Perspective on the current use of bortezomib in multiple myeloma

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Multiple myeloma (MM) remains an incurable disease; therefore new treatment approaches are needed in order to improve the outcome of patients with this disease.[1] We have recently learned that the ubiquitin-proteasome pathway represents an attractive therapeutic target in cancer. Proteasomes are a large complex of proteolytic enzymes responsible for the intracellular degradation of ubiquitinated proteins, including proteins that govern important cellular functions such as cell cycling, cell growth and cell differentiation.[2,3]

Bortezomib (Velcade®, formerly PS-341) is a novel dipeptide boronic acid which induces reversible inhibition of the 26S proteasome. In addition to its antiproliferative and pro-apoptotic effects (via NF-κB blockage) it downregulates the expression of adhesion molecules, inhibits angiogenesis, inhibits effectors involved in DNA repair, and blocks the unfolded protein response, resulting in accumulation of improperly folded proteins and subsequent endoplasmic reticulum stress and cell death.[2,3] Although other proteasome inhibitors, including oral formulations,[4] are under investigation, bortezomib is the only one that has been introduced into clinical practice.

Based on preclinical studies and a promising phase 1 trial, two pivotal phase 2 studies, SUMMIT[5] and CREST,[6] were developed in relapsed/refractory MM patients. Patients were treated with bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11 every 3 weeks; Dexamethasone was allowed in patients with suboptimal responses to bortezomib alone. The overall response rate was 35%, including 10% complete or near complete responses with an overall survival of 17 months. The randomized CREST study,[6] comparing two dosages of bortezomib (1.3 vs 1.0 mg/m^2) showed that a reduced dose was able to produce responses in up to one third of the patients with a trend towards a lower toxicity. This is important for the patients who do not tolerate the full doses of bortezomib since they have still a chance to respond to the dose level of 1 mg/m^2. In this issue of Hematologica/The Hematology Journal, Jagannath *et al.* report[7] on the improvement of response by adding dexamethasone in patients who showed suboptimal response to bortezomib. The addition of dexamethasone resulted in an improvement in the response degree in 18% and 33% of patients with suboptimal response included in the SUMMIT and CREST trials, respectively. A subsequent randomized phase 3 trial (APEX)[8] including 669 patients with relapsed MM has shown that bortezomib is more effective than high-dose dexamethasone as demonstrated by a significant improvement in response rate (43% vs 18%), median time to progression (6.2 vs 3.4 months) and 1-year survival rate (80% vs 67%, respectively) (updated at ASH 2005).[9] Concerning the characteristics of response to bortezomib it is important to note that the response is usually very quick (1 or 2 cycles), independently of previous therapy and that this agent is highly effective on extremedullary plasmacytomas.[10] Although these results are encouraging, a substantial proportion of patients do not respond to bortezomib, and acquired resistance has already been observed. These facts together with the well documented *in vitro* synergy of bortezomib with other agents, clearly justify combination therapy. Two pilot studies have shown that bortezomib in combination with melphalan[11] or pegylated liposomal doxorubicin[12] or cyclophosphamide plus dexamethasone[13] produces a response rate of 50% to 76% in refractory MM, including a substantial number of complete responses (6 to 30%). Bortezomib has also been combined with thalidomide. In a series of 56 refractory MM patients these two drugs yielded an overall response of 70%, with 22% complete or near complete responses, without increased toxicity regarding neuropathy and myelosuppression.[14] A combination of thalidomide and bortezomib with adriamycin and dexamethasone is also being explored; the complete+partial response rate is about 55% and toxicities are manageable.[15] These responses rates are clearly superior to those obtained with bortezomib alone, and confirm the synergistic effect found in *in vitro* studies. The next obvious step was to explore the efficacy of bortezomib in previously untreated MM patients. At the ASH 2005 meeting several pilot studies on this setting were presented. The results with bortezomib as a single agent were rather discrepant, since while Richardson *et al.*[16] reported a response rate of 30%, with 11% complete remission (a figure which is similar to that previously reported in refractory patients), Dispenzieri *et al.*,[17] using the same dose and schedule observed a higher response rate (73% partial responses). These differences may be due to the number of cycles administered (median 2 vs 5, respectively). The addition of dexamethasone was associated with a higher overall response rate (≥ partial response 80-90%, with 18% complete or near complete responses).[18,19] Similar results were obtained with the PAD regimen[20] (bortezomib, adriamycin, and dexamethasone) (89% response rate, with 16% complete or near complete responses) and the VTD scheme[21] (bortezomib, thalidomide and dexamethasone) (92% response rate with 19% complete responses). These results show that the vast majority of newly diagnosed MM patients will respond to bortezomib-based regimens and around one in five will achieve complete remission, resulting in a picture similar to that observed after autologous stem cell transplantation. One important issue in these studies was to evaluate the influence of bortezomib on stem cell collection. All these studies, showed that stem cell mobilization was unaffected with adequate hematologic recovery.[18-21] Moreover, the use of high dose melphalan after these bortezomib-based induction regimens was associated with an up-grade in the complete response rate. Thus, in the PAD[20] study the 16% complete or near complete

responses prior to transplantation increased to 54% after Mel200; in the DT-PACE[22] study the percentage of complete responses increased from 16% to 58%, and in the VTD[21] from 19% to 31%. These data strongly support the complementary value of this sequential strategy (i.e., novel drugs combinations upfront, followed by autologous stem cell transplantation).

Nevertheless, it is important to bear in mind that half of all MM patients are 65 years old or more and therefore are not candidates for high dose therapy. We have explored the efficacy of adding bortezomib to the conventional melphalan-prednisone scheme in elderly untreated MM patients. After a median of five cycles the response rate was 86% with 30% complete responses by immunofixation plus 13% near complete responses.[23] Interestingly, responses were not influenced by the presence of cytogenetic abnormalities. These data together with the results reported by Italian[24] and French[25] groups with melphalan, prednisone and thalidomide suggest that new gold standards may become available for elderly MM patients. An important aspect of all these studies is the toxicity profile of bortezomib, particularly when used in combinations with other agents. The most common side effects of bortezomib, used alone in refractory patients, were gastrointestinal symptoms, fatigue, and anorexia, although these were mostly grade 1-2.[26] Thrombocytopenia grade 3-4, due to a reversible blockage in platelet release, was found in 30% of cases, while anemia and neutropenia are uncommon (<10%).[5-8,26] The most troublesome side effect is painful/sensory peripheral neuropathy (37%, with only 9% grade 3), although this resolved or improved in two-thirds of patients after completion or discontinuation of therapy.[5-8,26,27] Clinicians should be aware that an early reduction of the dose as soon as peripheral neuropathy emerges, according to well established guidelines, helps to avoid more severe symptoms and the need for interruption of treatment. However, clinicians should also be aware that exceptional cases of life-threatening motor neuropathy, such as the two cases reported in a recent issue of this journal,[28] may occurr in association with bortezomib therapy. Unusual toxicities such as tumor lysis syndrome, severe pulmonary failure, toxic hepatitis or rhabdomyolysis have also been reported.[29-31] So far the reported side effects with the combination therapies in newly diagnosed patients are similar to those previously reported in refractory treated patients. Therefore, overall, the toxicity profile of bortezomib is now well defined and most complications are predictable and manageable.

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