Bortezomib based therapy in Waldenstrom's Macroglobulinemia

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Bortezomib is a proteasome inhibitor which induces cell death of primary WM lymphoplasmacytic cells, as well as the WM cell lines at pharmacologically achievable levels. Moreover, bortezomib may also impact on bone marrow microenvironmental support for lymphoplasmacytic cells. In a multi-center study of the Waldenstrom's Macroglobulinemia Clinical Trials Group (WMCTG), 27 patients received up to 8 cycles of bortezomib at 1.3 mg/m^2 on days 1, 4, 8, and 11. All but one patient had relapsed/or refractory disease. Following therapy, median serum IgM levels declined from 4,660 mg/dL to 2,092 mg/dL. The overall response rate was 85%, with 10 and 13 patients achieving a minor (<25% decrease in IgM) and major (<50% decrease in IgM) response. Responses were prompt, and occurred at median of 1.4 months. The median time to progression for all responding patients in this study was 7.9 months, and the most common serious toxicities occurring in $\geq$ 5% of patients were sensory neuropathies (22.2%); decrease in white blood count (18.5%); decrease in neutrophils (14.8%); dizziness (11.1%); and decreased platelet count (7.4%). Importantly, sensory neuropathies resolved or improved in nearly all patients following cessation of therapy. As part of an NCI-Canada study, Chen *et al* treated 27 patients with both untreated (44%) and previously treated (56%) disease. Patients in this study received bortezomib utilizing the standard schedule until they either demonstrated progressive disease, or 2 cycles beyond a complete response or stable disease. The overall response rate in this study was 78%, with major responses observed in 44% of patients. Sensory neuropathy occurred in 20 pts, 5 with grade >3, and occurred following 2-4 cycles of therapy. Among the 20 patients developing a neuropathy, 14 patients resolved and one patient demonstrated a one-grade improvement at 2-13 months. In addition to the above experiences with bortezomib monotherapy in WM, Dimopoulos *et al* observed major responses in 6 of 10 (60%) previously treated WM patients, while Goy *et al* observed a major response in 1 of 2 WM patients who were included in a series of relapsed or refractory patients with non-Hodgkin's lymphoma (NHL). In view of the single agent activity of bortezomib in WM, we examined the combination of bortezomib, dexamethasone and rituximab (BDR) as primary therapy in patients with WM. An overall response rate of 96%, and a major response rate of 83% were observed with the BDR combination. The incidence of serious sensory neuropathy was about 30% in this study, but was reversible in most patients following discontinuation of therapy. An increased incidence of herpes zoster (shingles) was also observed prompting the prophylactic use of antiviral therapy with BDR. Alternative schedules for administration of bortezomib (i.e. once weekly at higher doses) in combination with rituximab are also being examined by Ghobrial *et al* and Agathocleous *et al* in patients with WM with overall response rates of 80-90%. The impact of these schedules on the development of bortezomib related peripheral neuropathy remains to be clarified, though in one study appeared diminished.