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## Bortezomib-combination based therapy in relapsed-refractory myeloma patients

The encouraging results obtained by Bortezomib (Velcade®) as single agent in relapsed-resistant multiple myeloma (MM) patients has brought to test effective combinations with conventional myeloma agents in order to improve the response and the survival of this difficult setting of patients.

The main action of Bortezomib (Velcade®) is the inhibition of the transcription factor NF- $\kappa$ B, down regulating the expression of several apoptosis inhibitors, and inducing apoptosis of drug resistant multiple myeloma cell lines. Moreover, the inhibition of NF- $\kappa$ B determines a down regulated transcription of several effectors of the protective cellular response to genotoxic stress, like topoisomerase II beta. As a consequence, Bortezomib (Velcade®) sensitizes myeloma cells to chemotherapy and overcomes resistance to genotoxic agents. These results have been confirmed by oligonucleotide gene microarray and proteomic analysis which show that Bortezomib (Velcade®) induces changes in transcripts involved in the regulation of apoptosis. Activity towards multiple myeloma cells selected for resistance to doxorubicin or melphalan or mitoxantrone has been demonstrated.<sup>1,2</sup> Other preclinical studies support the use of Velcade in addition with other active drugs, as dexamethasone or immunomodulatory derivatives (IMiDs) of thalidomide.<sup>3</sup>

### Clinical studies

#### ***Bortezomib (Velcade®) and pegylated liposomal doxorubicin***

On the basis of *in vitro* synergistic proapoptotic effects of Bortezomib (Velcade®) and anthracycline agents, Orlowski and coworkers treated 24 patients, relapsed or refractory to at least one prior line of therapy, with Bortezomib (Velcade®) and pegylated liposomal doxorubicin. The reported response rate in 22 evaluable patients was high with CR+nCR of 36.4% (8 patients), PR

of 36.4% (8 patients). Interestingly, a CR was achieved in 5 patients (22.7%) who previously received anthracycline-based regimens. Grade 3 or 4 toxicity was limited (10%) and the recommended dose was 1.3 mg/m<sup>2</sup> for Bortezomib (Velcade®) and 30 mg/m<sup>2</sup> for pegylated liposomal doxorubicin.<sup>4</sup>

#### ***Bortezomib (Velcade®) and thalidomide ± dexamethasone***

Zangari and colleagues at the last ASH meeting reported the updated results of a study on 85 MM patients treated with incremental dosing scheme of a combination Bortezomib (Velcade®) + Thalidomide.<sup>5</sup> Bortezomib (Velcade®) was given at a starting dose of 1.0 mg/m<sup>2</sup> (group A) on days 1, 4, 8, 11 every 21 days and Thalidomide was added in the second cycle at escalating doses of 50, 100, 150 and 200 mg daily. The dose of Bortezomib (Velcade®) was increased to 1.3 mg/m<sup>2</sup> in the absence of grade >2 neuropathy with Bortezomib (Velcade®) 1.0 mg/m<sup>2</sup> and Thalidomide 200 mg (group B). Dexamethasone 20 mg (1, 2, 4, 5, 8, 9, 11, 12 days) was added if at least a PR was not achieved at cycle 4. The overall response rate was 70% with a 16% of CR+nCR and median EFS/OS of 9/22 months: EFS was significantly lower in patients with prior thalidomide history (73% of patients) and OS was shorter in the presence of abnormal cytogenetics. The most common 3 or 4 grade toxicity was myelosuppression, whereas peripheral neuropathy, present in 41% of patients at study entry, only slightly worsened during treatment, with no thalidomide dose effect. The absence of uniformity of prognostic factors between the two groups precludes a definition of the recommended dose.

#### ***Summing up***

This drug combination have shown remarkable activity in refractory/relapsed myeloma with acceptable toxicity even if a longer follow up is needed to confirm the results. The definition of the optimal dose of

**Table 1. Clinical trials on Bortezomib (Velcade®)-based combinations in relapsed-refractory myeloma patients: preliminary data presented at ASH meeting 2005.**

Author	Regimen	Patients	EFS	PR %	CR + nearCR %	Comments
Zangari <i>et al.</i> <sup>5</sup>	VTD (Velcade + Thalidomide ± Dex)	85	9 months	39	16	Better survival if normal cytogenetics and no prior Thal
Richardson <i>et al.</i> <sup>10</sup>	Velcade + Lenalidomide	19	-	47	12	MTD: Velcade 1.3 mg/m <sup>2</sup> ; Lenalidomide 25 mg/d
Kropff <i>et al.</i> <sup>6</sup>	Velcade + LD-EDX + HD-Dex	50	Not reached after 10 months	66	10	High OR. Infections in 39%
Palumbo <i>et al.</i> <sup>8</sup>	VMPT (Velcade + Melphalan + Prednison + Thalidomide)	20	-	35	15	Grade 3 neutropenia and thrombocytopenia in 40%
Popat <i>et al.</i> <sup>9</sup>	Velcade + LD i.v. Melphalan ± Dex	18	-	33	5	Better OR with Dex (75% versus 50%); high SAEs or discontinuation rate
Terpos <i>et al.</i> <sup>7</sup>	VMDT (Velcade + LD Melphalan + Thalidomide + Dex)	31	9.6 months (PFS)	48	8	Effective and safe in heavily pre-treated patients
Berenson <i>et al.</i> <sup>11</sup>	Velcade + ATO + Ascorbic Acid	22	-	9	-	Low efficacy and feasibility. OR: 27%; SAE: 23%

Legend: LD-EDX: Low dose-Endoxan; HD-Dex: High dose Dexamethasone; LD i.v. Melphalan: Low dose intravenous Melphalan; OR: Overall Response; SAE: Serious Adverse Events; PFS: Progression Free Survival; MTD: Maximum Tolerated Dose.

Bortezomib (Velcade®) is crucial because of the association of two neurotoxic agents; therefore it could be evaluated in future trials.

### **Bortezomib (Velcade®), dexamethasone and cyclophosphamide**

Kropff and colleagues reported the results of a German multicenter study on 50 patients treated with Bortezomib (Velcade®) 1.3 mg/m<sup>2</sup> on days 1, 4, 8, 11 every 21 days for 8 cycles, Dexamethasone 20 mg (1, 2, 4, 5, 8, 9, 11, 12 days) and continuous Cyclophosphamide 50 mg orally.<sup>6</sup> The response rate was very high (88%) with 10% of CR. On an intention to treat basis, after a median follow up of 10 months, EFS was 10 months and OS was still not reached. The presence of chromosome 13 deletion was surprisingly associated with high response rate and better EFS. Grade 3-4 hematological toxicity was demonstrated in less than 20% of patients, whereas grade 3-4 non hematological toxicity consisted in neuropathy (25%), cardiovascular events (11%), fatigue (15%) and infectious complications in 39% of patients including 13% of *Herpes Zoster*.

### **Summing up**

The response and survival data are very promising.

Whereas the hematological toxicity is limited, the incidence of infections is high; the hospitalisation need is not reported. A prophylactic antiviral therapy could be considered.

### **Bortezomib (Velcade®) and melphalan**

At the last ASH meeting, three studies have been presented on Bortezomib (Velcade®) based combinations including melphalan.

Terpos reported the preliminary results of an ongoing study on VMDT association:<sup>7</sup> Bortezomib (Velcade®) (1 mg/m<sup>2</sup> days 1, 4, 8, 11), oral Melphalan (0.15 mg/kg days 1-4), Thalidomide (100 mg days 1-4, 17-20 in 28 days cycles) and Dexamethasone (12 mg/m<sup>2</sup> days 1-4, 17-20 in 28 days cycles). The aims were to evaluate safety, efficacy and angiogenesis and bone remodeling modifications. Besides the high response rate (OR 76%), a prevalence of non-hematological toxicity was demonstrated with 48% of grade 1-2 neuropathy and 36% of infections. Of note, no 3-4 grade neuropathy was observed probably due to the intermittent administration of thalidomide. After 4 cycles of VMDT and bisphosphonates biochemical markers of bone resorption were significantly reduced.

Palumbo and co-workers<sup>8</sup> reported the initial data on 20 patients treated with Bortezomib (Velcade®) at

three sequential dose levels (1.0, 1.3, 1.6 mg/m<sup>2</sup> on days 1, 4, 15, 22 followed by 13 days of rest), Melphalan 6 mg/m<sup>2</sup> (days 1–5), Prednisone 60 mg/m<sup>2</sup> (days 1–5) and Thalidomide 100 mg/day (V-MPT). The overall response was 80% with grade 3 hematological toxicity demonstrated in 8 patients (40%).

Efficacy and safety of the combination of Bortezomib (Velcade®) (1.3 mg/m<sup>2</sup> days 1, 4, 8, 11) with low-dose intravenous Melphalan (10 mg/m<sup>2</sup> on day 2) and Dexamethasone added in stable/progressive disease after 4/2 cycles, was evaluated by Popat group in 18 patients.<sup>9</sup> The dose of melphalan was decreased to 2.5 mg/m<sup>2</sup> because of high incidence of thrombocytopenia shown by the first 10 patients enrolled and then escalated to 7.5 mg/m<sup>2</sup>. The response rate is promising (75%) even though the toxicity is high (mainly 3–4 grade hematologic complications). The median follow-up (3 months) is too short for definitive conclusions.

In Table 1 are reported the most significant trials on Bortezomib (Velcade®) combinations treatments with the principal clinical data reported at the last ASH meeting in December 2005.

## Conclusions

The preliminary data on Bortezomib (Velcade®) combinations demonstrating an effective antineoplastic activity in high risk MM patients, confirm *in vivo* the possibility to overcome the acquired drug resistance.

More studies, however, are needed to better define the optimal dose and the schedule of the drugs given in combination to minimize toxicity in this setting of patients intrinsically prone to hematologic and non hematologic complications.

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