Peripheral neuropathy induced by subcutaneous bortezomib-based induction therapy for newly diagnosed multiple myeloma

Lok *et al.*[1] recently reported in this Journal on the efficacy and toxicity of subcutaneous (sc) bortezomib given at a reduced dose in combination with thalidomide and dexamethasone (sc vTD) as induction therapy before, and as consolidation after, autologous stem-cell transplantation (ASCT) in 31 patients with newly diagnosed multiple myeloma (MM). The treatment plan included four cycles of induction therapy and two cycles of consolidation, both comprising sc bortezomib (1.0 mg/m^2 twice weekly), thalidomide (100 mg per day) and dexamethasone (total dose 320 mg per cycle on the first two cycles and 160 mg per cycle on the subsequent two cycles of the induction phase). The rate of at least very good partial response (VGPR) after induction therapy was 52% for all patients and increased up to 73% among patients who actually received consolidation therapy. The incidence of treatment-emergent peripheral neuropathy (PN) after the induction phase (16% grade 1-2, including 3% grade 2) was lower than that previously reported by the same group after four cycles of either vTD at the same doses but using intravenous (iv) bortezomib (53% all grades, including 14% grade 2 or higher) or iv standard dose bortezomib (1.3 mg/m^2) and dexamethasone (VD) (70% all grades, 34% >grade 2, 11% grade 3-4).[2] We report, herein, on the outcomes of 22 newly diagnosed, ASCT-eligible, MM patients who were programmed to receive at our center four 21-day cycles of sc bortezomib (1.3 mg/m^2 twice weekly) plus dexamethasone (total dose 320 mg per cycle) and either thalidomide (100 mg per day) (sc VTD: 13 patients) or cyclophosphamide (500 mg/m^2 on Days 1 and 8 per cycle) (sc VCD: 9 patients). All patients were prospectively evaluated for efficacy and toxicity of sc bortezomib-based induction therapy. Presence of higher than grade 1 PN at diagnosis was an exclusion criterion for enrollment. Symptoms and signs of PN were carefully assessed at every programmed clinical appointment and were graded according to National Cancer Institute's Common Toxicity Criteria (NCI CTCAE) v.3.0. No electrophysiological study was performed. Base-line patients' characteristics and treatment response are summarized in Tables 1 and 2. A median of four cycles was administered. The overall response rate among all patients was 95%, including 27% stringent complete response (sCR) and 77% VGPR or better. Treatment-emergent grade 1-3 PN was observed in 14 patients (64%), including 18% (4 patients: 2 treated with VCD and 2 with VTD) grade 2 and 14% (3 patients: 2 receiving VTD and one VCD) grade 3. In one of these 3 patients, treatment was discontinued after the third cycle. Among the 7 patients with grade 2-3 PN, the median time from start of induction therapy to the first onset of PN was 72 days (range 48-109). In 3 patients, symptoms and signs of PN (grade 2 in 2 cases and grade 3 in the remaining one) emerged after the induction phase was completed, more specifically 103, 106 and 109 days after starting induction therapy. With appropriate treatment modifications,[3,4] symptoms and signs of PN resolved or improved to grade 1 in 9 out of 14 (64%) patients within a median time of 94 days.

Data reported here raise several considerations, but should be interpreted with caution due to the limited number of patients. The high overall response rate of 95%, including 27% sCR and 77% VGPR or better, further supports the conclusion that the efficacy of sc bortezomib reported in the relapsed/refractory setting[5] is retained when the drug is administered in patients with newly diagnosed MM.[1] Although cross-trial comparison is inadequate due to heterogeneities in the design of the studies and patients' characteristics, it is likely that the discrepancy in the rates of high-quality responses between our series and that reported by Lok *et al.*[1] reflects the lower activity of reduced-dose bortezomib used in the French study, with the possible contribution of the lower total dose of dexamethasone given in the third and fourth cycles of the induction phase. Differences between the two studies with respect to the doses of sc bortezomib incorporated into induction therapy may only explain in part the controversies about the frequency and severity of treatment-induced PN. Additional factors potentially compromising a meaningful interpretation of our data, as well as of those reported by others,[1,6,7] include: i) the retrospective nature of several analyses which were performed either on patients who, due to their age, were eligible or ineligible to receive ASCT or on patients who had plasma cell dyscrasias other than MM, such as systemic amyloidosis;[6,7] ii) the possible different methodological approaches used to assess PN. In our study, clinical evaluation of PN was performed at baseline, at the beginning of each cycle of induction therapy, before each dose of bortezomib, and every 21-28 days after the last dose of bortezomib was given. Neurological monitoring was continued until ASCT was received and allowed us to register 3 patients who suffered from late emergence of neurological toxicity, after induction therapy was completed. Although worsening of taxane-induced neurotoxicity was observed even after treatment was stopped,[8] to the best of our knowledge, a similar phenomenon has not been reported for bortezomib. As far as this last issue is concerned, it is important to highlight that all the patients described here had a late emergence of previously unde-

Table 1. Base-line patients' characteristics.

	Number of patients
Sex	
Male	16
Female	6
Median age (range) (years)	59 (30-68)
M protein isotype	
IgG	11
IgA	6
BJ	3
Other	2
ISS stage	
1	9
2	7
3	6
High-risk cytogenetic abnormalities by FISH*	
amp(1q)	5
t(4;14) and amp(1q)	1
del(17p)	1
del(17p) and amp(1q)	1

**Performed in CD138+ bone marrow plasma cells. BJ: Bence Jones; ISS: international staging system; FISH: fluorescence in situ hybridization; amp(1q): amplification of the long arm of chromosome 1; t(4;14): translocation 4;14; del(17p): deletion of the short arm of chromosome 17.*

Table 2. Efficacy and neurological toxicity of sc VTD or VCD induction therapy.

	Number (%) of patients in the overall population	Number of patients treated with sc VTD/VCD
Response		
sCR	6 (27%)	4/2
VGPR	11 (50%)	7/4
PR	4 (18%)	1/3
PD	1 (5%)	1/0
ORR	21 (95%)	12/9
Peripheral neuropathy		
Grade 1	7 (32%)	4/3
Grade 2	4 (18%)	2/2
Grade 3	3 (14%)	2/1

sc: subcutaneous; VTD: bortezomib, thalidomide, dexamethasone; VCD: bortezomib, cyclophosphamide, dexamethasone; sCR: stringent complete response; VGPR: very good partial response; PR: partial response; PD: progressive disease; ORR: overall response rate.

tected, typical bortezomib-induced PN (BiPN) and that in each of them any additional cause potentially contributing to the development of neurotoxicity was excluded. With the limits of the small sample size of patients analyzed, the 32% rate of grade 2 or higher PN is very similar to values previously reported after four cycles of iv VD or VTD incorporating standard-dose bortezomib.[2,9,10] Knowledge of the mechanisms underlying BiPN has remained limited for many years.[11] Recently, new insights into a better understanding of the pathogenesis of BiPN have been provided by analyses of gene expression profiles and single nucleotide polymorphisms of MM plasma cells.[12-14] Results of these studies, performed in patients treated in Western countries but whose ethnicity was not detailed, showed that differently expressed genes involved in drug-induced apoptosis, DNA repair, inflammatory pathways, and development and function of nervous system are related to a different risk for, and time to onset of, BiPN. In addition, the patient's inherited genetic background might also contribute to the individual risk for neurological toxicity.[12,13] The possibility that patient- and disease-related genetic profiles might have been differently expressed in our series of patients compared to those reported by Lok *et al.*,[1] thus partly contributing to the controversies observed in terms of frequency, severity and time to onset of PN, cannot be confirmed or ruled out. In conclusion, our data support the efficacy of sc bortezomib when incorporated into induction therapy for newly diagnosed, ASCT-eligible, MM patients. On the other hand, no conclusions about the different rate and severity of sc *versus* iv BiPN can be drawn. The possibility of late emergence of PN, even after an uneventful induction phase, should be taken into consideration and alert the physician to the need to continue close neurological monitoring after sc bortezomib-based induction therapy has been discontinued. Results of ongoing studies that aim to prospectively evaluate the efficacy and toxicity of sc bortezomib as part of first-line therapy will hopefully clarify the controversies discussed here.

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