicate the presentation and management of myeloma (Bringhen et al., 2013; Palumbo et al., 2015). Nevertheless, these patients are not fully characterized and they are underrepresented in clinical trials. Thus, frail patients usually receive regimens tested in fit patients, which may be too toxic for them and cause early treatment discontinuation, low efficacy and impaired quality of life. The management of these patients becomes particularly challenging. Recently the International Myeloma Working Group (IMWG) has proposed a frailty score, which identifies three groups of patients: fit, intermediate-fit and frail (Palumbo et al., 2015). In particular, older patients who are classified as intermediate-fit, might not benefit from full-dose standard regimens, and gentler approaches with doublets or low-dose triplets can be the preferable options, whereas frail patients may need doublets with lower doses. Of note, bortezomib-based therapy can be adopted in case of impaired renal function, and once-weekly administration and subcutaneous route may further reduce adverse events in this population. The doublet Rd is particularly advantageous for the oral administration of lenalidomide and the lack of peripheral neuropathy, therefore is a valuable option in these patients. (Palumbo et al., 2014b, 2011). Nevertheless, further prospective research specifically designed for frail patients is needed to improve treatment and management strategies in this setting.

Despite the reduction in early mortality observed in patients treated with novel agents, the occurrence of severe toxicities (grade 3-4 AEs) is still significantly related to a higher risk of death and progression/death. This phenomenon is particularly evident among patients over 80 years, in whom the occurrence of a severe toxicity dramatically shortens both OS and PFS as compared to patients who do not experience significant treatment-related toxicities. These data confirm that the cut-off age that defines frail patients is 80 years. Thus, a better definition of older patients who are at a higher risk for relevant toxicities, as well as preventive strategies, are urgently needed to reduce treatment-related toxicity and mortality.

Before the introduction of novel agents, the most common causes of death were infection and renal failure (Augustson et al., 2005; Holmström et al., 2015). Infections, especially pneumonia and sepsis, accounted for

approximately 50% of early deaths, and renal failure for 10-14%. In our analysis, cardiac (28%), infection (26%) and vascular disease (15%) were the most frequent causes of early death. Renal failure was rare (2%). In the past, causes of death were mainly active disease and slow reduction in tumor load. Now, they are associated with specific drug-related adverse events and coexisting co-morbidities. Subclinical organ dysfunction may emerge as clinically relevant after the organ stress induced by myeloma treatment. These data further suggest the need for a detailed organ evaluation before starting treatment in elderly patients.

Cardiac heart failure was the most frequent cause of cardiac death in our analysis. Approximately 70% of patients were older than 75 years and one third were older than 80 years. These deaths were associated with vascular risk factors, such as hypertension, renal impairment, diabetes or previous vascular events. Of note, older people are at high risk of cardio- and cerebral-vascular diseases. A careful monitoring of vital parameters and patient signs and symptoms during treatment is a valid strategy to detect and manage any subclinical alteration early.

The risk of death due to infection in the first months after diagnosis ranged from 45% to 51% (Augustson et al., 2005; Holmström et al., 2015). In our study, infections caused one third of early deaths and approximately 67% of these were due to pneumonia or sepsis. A limit of our dataset is the absence of microbiological data. Nevertheless, it is not easy to find a specific pattern of pathogens and often patients are infected with more than one pathogen. It could be interesting to evaluate these data in the future in order to provide patients with the best antibiotic treatment. Myeloma patients are predisposed to infection because of immunoparesis (Freifeld et al., 2011) with poor response to vaccination (Palumbo et al., 2008), neutropenia, lymphocytopenia (Undas et al., 2015), and impaired mucosal integrity owing to the effect of chemotherapy. A bimodal peak in incidence of infections was reported: 4-9 months from diagnosis (during induction), and 52-72 months from diagnosis (at disease progression) (Teh et al., 2015). Data about antibiotic prophylaxis with co-trimoxazole or quinolones are inconsistent and mainly refer to patients who received standard induction chemotherapy or autologous stem cell transplantation (Satlin et al., 2015; Vesole et al., 2012). Two guidelines recommended antibacterial prophylaxis with fluoroquinolones only in high risk patients with profound neutropenia expected to last for ≥ 7 days or with co-trimoxazole for patients receiving ≥ 20 mg of prednisone equivalents daily for ≥ 1 month (Flowers et al., 2013; Freifeld et al., 2011). Other factors to consider in assessing a patient's risk of infections are age ≥ 65 years, ECOG performance status ≥ 2,

nutritional status, prior infections and comorbidities. On the other hand, because there is no strong evidence that prophylaxis improves outcomes in patients at low risk, the use or overuse of antimicrobial agents may increase the spread of resistant strains (Flowers et al., 2013). In the era of novel agents, profound neutropenia expected to last for ≥ 7 days is very rare, but many elderly patients have a poor performance status, prior infections and comorbidities. Future trials are urgently needed to define the role of antimicrobial prophylaxis.

Patients with myeloma are at increased risk of venous thromboembolism, especially when treated with thalidomide or lenalidomide at diagnosis (Palumbo et al., 2008). A recent study showed that formation of denser plasma fibrin clots with reduced liability and increased thrombin generation at baseline could predispose patients to thrombotic complications regardless of antithrombotic prophylaxis (Undas et al., 2015). In our analysis, patients received antithrombotic prophylaxis and only one case of pulmonary embolism was reported. Of note, the majority of the events were strokes. These data are consistent with the age group of these patients. Stroke is the third most common cause of death in more developed countries. The incidence of stroke in the general population older than 65 years is 12.2 in white man and 9.9 in white women per 1000-person years (Go et al., 2014) and increased progressively with each decades of life, reaching an incidence of 12-20 per 1000-person years in people aged 75-84 years and 20-30 in those older than 85 years (Feigin et al., 2003). Premorbid conditions may be overlooked when faced with a new diagnosis of malignancy but a careful evaluation of risk factors, such as hypertension, obesity, hypercholesterolemia, smoking and alcohol use is useful to prevent these complications.

The strength of this analysis lies in the large number of patients analyzed and derived from two prospective studies. When we pooled data, we also collected information about concomitant diseases, and this made it possible to correct our results for comorbidity. On the other hand, the limit of this analysis is the presence of stringent inclusion and exclusion criteria for patient enrolment that could potentially underestimate the incidence of frail patients and toxic deaths observed in real life. Furthermore, data about geriatric assessment were available only in one trial, thus precluding an appropriate correlation with frailty status.

During first-line therapy, 10% of patients died for any causes; among them, 39% died due to occurrence of adverse events. To improve myeloma survival, future studies should focus not only on reducing the rate of disease progression with more powerful combinations, but also on avoiding early toxicities during treatment,

particularly in older patients. Despite impressive developments in myeloma therapy, further steps forward can be made in this patient population, particularly with the advent of new targeted agents.

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Titles and legends to tables and figures

Table 1. Characteristics of the trials included in the analysis

Table 2. Baseline characteristics

Table 3. Causes of toxic deaths during first-line therapy

Table 4. Fine & Gray Model for toxic death accounting for competing risks by other causes of death

Figure 1. Cumulative incidence of toxic deaths or deaths:

1A) Cumulative incidence of toxic deaths or deaths due to other causes

1B) Cumulative incidence of toxic deaths or deaths due to other causes according to age (< or ≥ 80 years)

Figure 2. Progression-free survival and overall survival:

2A) Progression-free Survival according to the occurrence of grade 3-4 adverse events

2B) Overall Survival according to the occurrence of grade 3-4 adverse events

Table 1 Characteristics of the trials included in the analysis.

Trial	Patients (Total No.)	Age (Median, years)	Trial Dates	Induction treatment	Patients (No.)	Progression-free survival (median, months)	Overall Survival
GIMEMA MM-03-05	511	71	2006-2009	VMPT-VT VMP	254 257	35.3 24.8	61% at 5 years 51% at 5 years
EMN 01	654	73	2009-2012	Rd MPR CPR	217 217 220	21 24 20	58% at 4 years 65% at 4 years 68% at 4 years

VMPT-VT, bortezomib-melphalan-prednisone-thalidomide followed by continuous bortezomib-thalidomide as maintenance; VMP, bortezomib-melphalan-prednisone; Rd, lenalidomide-dexamethasone; MPR, lenalidomide-melphalan-prednisone; CPR, lenalidomide-cyclophosphamide-prednisone.

Table 2. Baseline characteristics.

	Toxic death patients (n=47)		Other death patients (n=72)		Surviving patients (N=1027)	P Value
	≤ 60 days (N=12)	> 60 days (N=35)	≤ 60 days (N=7)	> 60 days (N=65)		
Age – years						
Median (IQR)	73.5 (72-83.3)	77 (73 - 79)	78 (70.5-79)	74 (70 - 77)	72 (69 - 75)	<0.001
<75 years – N (%)	7 (58)	13 (37)	3 (43)	35 (54)	715 (70)	
75-79 years – N (%)		14 (40)	3 (43)	21 (21)	228 (22)	
≥ 80 years – N (%)	5 (42)	8 (23)	1 (14)	9 (14)	84 (8)	
β2– microglobulin						
Median (IQR)	6.5 (4.1 - 9.5)	4.3 (3.4-5.9)	3.3 (3.1-3.5)	4.6 (3.4-6.6)	3.8 (2.8 - 5.4)	0.006
> 3.5 mg/L – N (%)	10 (83)	24 (69)	1 (14)	44 (68)	530 (52)	
Data missing – N (%)	1 (8)	2 (6)	1 (14)	5 (8)	81 (8)	
Albumin – g/dL						
Median (IQR)	3.6 (3.5 - 3.9)	3.5 (3.3-4.0)	3.3 (3.0-4.0)	3.7 (3.3-4.2)	3.8 (3.4 - 4.1)	0.631
≤ 3.5 g/dL – N (%)	4 (33)	16 (46)	4 (57)	26 (40)	359 (35)	
Data missing – N (%)	1 (8)	4 (11)	1 (14)	3 (5)	57 (6)	
LDH level – UI/L						
Median (IQR)	288 (258-465)	296 (231-369)	324 (301-338)	341 (210-413)	284 (203-356)	0.171
≥ 450 UI/L – N (%)	3 (25)	3 (9)		11 (17)	88 (9)	
Data missing – N (%)	2 (17)	7 (20)	4 (57)	13 (20)	181 (18)	
Creatinine – mg/dL						
Median (IQR)	1.4 (1.2 - 1.6)	1 (0.9 - 1.3)	0.8 (0.7-1.0)	1.0 (0.9-1.3)	1.0 (0.8 - 1.2)	0.006
≥ 2 mg/dL – N (%)	2 (17)	1 (3)		1 (2)	32 (3)	
Data missing – N (%)		1 (3)		1 (2)	25 (2)	
ISS stage						
1 – N (%)	0 (0)	4 (12)	0 (0)	11 (17)	279 (27)	0.004
2 – N (%)	4 (33)	20 (57)	5 (71)	28 (43)	434 (42)	
3 – N (%)	7 (58)	9 (27)	1 (14)	21 (32)	233 (23)	
Data missing – N (%)	1 (8)	2 (6)	1 (14)	5 (8)	81 (8)	
Male gender – N (%)	6 (50)	21 (60)	5 (71)	28 (43)	501 (49)	0.409
Chromosome abnormalities						0.741
Unfavorable profile* – N (%)	2 (17)	8 (23)	2 (29)	18 (28)	211 (21)	
Data missing – N (%)	3 (25)	7 (20)	2 (29)	11 (17)	236 (23)	
Karnofsky performance status						0.027
≥ 90% – N (%)	7 (58)	16 (48)	1 (14)	23 (35)	519 (51)	
70%-89% – N (%)	4 (33)	12 (34)	4 (57)	32 (49)	421 (41)	
50%-69% – N (%)	1 (8)	7 (20)	2 (29)	10 (15)	87 (8)	

IQR, Interquartile range; ISS, International Staging System; * t(4;14) or t(14;16) or del17

Table 3. Causes of toxic deaths during first-line therapy

	Bortezomib (N=18)	Lenalidomide (N=29)	Total (N=47)
Cardiac – N (%)	3 (19)	10 (34)	13 (28)
Heart failure	2	6	8
Cardiac arrest	0	3	3
Arrhythmia	1	1	2
Infection – N (%)	4 (25)	8 (28)	12 (26)
Sepsis	4	5	9
Pneumonia	0	2	2
Vascular – N (%)	3 (17)	4 (18)	7 (15)
Stroke	2	3	5
Pulmonary embolism	0	1	1
Other	1	0	1
SPM – N (%)	2 (13)	1 (3)	3 (6)
Bleeding – N (%)	3 (17)	1 (3)	4 (9)
Sudden death – N (%)	0	3 (10)	3 (6)
Pulmonary – N (%)	1 (6)	1 (3)	2 (4)
Gastro-intestinal – N (%)	2 (13)	0	2 (4)
Renal – N (%)	0	1 (3)	1 (2)

SPM, second primary malignancy

Table 4. Fine & Gray Model for toxic death accounting for competing risks by other causes of death

	HR	95% IC	P value
Therapy			
Lenalidomide vs Bortezomib	1.03	(0.53 - 1.99)	0.930
Age			
per 1-year increase	1.13	(1.06 - 1.19)	< 0.001
Gender			
Male vs Female	1.62	(0.90 - 2.94)	0.110
ISS stage			
2 vs 1	3.45	(1.20 - 9.92)	0.021
3 vs 1	3.73	(1.22 - 11.39)	0.021
Missing	2.95	(0.67 - 13.03)	0.150
Chromosome abnormalities			
Favourable vs Unfavourable	1.11	(0.53 - 2.31)	0.790
Missing	1.05	(0.50 - 2.20)	0.890
Karnofsky performance status			
70%-98% vs ≥ 90%	0.77	(0.40 - 1.49)	0.440
50%-69% vs ≥ 90%	1.73	(0.75 - 3.97)	0.200

Figure 1a

Figure 1 A

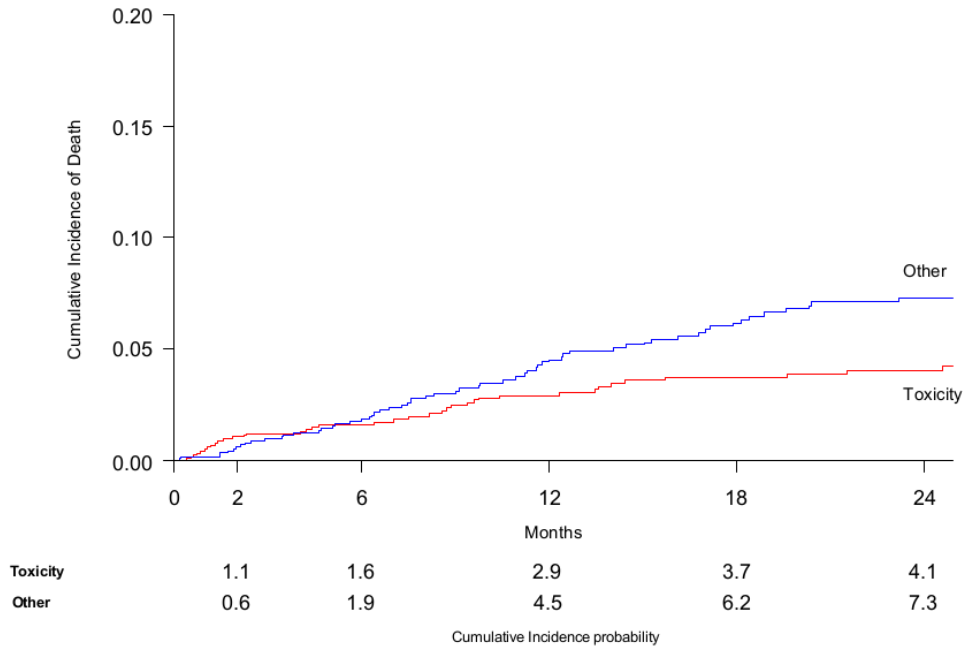

Figure 1b

Figure 1 B

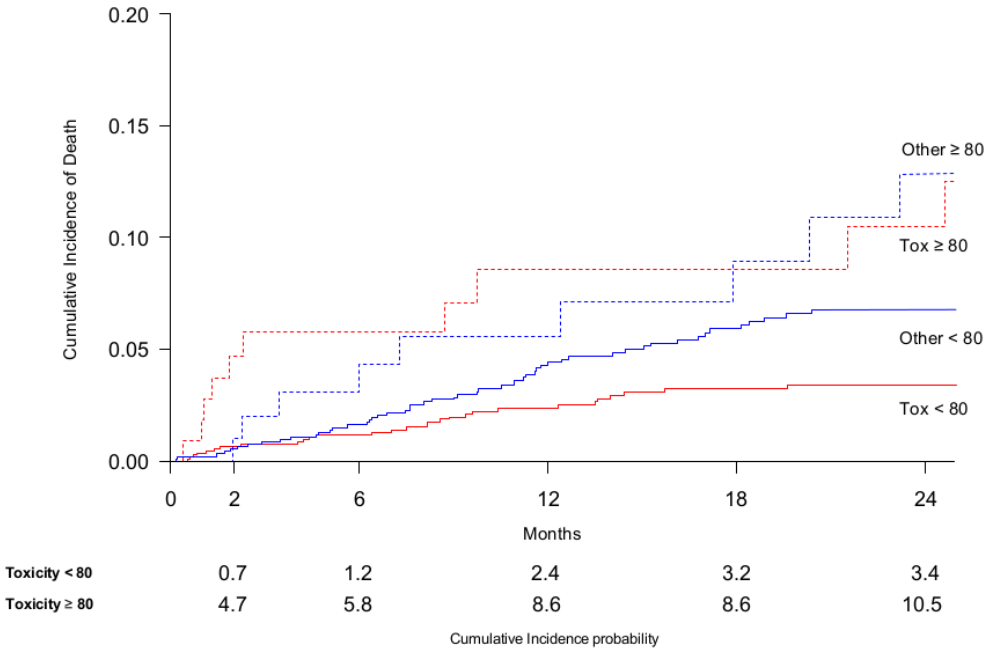

Figure 2a

Figure 2 A

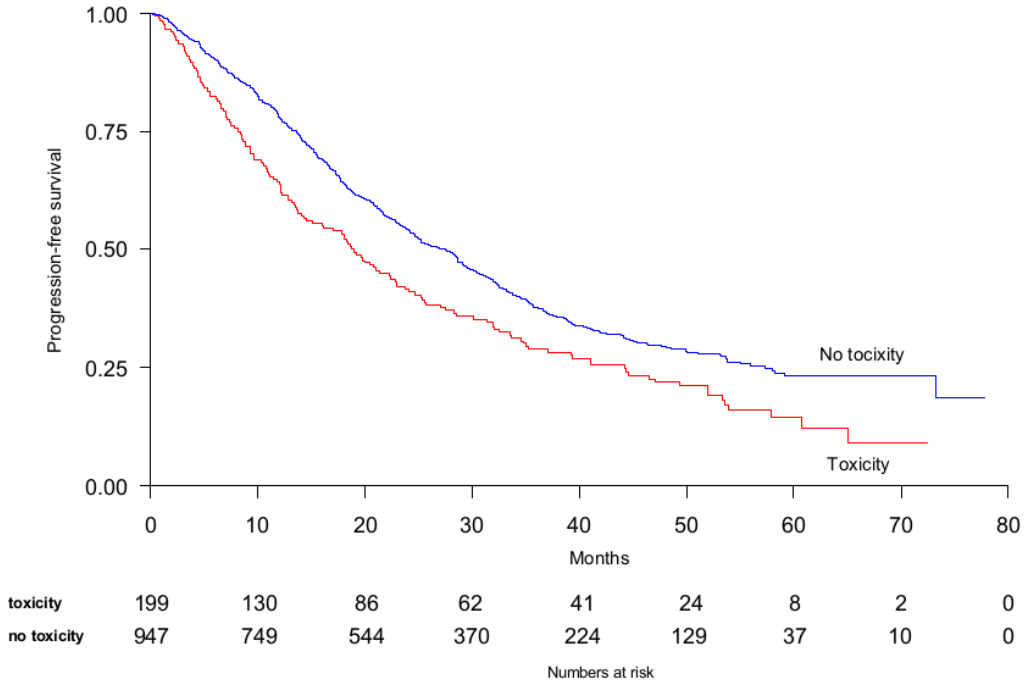

Figure 2b

Figure 2 B