Peripheral neuropathy associated with subcutaneous or intravenous bortezomib in patients with newly diagnosed myeloma treated within the GMMG MM5 phase III trial

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Supplemental material

Supplemental methods

Patients and study design

The multicentre, prospective GMMG MM5 study design has previously been reported (Eudract No. 2010-019173-16). In brief, newly diagnosed MM patients were randomly assigned to receive either 3 cycles of VCD (bortezomib 1.3 mg/m^2, days 1, 4, 8, 11; cyclophosphamide 900 mg/m^2 IV; day 1, dexamethasone 40 mg/d, orally, days 1-2, 4-5, 8-9, 11-12) or PAd (bortezomib 1.3 mg/m^2, days 1, 4, 8, 11; doxorubicin 9 mg/m^{2}IV, days 1-4; dexamethasone 20 mg/d, orally, days 1-4, 9-12, 17-20) induction therapy. Induction therapy is followed by high-dose therapy and autologous stem cell transplantation as well as lenalidomide consolidation and maintenance therapy for 2 years or until complete response (CR). Initially, 504 patients were randomly assigned to VCD or PAd induction therapy. Based on the data in relapsed MM, the route of administration for bortezomib was changed from IV to SC in February 2012 after 314 patients were enrolled. An additional amendment was filed to enrol another 100 patients to achieve a comparable IV- and SC-treated sample size. Recruitment was completed in November 2013. The study is performed in accordance with the Declaration of Helsinki, the European Clinical Trial Directive (2005) and was approved by local ethics committees of participating sites.

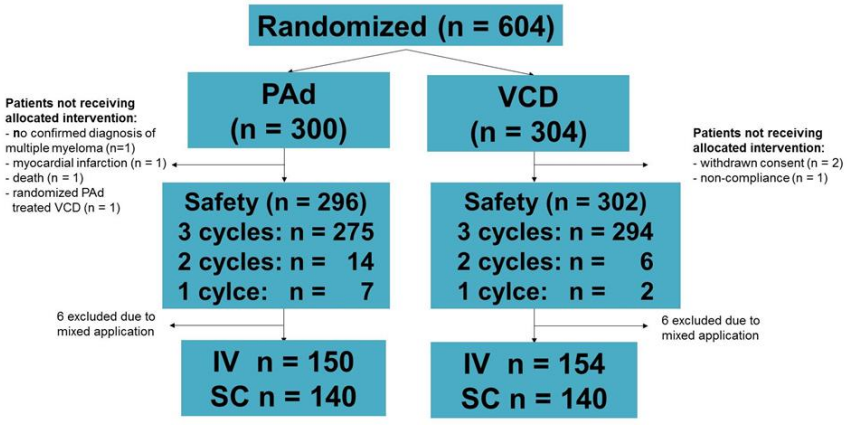
Assessments

Adverse events (AE) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. Peripheral neuropathy (PN) ≥ °II was recorded during and within 30 days after end of induction therapy on a per patient basis. The highest grade per organ class and patient is reported. Response assessment after induction therapy was performed according to International Myeloma Working Group (IMWG) recommendations. Patients achieving at least very good partial remission (VGPR) after 3 cycles induction therapy were considered as responders.

Statistical methods

The comparison of VCD and PAd with regard to remission is the first primary endpoint of the GMMG MM5 study and was already published after 504 patients finished 3 cycles[8]. The current explorative analysis was performed after the additional 100 patients finished induction therapy as of July 2014. Comparison of IV- and SC-treated patients was performed on the safety population, which consists of patients who received at least one dose of the trial medication (n=598). We further excluded 14 patients for this comparison, since the protocol was violated and administration of bortezomib was changed from IV to SC during ongoing induction therapy. Frequencies of AEs and response rates were compared with Fisher's exact test. Mann-Whitney Wilcoxon test was used to compare continuous parameters between groups. Multivariate logistic regression model was fitted to identify factors associated with occurrence of PN. The model accounted for route of administration (IV vs. SC), treatment arm (VCD vs. PAd) and prior PN (yes vs. no). All p-values were two-sided and values below 0.05 considered statistically significant. Analyses were carried out with software R (R Foundation, Vienna, Austria).

Consort diagram



Supplemental figure 1: Consort diagram. Safety = safety population consisting of patients receiving at least a single dose of trial medication

Dose reduction scheme for bortezomib

(Appendix VI from the GMMG MM5 trial protocol)

APPENDIX VI: Management of Patients with Bortezomib (Velcade®)-related Neuropathic Pain and/or Peripheral Sensory Neuropathy

			Peripheral sensory neuropathy				
			0	1	2	3	4
			normal	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling
Neuropathic pain	0	None	No action	No action	25% dose reduction	Hold, 50% dose reduction; schedule Δ required	Discontinue bortezomib
	1	Mild pain, not interfering with function	No action	No action	25% dose reduction	Hold, 50% dose reduction; schedule Δ required	Discontinue bortezomib
	2	Moderate pain; pain or analgetics interfering with function, but not daily activities	25% dose reduction	50% dose reduction	Hold; 50% dose reduction	Hold, 50% dose reduction; schedule Δ required	Discontinue bortezomib
	3	Severe pain; pain or analgetics severly interfering with daily activities	Hold, 50% dose reduction; schedule Δ required	Hold, 50% dose reduction; schedule Δ required	Hold, 50% dose reduction; schedule Δ required	Discontinue bortezomib	Discontinue bortezomib
	4	Disabling	Discontinue bortezomib	Discontinue bortezomib	Discontinue bortezomib	Discontinue bortezomib	Discontinue bortezomib