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Bortezomib in newly diagnosed multiple myeloma patients

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High-dose therapy represents today the standard of care for younger multiple myeloma (MM) patients candidates to transplant. The induction phase is performed usually with VAD or VAD-like schemes which, however, produce a complete remission rate (CR) in less than 10%. Bortezomib (Velcade®) has demonstrated to be very effective in relapsed/refractory myeloma patients giving as single agent a CR rate of 16%, and several evidences indicate that bortezomib shows a synergistic activity with dexamethasone or other cytotoxic agents. Thus, taking into account that the achievement of a CR is the main objective in the treatment of MM, it is reasonable to introduce Bortezomib (Velcade®) as part of front-line high-dose programs. The application of bortezomib to novel front-line therapies depends in part on its effects on subsequent stem cell mobilization and engraftment. Preliminary reports indicate that Bortezomib (Velcade®) is not significantly toxic to hematopoietic stem cells and that successful mobilization can be performed following its administration.

All these findings raise the suggestion that Bortezomib (Velcade®) may offer a valid alternative as initial remission induction therapy.

Velcade monotherapy

Richardson and colleagues[1] sought to investigate whether the efficacy of Bortezomib (Velcade®) would be further improved if it was used as front-line therapy. The objective of this multicenter phase 2 trial was to evaluate the activity and safety of Bortezomib (Velcade®) as monotherapy in previously untreated MM patients. The study aimed also to prospectively evaluate the entity and the frequency of peripheral neuropathy (PN) at baseline (BL) and across treatment.

Bortezomib (Velcade®) was administered at the standard dose and schedule: 1.3 mg/m^2 on d 1, 4, 8, 11 of a 21-d cycle. Patients with symptomatic measurable myeloma e no previously treated were eligible for the trial. No concomitant steroids (> 10 mg/d), platelet count <30x10^9/L within 14 d of enrollment or > grade (G) 2 PN were admitted. Neurologic evaluation involving a questionnaire and neurologist's exam was performed before and after treatment. A 33 pt subset had BL nerve conduction studies (NCS), quantitative sensory testing (QST), autonomic testing, and skin biopsy for quantitation of small-diameter neurite densities.

Sixty-three patients with a median age of 60 yrs were enrolled, and 46 were evaluable for response. A complete response was achieved in 5 (11%) patients, a partial response in 9 (20%) and a minimal response in 13% (28%), giving a CR+PR rate of 30%, and a CR+PR+MR rate of 59%. The most common adverse events were peripheral neuropathy, fatigue, rash, nausea, constipation and *varicella zoster* virus. Baseline PN was observed In a large proportion of patients, 46% by clinical examination and 75% by neurophysiological testing. In particular, BL small-fiber neuropathy was seen in 16/33 pts (48%), BL skin biopsy showed that 18/30 pts (60%) had small-fiber neurite densities, and nerve conduction studies revealed BL axonal PN in 3/33 (9%) patients. Of 16 pts with BL small fiber neuropathy, 7 had a worsening (by QST). Velcade was otherwise generally well tolerated. Treatment related PN was reported in 36 patients (55%) and was predominantly mild to moderate in severity. Of note, the neuropathy was both manageable and reversible when recommended dose schedule was followed. In conclusion, Velcade in monotherapy has shown activity in newly diagnosed MM patients with a CR of 11% and manageable toxicity. The study also provides evidence that peripheral neuropathy in under-recognized in newly diagnosed myeloma patients.

Velcade monotherapy ± dexamethasone

Front-line Bortezomib (Velcade®) was also investigated by Jagannath and co-workers.[2] Bortezomib (Velcade®) was administered using the same schedule of Richardson for a maximum of 6 cycles, but oral dexamethasone was added in patients who achieved less than a PR after 2 cycles or less than a CR after 4 cycles.

In Table 1 are reported the clinical characteristics and the response of 50 patients included in this study. Of 40 patients evaluable for response, the overall response rate (CR+nCR+PR) was 85%. Response to Bortezomib (Velcade®) was rapid with 41% achieving their best response after 2 cycles, 75% after 4 cycles and 85% after 6 cycles. Dexamethasone was added for 28 (70%) patients, resulting in an improved response in 18 (64%) of these.

Twelve patients went on to receive a stem cell transplant, and all had complete hematological recovery. Thirteen patients discontinued from the study: 9 for severe adverse events, 2 for progressive disease, and 2 withdrew. The most common toxicities were neuropathy (26%), fatigue (22%), constipation (17%), and neutropenia (14%).

Table 1. Characteristics and response of patients treated with Bortezomib alone ± Dex.

Patients enrolled/evaluable	50/40
Median age	58 yrs
Male/Female	26/24
Stage II/III, %	29/43
IgG/IgA, %	64/19
Response rate	
CR+nCR+PR, No (%)	34 (85)
Best response, %	
After cycle 2	41
After cycle 4	75
After cycle 6	85
No patients treated with Bort+Dex (%)	28 (70)
Improved response with Dex, No (%)	18/28 (64)
from MR to PR	11/18 (62)
from SD to CR	5 (28)
from SD to PR	1 (5)
from SD to MR	1 (5)

Velcade combinations

As with relapsed/refractory multiple myeloma, there is a large amount of interest in investigating the optimal front-line combination. Mateos and co-workers[3] performed a study in newly diagnosed myeloma patients aged ≥ 65 years to determine the appropriate dose of Bortezomib (Velcade®) used in combination with Melphalan (V-MP) and to evaluate the toxicity and the efficacy of this combination.

V-MP consisting of four 6-week cycles, followed by five 5-week cycles had the following schedule: Bortezomib (Velcade®) was administered at two sequential doses (1.0 and 1.3 mg/m^2) on days 1,4,8,11,22,25,29,32 in combination with Melphalan 9 mg/m^2 and prednisone 60 mg/m^2 once daily on days 1-4. When maximum tolerated dose (MTD) was defined (after two groups of 6 patients), the cohort of patients at the MTD was expanded up to 60 patients. No dose-limiting toxicity was registered during the phase I of the study, so the established dose of Bortezomib (Velcade®) was 1.3 mg/m^2. Results of this trial are reported in Table 2. As shown response rate on 53 evaluable patients (CR+nCR+PR) was 85% after a median of 3 cycles. Due to the grade 3-4 adverse events (table 2) the dose was modified in 6 patients for Bortezomib (Velcade®) and 2 for Melphalan, and 8 patients discontinued from the study for toxicity.

Table 2. Results of V-MP study in elderly untreated patients.

Patients enrolled/evaluable	60/53
Median age	74 yrs
Median no. for cycles (range)	3 (1-9)
Response rate	
CR+nCR+PR, No (%)	34 (85)
Analysis of response by cycle, %	
After cycle 1	72
After cycle 3	85
Toxicity grade 3/4, %	
Nausea	2
Vomiting	2
Diarrhoea	15
Constipation	8
Anemia	12
Neutropenia	39
Thrombocytopenia	46
Infection	14
Peripheral neuropathy	15

So V-MP seems to be very effective and safe in elderly untreated patients with an unprecedented 28% of complete remissions and a manageable toxicity. An international phase 3 randomized trial (VISTA) is in progress to evaluate if this combination could replace MP as a standard of care for elderly MM patients.

Table 3 presents some other ongoing studies adopting Bortezomib (Velcade®) in combination with other drugs as front-line therapy. As shown these regimens produce significant response rates ranging from 80 to 90% with impressive percentages of very good quality of response (CR+nCR) reaching nearly 50% in patients after stem cell transplant.

Table 3. Ongoing studies on Velcade in untreated patients.

Author	*Regimen*	*Pts*	*CR+PR %*	*CR + nCR %*	*Comments*
Popat *et al.*[4]	Bortezomib (1.0 mg/m^2) + ADM + Dex → SCT	19	89 (100 after SCT)	39 (46 CR after SCT)	Effective, well tolerated, stem cell mobilization not affected
Wang *et al.*[5]	Bortezomib + Thal+ Dex → SCT	36	92	18	Effective and safe, no more than 2 cycle seem to be necessary before intensification
Uy *et al.*[6]	ADM/Thal + Bortezomib → SCT	38	88	40	Stem cell collection successful in 97% of pts
Harousseau *et al.*[7]	Bortezomib + Dex → SCT	36	80	31	90% response rate after SCT

Conclusions

The trials reported in this review are a further demonstration of the efficacy of Bortezomib (Velcade®) in multiple myeloma patients. Actually, Bortezomib (Velcade®) even as front-line therapy alone or in combination with other agents produces high response rates with very high CR and near CR rates with a manageable toxicity.

Velcade together with other novel agents represent today new opportunities for patients affected by multiple myeloma. The task of hematologists will be to define the best way to combine these new drugs with those already in use in order to establish when, how, in which subset of patients, and in which phase of the disease is more appropriate to adopt one or another agent. The other point is also if is still valid the concept "the more is better" from the onset of the disease or if could be better to use the available tools in sequence.

References

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