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Bortezomib therapy for refractory/relapsed multiple myeloma

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The proteasome is a multienzyme complex found in all eukaryotic cells that functions to degrade most short-lived and long-lived intracellular proteins after their conjugation to ubiquitin. Many of these proteins are involved in cell cycle regulation, and their timely degradation after polyubiquitination is essential for normal cell cycling, function and survival. Inhibition of proteasome activity results in accumulation of these proteins within the cells, with subsequent cell-cycle arrest, apoptosis and downregulation of angiogenesis.

Bortezomib (VELCADE) is a dipeptide boronic acid derivative which reversibly inhibits proteasome function by targeting the chymotryptic-like site of the core 20S catalytic complex. In preclinical studies application of bortezomib to myeloma cell lines or fresh plasma cells isolated from patients with multiple myeloma (MM) was reported to directly inhibit proliferation and induce apoptosis. Moreover, in xenograft mouse models bortezomib significantly inhibited myeloma tumor growth, including complete tumor regression, and prolonged survival in comparison with controls. These results provided the basis for the investigational use of bortezomib in clinical practice and led to phase 1 dose-escalation studies aimed to determine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of this agent in heavily pretreated patients with advanced malignancies.

Orlowski *et al.* evaluated bortezomib at doses ranging from 0.4 to 1.38 mg/m^2 twice weekly for 4 weeks every 6 weeks as salvage therapy for 27 patients with various hematologic malignancies who were refractory to a median of three prior chemotherapy regimens. The maximum tolerated dose (MTD) for this patient population at this dosing schedule was 1.04 mg/m^2. Significant inhibition of 20S proteasome activity was seen within 1 hour of dosing, after which the inhibition slowly decayed and returned toward baseline by 72 hours. Importantly, among 9 assessable patients with plasma cell malignancies who completed one cycle of therapy, one patient experienced complete remission (CR), whereas variable reductions in monoclonal (M)-protein and/or bone marrow plasma cell infiltration were seen in the remaing 8 patients. In another phase 1 trial, bortezomib was explored in 43 patients with advanced solid tumors at doses ranging from 0.13 to 1.56 mg/m^2 twice weekly for 2 weeks every 3 weeks. At this dosing schedule, the MTD was 1.56 mg/m^2; dose-limiting toxicities were diarrhea and neuropathy. One major response was observed in a single patient with refractory non-small cell lung carcinoma.

Based on results of preclinical studies and phase 1 clinical trials described above, phase 2 or 3 clinical studies aimed to investigate the activity and toxicity of bortezomib in patients with advanced relapsed and/or refractory MM were subsequently designed.

The Study of Uncontrolled Multiple Myeloma managed with proteasome Inhibition Therapy (SUMMIT) was a nonrandomized, open-label, multicenter trial of bortezomib as salvage therapy for patients who had a relapse after receiving conventional chemotherapy and who were refractory to their last chemotherapy. In this study bortezomib was administered IV as a 3- to 5-second bolus injection at the dose of 1.3 mg/m^2 twice weekly for 2 weeks (e.g. on days 1, 4, 8 and 11), with cycles repeated every 3 weeks, up to a maximum of 8 cycles. Two hundred and two patients who had received a median of 6 number of previous therapies entered the study and 193 patients were assessable. Among these 193 patients, 92% had been treated with 3 or more of the major classes of agents active against MM and 91% were refractory to their most recent therapy. Using the criteria established by the European Group for Blood and Marrow Transplantation (EBMT) to classify responses, it was reported that the sum of the rates of CR, partial remission (PR) and minimal response (MR), was 35%.

Importantly, 4% of these heavily pretreated patients achieved CR and an additional 6% showed the disappearance of M protein at routine electrophoresis, but with positive immunofixation (nCR). The median overall survival was 16 months and median time to progression was twice that seen during the last treatment before study enrollment (7 vs. 3 months, respectively). Common adverse events (e.g. occurring in ≥ 10% of patients) of grade 3 or 4, regardless of their relationship to bortezomib, included thrombocytopenia (31%), neutropenia (14%), peripheral neuropathy (12%) and fatigue (12%). In 18% of patients bortezomib-related adverse events led to treatment discontinuation, whereas a reduction of the dose was required at least once in 12% of cases. Gastrointestinal symptoms attributable to bortezomib were common, albeit typically mild to moderate, and included nausea (55%), diarrhea (44%) and vomiting (27%).

The Clinical Response and Efficacy Study of bortezomib in the Treatment of relapsing multiple myeloma (CREST) was an exploratory phase 2 study aimed to evaluate the activity and safety of 2 doses of bortezomib (1.0 and 1.3 mg/m^2) in patients who were refractory to, or relapsed after, front-line therapy for MM. Fifty four patients who had received a median of 3 prior regimens were enrolled into the study and were randomized to receive three-week cycles, for up to 8 cycles, with bortezomib at either 1.0 mg/m^2 (N=28) or 1.3 mg/m^2 (N=26). Using EBMT response criteria, the overall rate of response (CR+PR+MR) to bortezomib alone was 33% in the 1.0 mg/m^2 dose group and 50% at the dose level of 1.3 mg/m^2. Median overall survival for patients in the 1.0 mg/m^2 dose group was 26.7 months and had not been reached for the 1.3-mg/m^2 dose by the time of publication. Several adverse events were reported more frequently (e.g. with a ≥20% difference in incidence rates) in the 1.3 mg/m^2 dose group, the most important including diarrhea, peripheral neuropathy and vomiting; however, divergence between the 2 groups occurred primarily in grade 1 and 2 events. At the opposite, thrombocytopenia occurred at a similar rate in both dose groups. Although the higher response rate and longer duration of response and time to progression observed among patients treated with the 1.3 mg/m^2 dose level suggested the possible existance of a dose-response relationship for bortezomib, this study supported both the feasibility and activity of a dose reduction strategy to manage bortezomib-related toxicities.

The results of SUMMIT and CREST led to the accelerated approval of bortezomib by the US Food and Drug Administration (FDA) in 2003 and approval in the European Union in 2004. Approval was for the treatment of MM patients who have received at least 2 prior therapies and who demonstrated disease progression on their last therapy.

Following these trials, a large international phase 3 randomized study was designed in an attempt to compare bortezomib with dexamethasone as salvage therapy for patients who had a relapse after 1-3 prior therapies (The Assessment of Proteasome inhibition for Extended remissions, APEX trial). A total of 669 patients entered the study and were randomized to receive either 8 three-week cycles of bortezomib (1.3 mg/m^2), followed by 3 five-week cycles, or high-dose dexamethasone. Patients who were assigned to receive dexamethasone were permitted to cross over to receive bortezomib in a companion study after disease progression. or pulsed dexamethasone. Results were analyzed based on treatment arms as a whole, as well as by number of prior lines of therapy (1 or >1) within each treatment arm. Significant differences between the overall groups were seen in favor of bortezomib on all efficacy measures, including time to progression (median, 6.22 months), response rate (CR + PR: 38%) and overall survival (80% at 1 year).

Based on results of APEX study, in March 2005 the U.S. FDA approved an extension of bortezomib's indication to include patients with MM who have received at least one prior therapy. The European CPMP approved a similar extension of the indication of monotherapy with bortezomib for MM patients with disease progression after at least one prior therapy and who have undergone or are unsuitable for bone marrow transplantation.