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Running head: Subcutaneous bortezomib-regimens in frail MM

Abstract

This phase 2 trial evaluated 3 low-dose intensity subcutaneous bortezomib-based treatments in patients ≥75 years with newly diagnosed multiple myeloma (MM). Patients received subcutaneous bortezomib plus oral prednisone (VP, N=51) or VP plus cyclophosphamide (VCP, N=51) or VP plus melphalan (VMP, N=50), followed by bortezomib maintenance, and half of the patients were frail. Response rate was 64% with VP, 67% with VCP and 86% with VMP, very good partial response rate or better was 26%, 28.5% and 49%, respectively. Median PFS was 14.0, 15.2 and 17.1 and 2-year OS was 60%, 70% and 76%, in VP, VCP, VMP respectively. At least one drug-related grade ≥3 non-hematologic adverse event (AE) occurred in 22% of VP, 37% of VCP and 33% of VMP patients; the discontinuation rate for AEs was 12%, 14% and 20% and the 6-month rate of toxicity-related deaths was 4%, 4% and 8%, respectively. The most common grade ≥3 AEs included infections (8-20%), constitutional (10-14%) and cardiovascular events (4-12%); peripheral neuropathy was limited (4-6%). Bortezomib maintenance was effective and feasible.

VP, VCP and VMP regimens demonstrated no substantial difference. Yet, toxicity was higher with VMP, suggesting that a two-drug combination followed by maintenance should be preferred in frail patients.

Introduction

In recent years, the introduction of novel agents such as immunomodulatory drugs and the proteasome inhibitor bortezomib, associated with standard chemotherapy, has changed the management of multiple myeloma and extended survival.[1] Data from the SEER registry showed a significant trend toward a better 5-year survival for patients diagnosed between 2003-2007, whereas no survival improvement was seen in older patients (≥65 years).[2]

The global population is rapidly aging. The proportion of the population aged 65 years or over is expected to increase in all European countries, from 17.08% in 2008 to 29.95% in 2060; in particular, the population aged 80 years or over is expected to almost triple.[3]

Approximately one third of patients with myeloma at diagnosis are older than 75 years and at least 30% are frail, because of the presence of concomitant disease, abnormal laboratory test results and symptoms or signs of disability, that may complicate the presentation and management of myeloma.[4,5] Although the majority of myeloma diagnoses and myeloma-related deaths occur in subjects over 65 years, elderly frail 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.

Today, bortezomib-melphalan-prednisone (VMP) and melphalan-prednisone-thalidomide (MPT) are the reference treatments for elderly myeloma patients.[6,7] Nevertheless, the efficacy of these regimens was less evident in patients aged 75 years or over. VMP induced a shorter overall survival in patients older than 75 years in comparison with younger patients (median 32.9 vs 50.7 months);[8] the incidence of any grade 3-4 adverse events (AEs) was 91% and bortezomib discontinuation rate due to AEs was 34%.[9] Similar results have been reported with MPT: the median progression-free survival (PFS) of patients over 75 years (10 months with MPT and 6 months with MP) was shorter compared with younger patients, and no improvement was observed in overall survival (OS).[10] In another trial including patients over 75 years, MPT led to a response rate of 62% and a median PFS of 24 months, but the median duration of treatment was 13.5 months and 45% of patients discontinued treatment for AEs.[11]

Furthermore advanced age (HR 1.44, P<0.001), the occurrence of severe cardiac, gastrointestinal AEs and infections (HR 2.53, P<0.001), and drug discontinuation (HR 1.67, P=0.01) predicted a higher risk of death in newly diagnosed myeloma patients treated with melphalan-prednisone, either alone or in combination with thalidomide and/or bortezomib. This was particularly evident with the use of more complex combinations including the association of bortezomib and thalidomide. In fact, different trials did not show a substantial advantage with multi-drug regimens over less intensive combinations, since they are often associated with higher toxicity rates and worse quality of life, especially in community-based populations.[12,13]

The morbidity associated with dexamethasone-based regimens was significantly higher than the one reported with prednisone, especially in terms of infections and gastrointestinal complications.[14] These findings raise the question of whether a lower dose-intensity treatment with two-drug combinations may improve tolerability, preserving efficacy, in very elderly and frail patients, and thus should be preferred to three-drug combinations.

To address this question, we designed a multicenter, community-based study to examine the efficacy and safety of weekly subcutaneous bortezomib plus continuous low-dose prednisone (VP) or cyclophosphamide-prednisone (VCP) or melphalan-prednisone (VMP) in patients over 75 years of age with newly diagnosed multiple myeloma.

Patients and methods

Patients aged ≥75 years old (or younger with abnormal organ function), unsuitable for standard treatments or usually excluded from clinical protocols with standard inclusion/exclusion criteria, with measurable disease and a Karnofsky Performance Status (KPS) ≥50%, were enrolled.[15]

Diagnosis of myeloma was made using standard criteria.[16] Exclusion criteria included grade ≥2 peripheral neuropathy; creatinine clearance <20 ml/min; absolute neutrophil count <1,000/μL; platelets <80,000/μL; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times upper limit of normal (ULN); or total bilirubin >1.5 times ULN.

All patients provided written informed consent. Review boards at each participating site approved the study, which was conducted in accordance with the Declaration of Helsinki. This trial is registered at www.clinicaltrials.gov, NCT01190787.

Study design

This phase 2, non-randomized study was conducted at 23 centers. Patients were enrolled in either one of the three, independent bortezomib cohorts, namely VP, or VCP, or VMP. Subjects were recruited from October 2010 to August 2012; the cut-off date was March 15, 2014.

The primary objective was to determine the rate of very good partial response (VGPR) in patients with newly diagnosed multiple myeloma treated with VP, VCP and VMP regimens.

Secondary objectives included safety and tolerability, overall response rates (ORR), time to response (TTR), time to progression (TTP), PFS, and overall survival (OS).

Study Treatment

Patients were enrolled in three cohorts of treatment with VP, VCP and VMP. Treatment consisted of nine 28-day cycles of induction therapy with subcutaneous bortezomib 1.3 mg/m^2 on days 1, 8, 15, 22 plus oral prednisone 50 mg every other day (VP) or VP plus oral cyclophosphamide 50 mg every other day (VCP) or plus oral melphalan 2 mg every other day (VMP); followed by maintenance with subcutaneous bortezomib on days 1, 15, until progression.

Patients could receive supportive therapy including bisphosphonates, granulocyte colony-stimulating factor (G-CSF), erythropoietin and transfusions, as necessary. Prophylactic acyclovir for herpes zoster was recommended.

Assessments

At baseline a geriatric assessment (GA) was performed. The GA consisted of three tools: Katz's Activities of Daily Living (ADL) and Lawton's Instrumental Activities of Daily Living (IADL) scores to assess self-care activities, tasks of household management and independence status; Charlson comorbidity index (CCI) to estimate the number and the severity of comorbidities.[17,18]

AEs were graded according to NCI-CTCAE version 3.0.[19] Response was assessed prior to every treatment cycle. Response categories were based on the International Myeloma Working Group uniform response criteria.[16]

Statistical methods

Based on the primary objective (VGPR rate), sample size was estimated at the significance level of $\alpha = 0.05$, power of 80%, a null hypothesis VGPR rate of 10%, and an alternative hypothesis VGPR rate of 25%.

Based on Simon's optimal two-stage design,[20] for each cohort 43 patients were required (18 patients in the first phase, 25 in the second one). Assuming 15% of patients lost to follow-up, to obtain 129 response-evaluable patients, the enrollment of ~150 patients was targeted (50 per cohort).

Given the non-comparative nature of the study, no formal statistical comparisons between the 3 treatment cohorts were made.

All patients who received at least one dose of any study drug were included in the safety analyses. The response-evaluable population was defined as a subset of the intention to treat (ITT) population with measurable disease at baseline and with at least one post baseline response assessment.

OS was calculated from the start of the treatment until the date of death or the date the patient was last known to be alive. PFS was calculated from the start of the treatment until the date of disease progression or death (regardless of cause of death). Time-to-event analyses were performed with the Kaplan–Meier method.[21] The analyses were performed using SAS software version 8.2 (SAS Institute).

Results

Patient characteristics

One-hundred-fifty-two patients were enrolled, 51 in the VP, 51 in the VCP and 50 in the VMP cohorts. Patient disposition is shown in Figure 1. The median follow-up from enrolment was 27.2 months (range: 0–42).

The median age was 78 years (range: 59–88) with 33% of patients ≥80 years of age. Overall, 27%, 29% and 44% of patients had ISS stage I, II or III disease, respectively. Eighteen percent of patients had high-risk myeloma, defined by the presence of any of t(4;14), t(14;16), or del17p13 by FISH. According to the frailty scoring system,[4] based on age, comorbidities, cognitive and physical conditions, 3 groups of patients were identified: fit (score=0, 16%); intermediate (score=1, 30%), and frail (score≥2, 54%) (Appendix).

Baseline characteristics were similar between the treatment cohorts (Table 1), except for the VP group, where a higher proportion of patients ≥80 years (41%), frail (72%) and with ISS stage III (53%) was observed.

Efficacy

One-hundred-forty-eight out of 152 patients started treatment. Four patients did not start treatment for withdrawal of consent (2 patients), lost to follow-up (1 patient) and patient condition (1 patient) (Figure 1).

The median number of cycles administered was 9 (range: 1–9), with similar distribution across groups. The median time on therapy was approximately 11 months in all treatment groups.

Ninety-three patients across the 3 cohorts completed all 9 cycles of induction, and 79 patients started maintenance as planned.

Overall 148 patients could be evaluated for response. After induction, the ORR was 64% with VP, 67% with VCP, and 86% with VMP, including a VGPR or better of 26%, 28.5%, and 49%, and a complete response (CR)/ stringent CR (sCR) of 8%, 2% and 14% in the three cohorts, respectively (Table 2). The median time to at least a VGPR was 5.7 months.

The median PFS was 14.0, 15.2, and 17.1 months, and the 2-year OS estimate was 60%, 70%, 76% for the VP, VCP and VMP groups, respectively. (Figure 2) The median PFS was 14.1 months

for patients <80 years and 16.1 for patients ≥80 years, and the respective 2-year OS rates were 70% and 67%.

We examined the impact of frailty on outcome. Among patients enrolled in the VP group, the majority were frail (72%) and ≥80 years (41%). More fit patients received triplet regimens. In the overall population, the median PFS was 22.4, 15.2 and 13.8 months, and the 2-year OS was 84%, 76% and 60% in fit, intermediate and frail patients, respectively.

Safety

One-hundred-forty-eight patients could be evaluated for toxicity. Hematological toxicity was infrequent; the rate of at least one grade ≥ 3 hematologic AE was 6% with VP, 8% with VCP and 10% with VMP groups and they were considered drug-related according to investigators' opinion. Overall, grade 3 or higher thrombocytopenia was observed in 2% of patients.

The incidence of at least one drug-related grade ≥ 3 non-hematologic AE was 22% with VP, 37% with VCP and 33% with VMP. The most common toxicities were infections (8-14%) mostly pulmonary; constitutional (6-10%) mostly fatigue; and cardiac events (4-8%), mostly heart failure. Grade ≥ 3 peripheral neuropathy occurred in 8 patients (5%) (Table 3). Five solid second primary malignancies (pancreas, bowel, breast, liver and lung) were reported: 2 cases were diagnosed within 6 months from the start of myeloma therapy and 3 after more than 17 months.

At least one drug-related non-hematologic serious AE (SAE) was reported in 8%, 8% and 20% in the VP, VCP and VMP groups. The most frequent SAEs were cardiologic events (heart failure in 4 patients and atrial fibrillation in 2 patients) and infections (bronchitis in 2 patients, pneumonia in 5 patients and sepsis in 1 patient).

Twelve percent of patients in the VP, 14% in the VCP, and 20% in the VMP groups discontinued treatment due to AEs.

Fifteen, 13 and 10 deaths occurred during induction treatment in the VP, VCP and VMP groups respectively; among them 27%, 31% and 50% were due to AEs. Toxicity-related deaths within 60 days occurred in 3.4% of the patients, mainly due to infections (2 patients) and cardiovascular events (3 patients). Within 6 months of start of therapy, 15 patients (10%) died for any cause, and

8 (5%) due to AEs: infections (4 patients), cardiovascular events (3 patients) and one second cancer (pancreas).

At least one drug-related SAE was reported in 13% of frail patients and none in fit ones. The drop-out rate during induction was higher in frail patients (55%) as compared with fit ones (28%). The discontinuation rate due to AEs was 26% in frail patients and 8% in fit ones. The majority of early deaths due to toxicity within 6 months of the start of therapy occurred in frail patients (5/6, 83%).

Maintenance

Seventy-nine patients started maintenance, 25 in the VP, 25 in the VCP and 29 in the VMP groups. After a median follow-up of 18 months (range 1-43 months) from the initiation of maintenance, an improvement in the depth of response was observed in 14 patients (18%): 1 patient in CR upgraded to sCR, 5 patients in VGPR upgraded to CR/sCR, 4 patients in PR upgraded to either CR or VGCR, and 4 patients in SD upgraded to VGPR or PR. Overall, 51% of patients had a stability of response. Response to maintenance therapy was not influenced by the previous induction regimen.

The median PFS from the start of maintenance was 27.7 months; the 2-year OS estimate was 88% (Figure 2).

Approximately half of frail patients enrolled in the trial started maintenance. No significant difference in PFS was observed among fit, intermediate and frail patients.

No grade 3 or higher hematologic AEs related to bortezomib were reported. At least one grade ≥ 3 non-hematologic AE was seen in 16% of the patients; only 7.5% of them were considered related to the study drugs. The most frequent drug-related AEs were infections. The rate of discontinuation due to AEs was 14%.

Discussion

To our knowledge, this is the first prospective study assessing bortezomib-based treatments in very elderly (≥75 years) and frail patients with comorbidities and/or disabilities, who are usually excluded from clinical trials.

This study shows that low dose intensity bortezomib-based regimens are well tolerated and are effective in a community-based setting, with similar efficacy between the doublet VP and the triplets VCP and VMP. Toxicities, discontinuation rate and early deaths due to toxicity were higher in the VMP group, particularly in frail patients.

Our data compares favorably with the US community-based, phase 3b randomized, UPFRONT trial, which compared bortezomib-dexamethasone (VD), bortezomib-thalidomide-dexamethasone (VTD), and bortezomib-melphalan-prednisone (VMP), followed by weekly bortezomib maintenance, in elderly patients with newly diagnosed MM.[12] The median age was 73 years, 18% of patients were ≥80 years and 48% had at least one comorbidity. All three regimens demonstrated substantial activity, with an ORR of 73%, 80% and 70%, respectively, and no significant difference in median PFS (14.7 months with VD, 15.4 months with VTD and 17.3 months with VMP).

Our results confirm these data, highlighting that the doublet therapy may be as effective as the triplets, considering both efficacy and treatment-related toxicities.

In our study, these low dose intensity regimens were well tolerated. Only 5% of patients reported grade ≥3 neuropathy and a very low incidence of severe thrombocytopenia was observed. The use of subcutaneous once-weekly bortezomib significantly reduced peripheral neuropathy, which was reported in approximately 20% of patients treated with twice-weekly bortezomib.[12] The most common AEs included infections (8%-14%) and cardiac events (4-8%), which occurred mostly in VMP patients. The incidence of infections and cardiac complications in our trial seems higher as compared to the Spanish trial in which bortezomib was administered once-weekly, but the patient populations of the two trials are not comparable (fit patients with a median age of 73 years versus frail patients with a median age of 78 years).[22] Thus prophylactic antibiotics during the first 3-4 months of induction and a more accurate upfront cardiac screening should be considered.

In the French MPT trial designed for patients over 75 years, 45% of patients discontinued treatment for AEs.[11] In the UPFRONT study, 22-28% discontinued treatment for drug-related AEs. The toxicity profile was influenced by the use of twice-weekly bortezomib, combined with thalidomide or full dose melphalan (9 mg/m^2 for 4 days). In our trial bortezomib was given once-weekly and melphalan at lower doses, thus producing similar responses and outcomes, but a lower

toxicity, in a comparable setting. In our study the discontinuation rate was low, from 8% to 20% in the VMP group, suggesting that a low dose intensity treatment could be an option in this subset of patients, to avoid early discontinuation.

Concerning early deaths, 5% of patients died due to AEs and 3% due to progressive disease in the first 6 months from start of therapy. The 2-fold higher risk of early deaths for toxicity as compared to disease progression confirms the need for a careful assessment of frail patients who may benefit from a gentler or even palliative approach. Furthermore the improvement in supportive therapy together with prevention, prompt recognition and treatment of complications are urgently needed to reduce the risk of deaths due to toxicity.

In our trial bortezomib maintenance was associated with an improvement in response, a longer PFS and very few AEs. Furthermore, during maintenance the discontinuation rate due to any cause and particularly due to AEs, was low, indicating that the schedule of bortezomib planned in this study is feasible. Previous studies have evaluated the role of frontline continuous bortezomib-based treatment.[23,24] The Spanish trial including fit elderly patients, evaluated bortezomib maintenance after VMP or VTP induction, and found that VP maintenance induced a median PFS of 32 months. In our study, maintenance therapy with bortezomib resulted into a long PFS (27.7 months), which is quite comparable with the PFS reported in fit patients.

The benefit of a continuous treatment with lenalidomide after an alkylator-based regimen was less evident in patients older than 75 years of age;[25] whereas its activity was confirmed in the continuous treatment lenalidomide-dexamethasone, irrespective of age. In our trial the beneficial effect of bortezomib maintenance was evident irrespective of age and frailty status. In this community-based setting a prolonged time without symptoms of disease progression and without major toxicities would translate into a physical and emotional benefit for the patient. Therefore the final benefit of a prolonged maintenance versus a treatment-free-interval remains still unknown. Thus it would be essential in future trials to validate this hypothesis, also through quality of life studies.

Until now, advanced age was usually the only criterion to define frail patients, which sometimes led to an improper under-treatment or over-treatment of patients. In this study no difference was

observed in patients younger or older than 75 or 80 years, confirming that age is no longer sufficient to appropriately identify frail patients. As recently reported in a large analysis including also the present trial, by applying a frailty score that combines age, functional status (measured with ADL and IADL scores) and comorbidities (assessed with CCI), we were able to stratify patients into fit, intermediate and frail; of note, the latter group showed an inferior survival, a higher risk of non-hematologic AEs and treatment discontinuation.[4]

In the current study the majority of patients were frail (54%), and the majority of frail and older patients (≥80 years) were enrolled in the VP group.

The main limit of this non-randomized trial is that the patients were not stratified at enrolment. The unbalanced distribution of frail and older patients among the 3 treatment groups may in part explain the lower rate of response observed in the VP group. On the other hand, the standard approved treatment MPT and VMP with twice-weekly bortezomib for newly diagnosed myeloma patients induced response rates of 71% and 59%, a median PFS of 24 and 20.3 months, with a rate of treatment discontinuation for toxicity of 34%-40%, respectively.[6,7] In our study, the majority of fit patients received the triplet VMP and VCP (84%); in fit patients response rate was 76%, the median PFS was 22.4 months, and the rate of treatment discontinuation for toxicity was 8%. In frail patients treated with VMP the discontinuation rate for toxicity was 29%. The shorter PFS observed in frail patients (13.8 months) may be due to the higher toxicity and treatment discontinuation, highlighting the difficulty in treating frail patients even with low dose intensity regimens. These data confirm the activity of VMP or triplet bortezomib-based treatments in fit elderly patients, which still appear too toxic for frail patients.

In conclusion, the current study, with the limits of its phase 2 design, did not show a substantial advantage for the three-drug regimens. The VMP group showed significant activity, at the expense of a higher toxicity.

The growing number of older adults with myeloma is increasing the need for practical strategies to recognize and appropriately manage frail patients. The efficacy and safety results, as well as the costs associated with treatment, suggest that full dose triplet combinations can be indicated in fit patients, where a good quality response and a prolonged PFS and OS are the goals of treatment.

A doublet therapy should be preferred in frail patients, where the real goals of care are stabilization of the disease, symptoms control, maintenance of quality of life and independence status, over prolonged survival. In this setting a doublet combination with subcutaneous bortezomib and low dose steroid followed by maintenance could be recommended as upfront treatment.

This study represents a starting point for a prospective evaluation of two-drug regimens in frail elderly patients.

Authorship: AL, MB, PS, and AP designed the study, and supervised its conduct and the data analysis. AL, SB, MTP, SO, RB, APF, TC, OV, GB, AML, FM, VM, RP, LDR, PO, IDV, SS,AMC, EP, DD, MG, TG, CN, EA, LDP, CC, CM, MO recruited patients in the source studies and/or provided relevant data. AL collected and assembled the data. RP and SS performed the statistical analysis. AL and AP analysed and interpreted the data. AL and AP drafted the initial manuscript. All authors were given unrestricted access to the data, critically reviewed the manuscript drafts, approved the final version, and made the decision to submit it for publication.

Conflicts of interest: AL has received honoraria from Celgene and Jannsen-Cilag. SB has received honoraria from Celgene, Janssen-Cilag and Novartis, consultancy fees from Onyx, and served on the advisory committee for Merck Sharp & Dohme. MTP has received honoraria from Celgene, Janssen-Cilag, Mundipharma, Sanofi, Amgen, Bristol-Myers Squibb. TC has received honoraria from Celgene, J&J, Amgen, Bristol-Myers Squibb. TG has received research funding from Celgene. CN has received honoraria from Celgene, Janssen-Cilag and Mundipharma. MO has received honoraria from honoraria from Janssen-Cilag. MB has received consultancy fees from and served on the scientific advisory board for Jannsen-Cilag, Sanofi, Amgen, Celgene. PS has received research support from Onyx, Janssen, Celgene, Millennium, and served on the advisory board for Onyx, Janssen, Celgene, Millennium. AP has received consultancy fees and honoraria from Jannsen-Cilag.

Acknowledgements: We thank all the patients who participated in the study, the nurses Rosalia Capobianco and Giacomo Castorina, the datamanagers Giulia Lupparelli, Marta Santoro, and the editorial assistant Giorgio Schirripa.

Refereces

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Figure legend.

Figure 1. Patient disposition

Figure 2. Kaplan-Meier analyses of treatment outcomes. Panel A shows Progression Free Survival from start of treatment. Panel B shows Overall Survival from start of treatment. Panel C shows Progression Free Survival from start of maintenance. Panel D shows Overall Survival from start of maintenance

Figure 1 Patient disposition

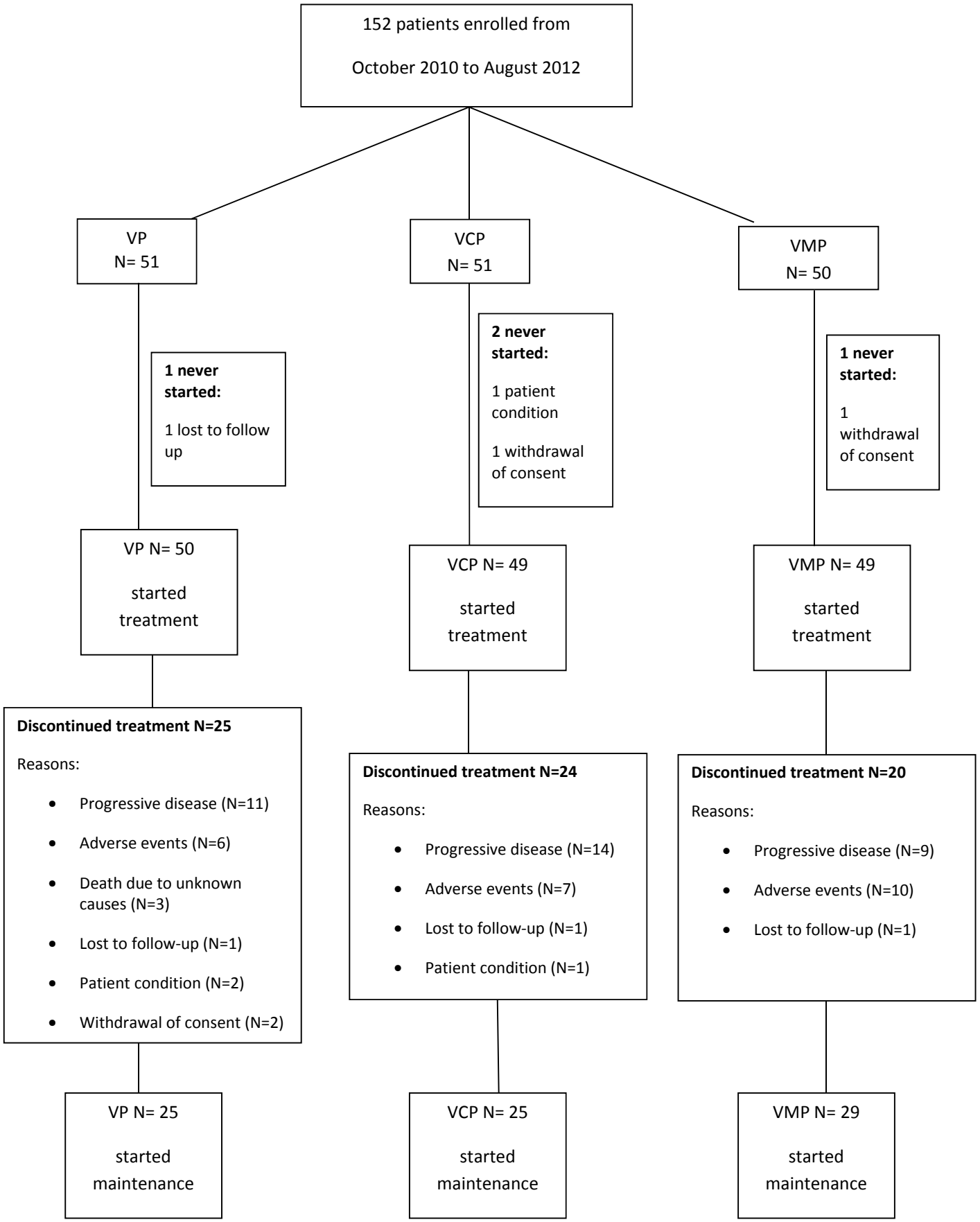
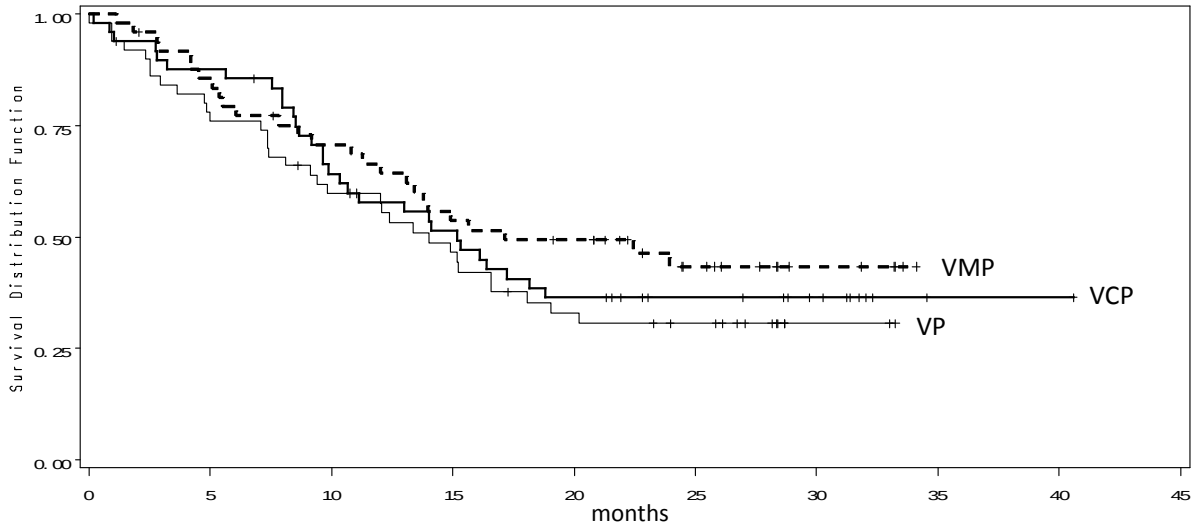


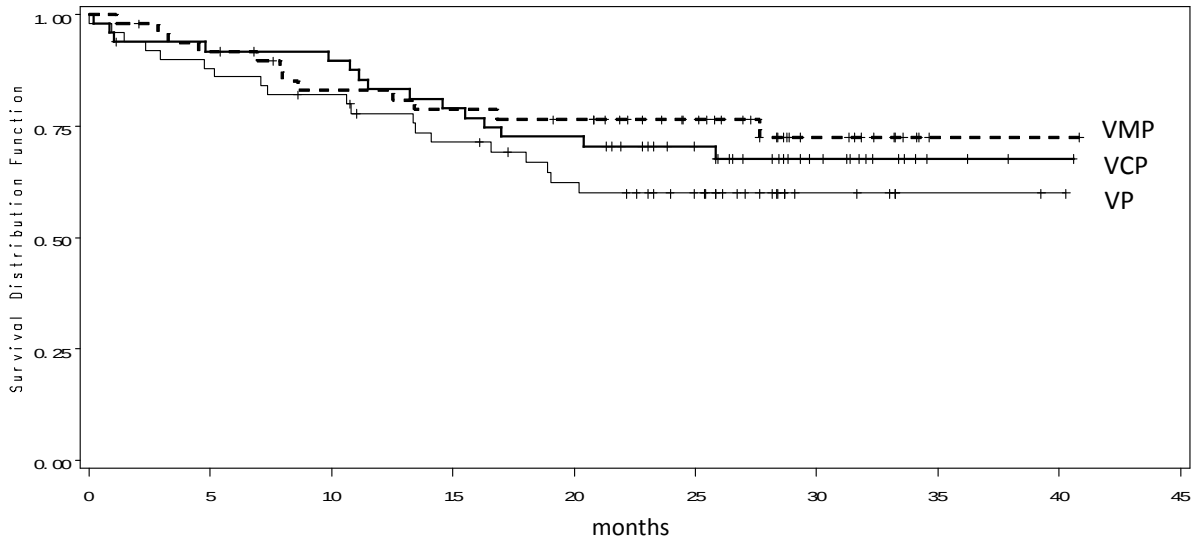
Figure 2

Kaplan-Meier analyses of treatment outcomes

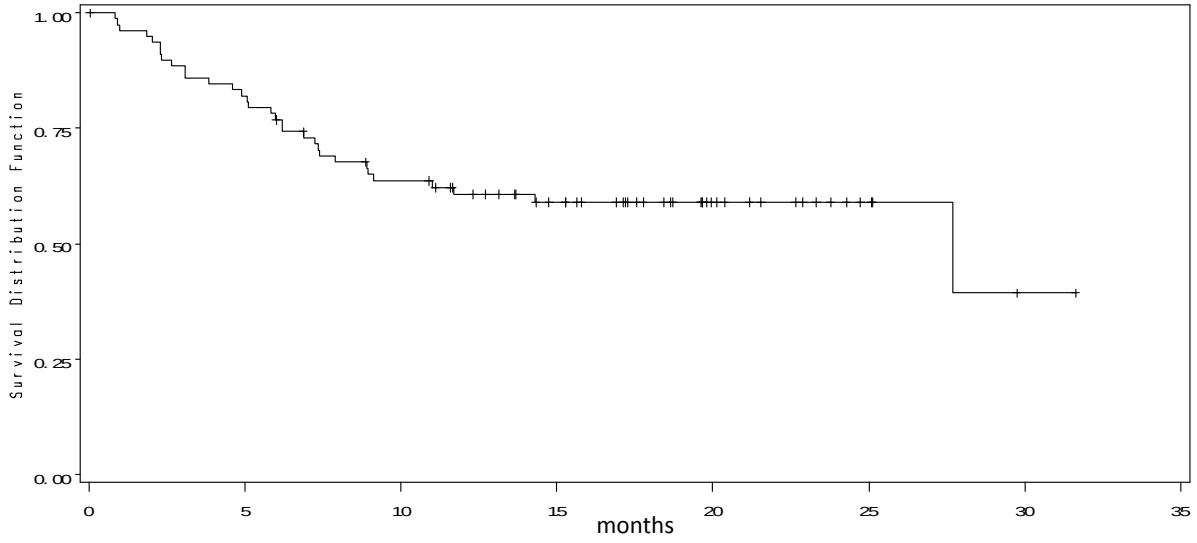
A. Progression Free Survival from start of treatment



B. Overall Survival from start of treatment



C. Progression Free Survival from start of maintenance



D. Overall Survival from start of maintenance

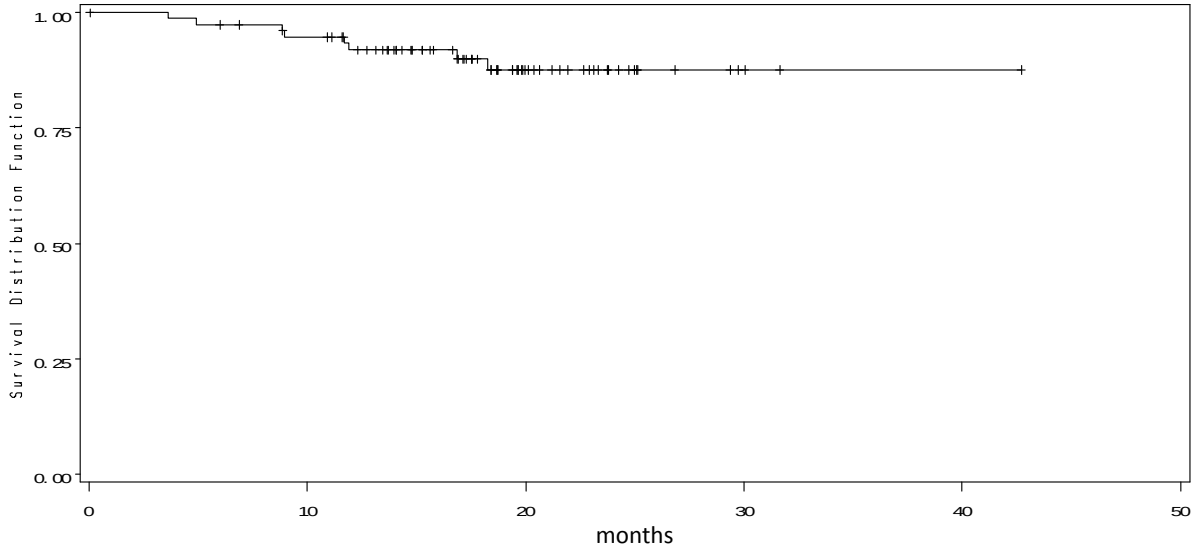


Table 1 Baseline patient characteristics

Characteristics	VP (n=51)	VCP (n=51)	VMP (n=50)
Median age, years (IQR)	78 (76-82)	77 (73-80)	78 (75-81)
Age ≥ 80 years, n (%)	21 (41)	14 (27)	15 (30)
Gender, male, n (%)	22 (43)	26 (51)	30 (60)
Myeloma type, n (%)			
IgG	33 (65)	30 (58)	27 (54)
IgA	11 (21)	10 (20)	18 (36)
Light chain	7 (14)	10 (20)	5 (10)
Other	0	1 (2)	0
ISS stage, n (%)			
I	12 (23.5)	15 (29)	14 (28)
II	12 (23.5)	12 (24)	20 (40)
III	27 (53)	24 (47)	16 (32)
Karnofsky performance status, n (%)			
50-60%	5 (10)	4 (8)	3 (6)
70-80%	21 (41)	21 (41)	23 (46)
90-100%	25 (49)	26 (51)	24 (48)
Serum creatinine >1.5 mg/dl, n (%)	15 (29)	8 (16)	12 (24)
Creatinine clearance <60 ml/min	30 (59)	26 (51)	28 (56)
LDH >450 u/L, %	6 (12)	6 (12)	5 (10)
Bone disease present, %	29 (57)	28 (55)	26 (52)
Chromosomal abnormalities			
t(4;14)	4 (8)	0	5 (10)
t(14;16)	1 (2)	4 (8)	0
-17p13	6 (12)	7 (14)	6 (12)
High risk*	9 (20)	9 (19)	10 (23)
Frailty assessment°			
Fit	4 (8)	13 (26)	8 (16)
Intermediate	10 (20)	18 (35)	17 (34)
Frail	37 (72)	20 (39)	25 (50)

VP, bortezomib-prednisone; VCP, bortezomib-cyclophosphamide-prednisone; VMP, bortezomib-melphalan-prednisone

*High risk defined as any of the following t(4;14), t(4;16) or -17p13 by FISH.

° Fit defined as age<80 years, ADL= 6, IADL=8, Charlson score= 0, unfit defined as age >80 years or ADL=5, IADL=6-7, Charlson score=1, or frail defined as age >80 years or ADL≤4, IADL ≤5 and Charlson score ≥2.

Table 2 Treatment exposure and response

Treatment exposure	**VP (n=51)**	**VCP (n=51)**	**VMP (n=50)**
Median follow-up, months	26.1	28.5	27.3
Median cycles, n (range)	9 (1-9)	9 (1-9)	9 (1-9)
Completed induction, n (%)	29 (57)	32 (63)	32 (64)
Started maintenance, n (%)	25 (49)	25 (49)	29 (58)
Best response to induction*	**VP (n=50)**	**VCP (n=49)**	**VMP (n=49)**
ORR (PR or better)	32 (64)	33 (67)	42 (86)
VGPR or better	13 (26)	14 (28.5)	24 (49)
sCR/CR	4 (8)	1 (2)	7 (14)
VGPR	9 (18)	13 (26.5)	17 (35)
PR	19 (38)	19 (39)	18 (37)
SD	16 (32)	14 (28.5)	7 (14)
PD	0	1 (2)	0
NA	2 (4)	1 (2)	0
Best response to maintenance*	**VP (n=25)**	**VCP (n=25)**	**VMP (n=29)**
ORR (PR or better)	13 (52)	14 (56)	24 (83)
VGPR or better	9 (36)	9 (36)	14 (48)
CR/sCR	5 (20)	2 (8)	8 (28)
VGPR	4 (16)	7 (28)	6 (21)
PR	4 (16)	5 (20)	10 (34)
SD	7 (28)	4 (16)	3 (10)
PD	4 (16)	5 (20)	0
NA	1 (4)	2 (8)	2 (7)

VP, bortezomib-prednisone; VCP, bortezomib-cyclophosphamide-prednisone; VMP, bortezomib-melphalan-prednisone; ORR, overall response rate; PR, partial response rate; VGPR, very good partial response; CR complete response; sCR, stringent complete response; SD, stable disease; PD, progressive disease; NA, not available.

* patients starting treatment

Table 3 Grade 3 or higher adverse events (during induction)

	VP (n=50)	VCP (n=49)	VMP (n=49)
Hematological AEs, n (%)			
Anemia	4 (8)	4 (8)	3 (6)
Drug-related	3	3	3
Neutropenia	2 (4)	1 (2)	0
Drug-related	2	1	0
Thrombocytopenia	1 (2)	0	2 (4)
Drug-related	1	0	2
At least one hematological AE			
Drug-related	3 (6)	4 (8)	5 (10)
Non-hematological AEs, n (%)			
Cardiac	3 (6)	2 (4)	6 (12)
Drug-related	2	1	4
Heart failure (related)	1	1	3
Atrial fibrillation (related)	1	0	1
Gastro-hepatic	2 (4)	2 (4)	1 (2)
Drug-related	1	2	1
Diarrhea (related)	0	2	0
Constipation (related)	1	0	0
Constitutional	5 (10)	7 (14)	5 (10)
Drug-related	3	5	3
Fatigue (related)	0	3	0
Edema limbs (related)	0	1	1
Infections	4 (8)	6 (12)	10 (20)
Drug-related	4	5	7
Lung (related)	2	2	4

Investigational	2 (4)	4 (8)	2 (4)
Drug-related	1	4	1
Creatinine increased (related)	0	3	1
Nervous	4 (8)	6 (12)	5 (10)
Drug-related	2	6	3
Peripheral neuropathy (related)	2	3	3
Renal	3 (6)	1 (2)	3 (6)
Drug-related	1	1	1
Respiratory	4 (8)	1 (2)	3 (6)
Drug-related	3	0	1
Pulmonary fibrosis (related)	0	0	1
Skin	0	4 (8)	1 (2)
Drug-related	0	4	0
Rash (related)	0	3	0
Vascular	3 (6)	2 (4)	3 (6)
Drug-related	1	1	3
Thromboembolic event (related)	1	0	0
Hypertension/hypotension (related)	0	0	2
Hematoma (related)	0	0	1
At least one non-hematological AE			
Drug-related	11 (22)	18 (37)	16 (33)
At least one non-hematological SAE			
Drug-related	4 (8)	4 (8)	10 (20)
Discontinuation rate and early death			
Discontinuation rate due to AE (%)	12	14	20
Discontinuation rate due to AE in frail patients**	11	10	29

Early toxic deaths (%)	4	4	8

AE, adverse event; SAE, serious adverse event; VP, bortezomib-prednisone; VCP, bortezomib-cyclophosphamide-prednisone; VMP, bortezomib-melphalan-prednisone

AEs occurred during induction.

Drug-related AEs, according to investigator opinion.

** The percentage is calculated on frail patients n=36 in VP, n=20 in VCP, n=24 in VMP group.