Subcutaneous *versus* intravenous bortezomib in two different induction therapies for newly diagnosed multiple myeloma: an interim analysis from the prospective GMMG-MM5 trial

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ABSTRACT

We investigated the impact of subcutaneous *versus* intravenous bortezomib in the MM5 trial of the German-Speaking Myeloma Multicenter Group which compared bortezomib, doxorubicin, and dexamethasone with bortezomib, cyclophosphamide, and dexamethasone induction therapy in newly diagnosed multiple myeloma. Based on data from relapsed myeloma, the route of administration for bortezomib was changed from intravenous to subcutaneous after 314 of 604 patients had been enrolled. We analyzed 598 patients who received at least one dose of trial medication. Adverse events were reported more frequently in patients treated with intravenous bortezomib (intravenous=65%; subcutaneous=56%, *P*=0.02). Rates of grade 2 or more peripheral neuropathy were higher in patients treated with intravenous bortezomib during the third cycle (intravenous=8%; subcutaneous=2%, *P*=0.001). Overall response rates were similar in patients treated intravenously or subcutaneously. The presence of International Staging System stage III disease, renal impairment or adverse cytogenetic abnormalities did not have a negative impact on overall response rates in either group. To our knowledge this is the largest study to present data comparing subcutaneous with intravenous bortezomib in newly diagnosed myeloma. We show better tolerance and similar overall response rates for subcutaneous compared to intravenous bortezomib. The clinical trial is registered at eudract.ema.europa.eu as n. 2010-019173-16.

Introduction

Proteasome inhibition with bortezomib is a cornerstone in the treatment of multiple myeloma (MM). Initially approved as a single agent for the treatment of relapsed disease, bortezomib is used in frontline therapy for transplant-eligible and -ineligible patients. Bortezomib prolonged progression-free and overall survival as induction therapy in candidates for autologous stem cell transplantation.[1,2] In patients with relapsed MM, Moreau *et al.* demonstrated with the randomized, prospective MMY-3012 study that subcutaneous (SC) administration of bortezomib reduced toxicity without loss of efficacy compared to the conventional intravenous (IV) bolus injections.[3,4] Limited data are available on toxicity and efficacy of SC bortezomib as a combination partner in newly diagnosed, transplant-eligible patients.[5,6]

The primary end-points of the randomized, prospective MM5 phase III trial of the German-Speaking Myeloma Multicenter Group (GMMG) were responses to VCD (bortezomib, cyclophosphamide, dexamethasone) compared to PAd (bortezomib, doxorubicin, dexamethasone) induction therapy with respect to high-quality remissions [very good partial response or better (≥VGPR)] and progression-free survival.[7] Based on the data published by Moreau *et al.*, the route of administration for bortezomib was changed from IV to SC in both trial arms after 314 of the planned 504 patients had been enrolled in the MM5 trial. By a protocol amendment the recruitment of 100 additional patients was decided to get comparable group sizes for IV and SC bortezomib administration. We were, therefore, able to perform the largest explorative analysis comparing toxicity and efficacy of IV and SC bortezomib in two different induction therapies for newly diagnosed MM.

Methods

Patients

Patients with newly diagnosed symptomatic MM according to CRAB criteria[8] were enrolled in the prospective, randomized, open-label GMMG MM5 phase III trial (EudraCT n. 2010-019173-16) in 31 transplantation centers and 75 associated trial sites throughout Germany. Patients with systemic AL-amyloidosis or peripheral neuropathy ≥ grade 2 (National Cancer Institute Common Terminology Criteria for Adverse Events, NCI CTCAE, version 4.0) were excluded (more detailed criteria are available at clinicaltrialsregister.eu). The ongoing study is being performed in accordance with the Declaration of Helsinki and the European Clinical Trial Directive (2005) and was approved by the local ethics committees of all participating institutions.

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Study design

The trial was designed to assess two primary objectives: (i) the non-inferiority of VCD to PAd induction therapy with respect to rates of VGPR or better; (ii) the best treatment strategy with regards to progression-free survival. Treatment was PAd or VCD induction therapy, high-dose melphalan followed by autologous stem cell transplantation as well as consolidation and maintenance therapies with lenalidomide for 2 years or until complete response (Figure 1). Recruitment of the final 604 patients was completed in November 2013.

Induction therapy

Patients' randomization was stratified by International Staging System (ISS) stage.[9] The patients were equally distributed in four treatment arms to receive three cycles of PAd (bortezomib 1.3 mg/m^2, days 1, 4, 8 and 11; doxorubicin 9 mg/m^2 IV, days 1-4; dexamethasone 20 mg/day, orally, days 1-4, 9-12 and 17-20, repeated every 28 days) or three cycles of VCD (bortezomib 1.3 mg/m^2, days 1, 4, 8 and 11; cyclophosphamide 900 mg/m^2 IV; day 1, dexamethasone 40 mg/day, orally, days 1-2, 4-5, 8-9 and 11-12, repeated every 21 days). After 314 patients had been enrolled, the route of administration of bortezomib was changed from IV to SC in February 2012.

Assessments

Adverse events were graded using the NCI CTCAE catalogue, version 4.0. All CTCAE grade ≥3 adverse events were recorded as were grade ≥2 infections, cardiac disorders, peripheral neuropathy and thromboembolic events. Response after three cycles was evaluated according to International Myeloma Working Group recommendations, which were modified to include near complete remission.[10] Interphase fluorescence *in situ* hybridization analysis was accomplished on CD138-purified plasma cells to identify cytogenetic abnormalities. As described previously, deletion 17p, t(4;14) and gain 1q21 >2 copies were defined as adverse cytogenetic abnormalities.[11]

Statistical analysis

Comparison of IV *versus* SC bortezomib in the PAd and VCD regimens was performed after 604 patients had finished induction therapy as of July 2014. An explorative analysis was based on the safety population, which comprises all patients who received at least one dose of trial medication. Adverse events associated with induction are defined as adverse events during induction cycles and within 30 days after the end of the last induction cycle and prior to the start of mobilization. Adverse events are summarized on a per patient basis with the highest CTC grade per site and patient reported. A Fisher exact test was used to compare frequencies of adverse events and response rates. All *P*-values were two-sided. *P*-values below 0.05 were considered statistically significant. Analyses were carried out with software R (R Foundation, Vienna, Austria).

Results

Patients

Out of 604 randomized patients, six patients did not receive the allocated trial medication and were excluded from the safety population. In total, 296 patients were treated with PAd and 302 patients with VCD. In both arms 51% of patients were treated with IV bortezomib (PAd n=150; VCD n=154) and 46-47% with SC bortezomib (PAd n=140; VCD n=140). Since route of administration was changed during ongoing induction therapy, 14 patients were excluded from the current analysis. The CONSORT diagram for the study is depicted in Figure 2. The patients' baseline characteristics are summarized in Table 1.

Trial medication

In the PAd group 92% of IV-treated and 97% of SC-treated patients completed the scheduled three cycles. In the VCD arm, 98% of both IV- and SC-treated patients completed three cycles. Proportions of patients receiving scheduled or delayed full dose trial medication and dose modifications for bortezomib are reported in *Online Supplementary Table S1*. Cumulative bortezomib doses were significantly higher for SC-treated patients in both

Table 1. Baseline patients' and disease characteristics.

	PAD n. (%)		VCD n. (%)	
	IV 150 (52)	SC 140 (48)	IV 154 (52)	SC 140 (48)
Age				
median (range)	59 (32 - 70)		58 (33 - 70)	
> 65 years	39 (26)	40 (29)	25 (16)	35 (25)
Sex (female)	68 (45)	59 (42)	64 (42)	55 (39)
Body mass index (> 30 kg/m^2)	24 (16)	29 (21)	31 (20)	22 (16)
Immunoglobulin				
IgG	88 (59)	85 (61)	88 (57)	97 (69)
IgA	32 (21)	30 (21)	34 (22)	22 (16)
Bence Jones	28 (19)	23 (16)	29 (19)	18 (13)
Other	2 (1)	2 (1)	3 (2)	3 (2)
Creatinine (> 2 mg/dL)	25 (17)	16 (11)	19 (12)	19 (14)
LDH (>ULN)	25 (17)	26 (19)	25 (16)	25 (18)
ISS stage III	41 (27)	37 (26)	42 (27)	37 (26)
t(4;14)	19 (13)	11 (8)	17 (11)	7 (5)
Del17	20 (13)	14 (10)	15 (10)	13 (9)
+1q21 > 2 copies	61 (41)	56 (40)	61 (40)	60 (43

PAD: bortezomib / doxorubicin / dexamethasone; VCD: bortezomib / cyclophosphamide / dexamethasone; IV: intravenous; SC: subcutaneous; LDH: lactate dehydrogenase; ULN: upper limit of normal; ISS: International Staging System; t: translocation; del: deletion.

arms (median doses PAd: IV 27.6 mg / SC 28.9 mg; VCD: IV 27.9 mg / SC 28.8 mg; *P*=0.04).

Safety and toxicity

Safety profiles of SC and IV bortezomib are shown in Table 2. Grade ≥2 and ≥3 adverse events were reported more frequently in patients treated with IV bortezomib than in those treated with SC bortezomib (grade ≥2: 65% *versus* 56%; grade ≥3: 55% *versus* 44%, respectively). In detail, IV-treated patients more often developed grade ≥2 peripheral neuropathy during the last cycle of induction therapy (8% *versus* 2%, *P*=0.001). There were no significant differences in reversibility of peripheral neuropathy between SC- and IV-treated patients, since 36% of patients in both groups showed no improvement of peripheral neuropathy (Table 2). Furthermore, IV-treated patients had significantly higher rates of gastrointestinal events (10% *versus* 4%; *P*=0.006) as well as metabolic and nutritional disorders (13% *versus* 5%; *P*=0.004). No significant differences were found for serious adverse events or deaths related to induction therapy (Table 2).

Response

There were no significant differences in overall response rates (defined as partial response or better) between IV- and SC-treated patients in the PAd (IV=73%; SC=71%) and VCD (IV=78%; SC=82%) groups (Table 3).

Analysis of high quality responses revealed that IV-treated patients in the VCD arm achieved higher rates of ≥VGPR than SC-treated patients (42% *versus* 29%, *P*=0.02). Differences in rates of ≥VGPR did not reach statistical significance in the PAd arm (IV: 37% *versus* SC: 31%, *P*=0.39). The difference was particularly pronounced in patients with adverse cytogenetic abnormalities (IV: 45% *versus* SC: 29%, *P*=0.05) (Table 3).

Subgroup analysis of patients with cytogenetic abnormalities, baseline creatinine values > 2mg/dL or ISS stage III did not reveal significant differences in overall response rates between patients treated with IV or SC bortezomib in the two arms (Table 3).

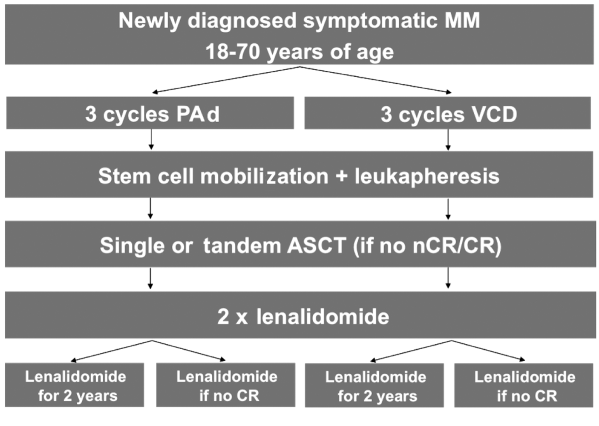

Figure 1. Flow chart of the GMMG MM5 study. Patients were randomized to four treatment arms with either PAd (2 arms) or VCD (2 arms) induction therapy and lenalidomide maintenance therapy either for 2 years or until complete remission was achieved. ASCT: autologous stem cell transplantation; CR: complete response; nCR: near complete remission.

Discussion

The present explorative analysis of the GMMG MM5 study is, to our knowledge, the largest comparison of IV and SC bortezomib from a prospective trial in newly diagnosed MM. We confirm data presented by Moreau *et al.* for relapsed disease.[3] We also observed reduced toxicity and non-inferiority in terms of overall response rate. The presence of ISS stage III disease, renal impairment or cyto-

Table 2. Summary of adverse events, serious adverse events and deaths.

Adverse event	IV n (%)	SC n (%)	*P*
Any ≥ grade 2	198 (65)	156 (56)	**0.02**
Infections and infestations	77 (25)	54 (19)	0.09
Cycle 1	41 (14)	28 (10)	n.s.
Cycle 2	27 (9)	22 (8)	
Cycle 3	13 (5)	13 (5)	
Blood and lymphatic system disorders	49 (16)	30 (11)	0.06
Cycle 1	36 (12)	20 (7)	n.s.
Cycle 2	17 (6)	13 (5)	
Cycle 3	11 (4)	10 (4)	
Hematotoxicity			
Anemia	22 (7)	12 (4)	n.s.
Leukopenia	72 (24)	57 (20)	
Thrombocytopenia	17 (6)	13 (5)	
Metabolic and nutritional disorders	38 (13)	15 (5)	**<0.01**
Cycle 1	24 (8)	11 (4)	n.s.
Cycle 2	11 (4)	4 (1)	
Cycle 3	10 (4)	5 (2)	
Gastrointestinal disorders	30 (10)	11 (4)	**<0.01**
Cycle 1	18 (6)	4 (1)	**<0.01**
Cycle 2	11 (4)	4 (1)	n.s.
Cycle 3	5 (2)	3 (1)	
Peripheral neuropathy	35 (12)	23 (8)	0.21
Cycle 1	5 (2)	7 (3)	n.s.
Cycle 2	7 (2)	10 (4)	
Cycle 3	23 (8)	5 (2)	**<0.01**
Grading of neuropathy			
grade 2	26 (9)	19 (7)	n.s.
grade 3	9 (3)	4 (1)	
grade 4	0 (0)	0 (0)	
Outcome of neuropathy per patient*			
not resolved	15 (36)	9 (36)	n.s.
improved	22 (52)	10 (40)	
other	5 (12)	6 (24)	
duration in days (median + range)	26 (7-243)	66 (20-229)	
Serious adverse event	**IV n (%)**	**SC n (%)**	***P***
Any	88 (29)	77 (28)	0.71
Infections and infestations	33 (11)	34 (12)	n.s.
Gastrointestinal disorders	18 (6)	8 (3)	
Musculoskeletal / connective tissue	9 (3)	7 (3)	
Renal and urinary disorders	8 (3)	5 (2)	
Cardiac disorders	5 (2)	6 (2)	
Deaths during induction therapy	4 (1)	3 (1)	

*Any adverse event affecting at least 10% of patients is shown, as is hematotoxicity. Adverse events CTCAE grade ≥3 were recorded as were grade ≥2 infections and peripheral neuropathy. With regards to serious adverse events, the five most reported are shown. IV: intravenous; SC, subcutaneous; n.s., not significant. *Evaluation of outcome was not summarized on a per patient basis in contrast to general adverse event assessment, i.e. patients who developed new symptoms after resolved neuropathy were recorded again. Statistically significant differences are shown in bold.*

genetic abnormalities at initial presentation did not have a negative impact on overall response rate in either SC- or IV-treated patients.

Early phase I trials of bortezomib in relapsed MM identified gastrointestinal as well as metabolic disorders (e.g. hypokalemia, hyponatremia) and peripheral neuropathy as dose-limiting toxicities.[12,13] In our current study we demonstrate that these adverse events can be reduced by SC administration of bortezomib, which is in line with data from Moreau *et al.*[3] (MMY-3021 trial). Although this trial is especially known for demonstrating a reduction of peripheral neuropathy with the use of SC bortezomib, the study also showed a reduction of gastrointestinal adverse events in accordance with our data.

Differences in peripheral neuropathy between SC- and IV-treated patients became evident in the last (third) cycle of induction therapy. An explanation for this finding is the cumulative dose-dependent occurrence of peripheral neuropathy in IV-treated patients.[14] In MMY-3021 the cumulative bortezomib dose was also linked to the incidence of peripheral neuropathy in SC-treated patients. However, for the same dose, peripheral neuropathy was less frequent with SC bortezomib than with IV bortezomib.[3] Because peripheral neuropathy leads to dose reductions, in our study and in MMY-3021 cumulative doses were higher in SC-treated patients than in IV-treated ones.[3] An explanation for reduced rates of peripheral neuropathy despite higher cumulative doses after SC administration is that maximum bortezomib plasma concentrations are lower than after IV bolus injections.[15,16] Since recent studies identified tumor and host factors associated with susceptibility for bortezomib-induced neuropathy,[17,18] the decisive factor remains uncertain. These studies underline that drug exposure alone does not determine the occurrence of bortezomib-induced peripheral neuropathy.

Thrombocytopenia is the most frequent dose-limiting hematologic toxicity of bortezomib.[13] Contrary to the MMY-3021 study that showed reduced thrombocytopenia in SC-treated patients,[3] no difference in grade ≥3 thrombocytopenia or any other hematologic toxicity was

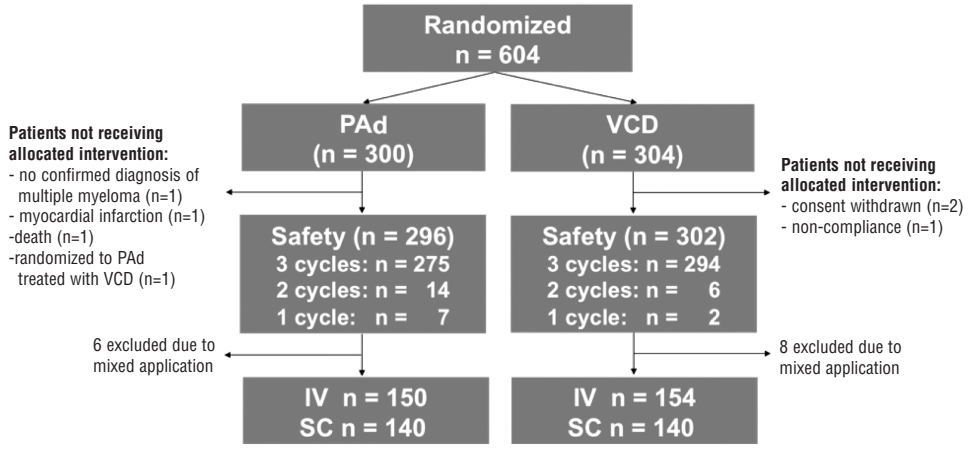

Figure 2. CONSORT diagram of the GMMG MM5 trial. Overall 604 patients were randomly assigned to four treatment arms with either PAd (2 arms) or VCD (2 arms) induction therapy. Analysis comparing IV with SC bortezomib in both arms was performed on the safety population which comprises all patients receiving at least one dose of allocated trial medication. Six PAd-treated and eight VCD-treated patients were excluded from the analysis since the treatment protocol was violated and route of administration was changed during ongoing induction therapy.

Table 3. Summary of treatment response after induction therapy.

	PAd n. (%)			VCD n. (%)		
All	IV	SC	*P*	IV	SC	*P*
≥ PR	109 (73)	99 (71)	0.79	120 (78)	115 (82)	0.39
≥ VGPR	55 (37)	44 (31)	0.39	64 (42)	40 (29)	**0.02**
nCR/CR	34 (23)	25 (18)	0.38	41 (27)	20 (14)	**0.01**
Baseline creatinine ≥ 2 mg/dL						
≥ PR	15 (60)	9 (56)	1.00	15 (79)	16 (84)	1.00
≥ VGPR	10 (40)	7 (44)	1.00	12 (63)	9 (47)	0.51
nCR/CR	4 (16)	3 (19)	1.00	9 (47)	2 (11)	**0.03**
ISS stage III						
≥ PR	25 (61)	23 (62)	1.00	28 (67)	30 (81)	0.20
≥ VGPR	15 (37)	13 (35)	1.00	17 (41)	15 (41)	1.00
nCR/CR	8 (20)	7 (19)	1.00	9 (21)	7 (19)	1.00
Adverse cytogenetic abnormalities						
≥ PR	52 (71)	42 (67)	0.58	54 (82)	56 (86)	0.63
≥ VGPR	33 (45)	18 (29)	**0.05**	29 (44)	19 (29)	0.10
nCR/CR	20 (27)	12 (19)	0.31	15 (23)	12 (19)	0.67

Overall response rates (partial response or better) as well as rates of ≥VGPR and (near) complete remission are shown for the whole study population. Subgroup analysis was performed for patients with renal impairment (baseline creatinine values ≥ 2 mg/dL), high tumor burden (ISS III) and adverse cytogenetic abnormalities. PAd: bortezomib / doxorubicin / dexamethasone; VCD: bortezomib / cyclophosphamide / dexamethasone; IV: intravenous; SC: subcutaneous; ≥PR: partial response or better; ≥VGPR: very good partial response or better; nCR: near complete remission; CR: complete remission; ISS: International Staging System.

observed in the current study. The comparison is hampered since patients in MM5 had no prior exposure to cytotoxic agents.

Our current study confirmed that overall response rates are not lower in patients treated with SC bortezomib than in those treated with IV bortezomib. The highest overall response rate among all analyzed subgroups was seen in patients treated with SC bortezomib and VCD. Furthermore, we showed for the first time that overall response rates in SC-treated patients are not influenced by the presence of adverse cytogenetic abnormalities, ISS stage III or renal impairment. In contrast to the results of MMY-3021 we observed lower rates of ≥VGPR in patients treated with SC bortezomib and VCD. This is also in contrast to findings of recent observational studies that incorporated SC bortezomib into VTD (bortezomib, thalidomide, dexamethasone) or VCD induction therapy.[5,6] In both non-comparative studies, which included small numbers of patients (n=31 and n=22),[5,6] rates of ≥VGPR exceeded 50% and were comparable to those of previously published trials of the VTD regimen with IV bortezomib.[19-21] In both studies and MMY-3021 response was assessed after four cycles, while in MM5 only three cycles of induction therapy were administered. Several phase II and phase III trials of bortezomib-based induction therapies reported higher rates of ≥VGPR after four to six cycles.[22] The reduced toxicity of SC bortezomib demonstrated in the current study enables prolonged pre-transplant treatment to achieve higher rates of ≥VGPR, which is an important predictor of survival after autologous stem cell transplantation.[23]

The issue concerning combination partners in bortezomib-based induction therapies also remains controversial.[1,22] The MM5 trial was the first phase III trial to show non-inferiority of two different bortezomib-based induction therapies with respect to rates of ≥VGPR.[7] Additionally, VCD was shown to have a better toxicity profile than PAd.[7] We, therefore, recommend VCD as induction therapy before autologous stem cell transplantation. Immunomodulatory drugs, such as thalidomide and lenalidomide,[24] are frequently used as combination partners in bortezomib-based induction therapies. Data on SC bortezomib incorporated into both regimens are limited and so far no phase III trial has addressed the comparison of conventional chemotherapy or an immunomodulatory drug as a combination partner for bortezomib. Data from the IFM 2013-04 trial (NCT trial n. 01971658) in newly diagnosed MM comparing VTD with VCD induction therapy will shed new light on this important issue. In both trial arms patients will receive SC bortezomib.

There are limitations to the present analysis, since the MM5 trial was not designed to prospectively evaluate toxicity and efficacy of IV and SC bortezomib in PAd or VCD. Furthermore, longer follow-up is needed to evaluate whether lower rates of ≥VGPR in SC-treated patients will lead to differences in progression-free and overall survival after autologous stem cell transplantation and lenalidomide consolidation / maintenance therapy.

In conclusion, compared to IV bortezomib, SC bortezomib in PAd and VCD induction therapy reduced toxicity and achieved similar overall response rates, regardless of whether adverse prognostic factors such as ISS stage III disease, renal impairment or cytogenetic abnormalities were present at initial diagnosis.

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Authorship and Disclosures

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