Primary Therapy of WM with Proteasome Inhibitor Therapy

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Waldenström's macroglobulinemia (WM) is an incurable B-cell lymphoproliferative disorder with a median survival of 5 years to 10 years in symptomatic patients. Current first-line treatment options include alkylating agents, nucleoside analogues, and rituximab-based therapies but complete responses are infrequent. New treatments that increase complete response could improve survival of patients with WM. Bortezomib, a first in class proteasome inhibitor (PI), is tumoricidal by blocking the ubiquitin-proteasome degradation pathway through reversible inhibition of the 26S proteasome, thereby affecting multiple signaling pathways resulting in apoptotic cell death. In preclinical studies bortezomib was active in WM cell lines and in primary tumor cells and had synergistic/additive in vitro activity in combination with numerous agents including rituximab, dexamethasone as well as other novel agents. Bortezomib showed activity in WM in multiple phase II studies, either alone or in combination. Initially, single agent bortezomib proved its activity in patients with relapsed or refractory WM[1-3], followed by the demonstration of significant activity in combination with rituximab with or without dexamethasone in relapsed or refractory patients[4]. In the frontline stetting, single agent bortezomib was given in 12 patients in the NCIC phase II study by Chen et al[3] and 25% achieved ≥PR using composite criteria of IgM paraprotein and imaging response. Bortezomib can rapidly decrease IgM levels, which is important for patients with symptoms of hyperviscosity or those with very high levels of circulating IgM. Treon et al[5] combined bortezomib with dexamethasone and rituximab (BDR) in 23 patients with previously untreated WM. Responses were rapid (median time to ≥25% IgM decrease 1.4 months) and overall response rate (≥MR) was 96% (≥PR in 83%) while 5 patients (22%) achieved CR/nCR. After a median follow-up of about 2 years, 18 of 23 patients remained progression free. Despite prophylactic pretherapy plasmapheresis in patients with very high levels of IgM, an "IgM flare" occurred in 2 patients (9%), both of whom required plasmapheresis. However, neurotoxicity remains the major reason for discontinuation of bortezomib. Based on data indicating that weekly bortezomib may be associated with similar efficacy but significantly less neurotoxicity, the European Myeloma Network (EMN) lunched a large phase II study that included 60 patients, in which an initial cycle of bortezomib at standard dose and schedule (1.3 mg/m^2 on days 1,4,8,11) was followed by 4 cycles of weekly bortezomib (at 1.6 mg/m^2) in combination with rituximab and dexamethasone (BDR). Preliminary results[6] showed a ≥PR in 65%, ≥MR in 80%, including 4% CRs. In responding patients, median time to ≥MR was 2.3 months. Importantly, plasmapheresis was not required in any patient before or after treatment with BDR and an "IgM flare" was not seen in any patient and this was attributed to the initial course of single agent bortezomib. Peripheral

sensory neuropathy was observed in 35%, but grade ≥3 neuropathy in only 5%; neuropathic pain in 19%, but grade ≥3 in only 1(2%) patient. Updates on duration of response and time to progression will be presented in 2012. The role of second generation PIs in WM is under investigation. The activity and safety of carfilzomib, a second generation PI which is not associated with significant neuropathy is investigated in a phase II study. However, based on the results from studies in both pretreated and untreated WM, bortezomib can now be considered as a major treatment option for patients with WM and in certain settings could be considered as a primary option.

References

1. Dimopoulos, M.A., et al., *Treatment of relapsed or refractory Waldenstrom's macroglobulinemia with bortezomib.* Haematologica, 2005. 90(12): p. 1655-8.
2. Treon, S.P., et al., *Multicenter clinical trial of bortezomib in relapsed/refractory Waldenstrom's macroglobulinemia: results of WMCTG Trial 03-248.* Clin Cancer Res, 2007. 13(11): p. 3320-5.
3. Chen, C.I., et al., *Bortezomib is active in patients with untreated or relapsed Waldenstrom's macroglobulinemia: a phase II study of the National Cancer Institute of Canada Clinical Trials Group.* J Clin Oncol, 2007. 25(12): p. 1570-5.
4. Ghobrial, I.M., et al., *Phase II trial of weekly bortezomib in combination with rituximab in relapsed or relapsed and refractory Waldenstrom macroglobulinemia.* J Clin Oncol, 2010. 28(8): p. 1422-8.
5. Treon, S.P., et al., *Primary therapy of Waldenstrom macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180.* J Clin Oncol, 2009. 27(23): p. 3830-5.
6. Dimopoulos, M.A., et al., *Primary Therapy of Waldenstrom's Macroglobulinemia (WM) with Weekly Bortezomib, Low-Dose Dexamethasone and Rituximab (BDR): A Phase II Study of the European Myeloma Network.* ASH Annual Meeting Abstracts, 2010. 116(21): p. 1941-.