Should Carfilzomib be given instead of bortezomib for WM- Yes

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WM is a B-cell malignancy characterized by bone marrow infiltration of clonal lymphoplasmacytic cells, which produce a monoclonal immunoglobulin M (IgM).
Proteasome inhibitors with bortezomib being the first in its class have shown significant responses in patients with WM with single agent or combination activity of 60-90% in both untreated and relapsed/refractory patients. Deep responses of VGPR or better have been seen in over 20% of patients in combinations with rituximab and dexamethasone. However, 70% of patients developed grade ≥ 2 peripheral neuropathy (PN) in a clinical trial that used twice a week bortezomib IV therapy and this led to premature discontinuation of bortezomib in 60% of patients for neurotoxicity. Clinical trials using weekly regimens have shown a decreased rate of neuropathy. However, in a recent European Myeloma Network study, the rate of Grade ≥ 2 PN was 24% of patients, leading to discontinuation of bortezomib in 8% and only 10% of patients achieved VGPR/complete response (CR). These results indicate that proteasome inhibitors are an important class of agents for this disease entity but neurotoxicity is a major toxicity that is common, severe and long lasting in many patients and does not allow appropriate dosing/continuation of therapy for patients leading to suboptimal responses with this class of drugs.

Therefore, the search for a neuropathy-sparing proteasome inhibitor was critical for patients with WM more than any other disease entity. Carfilzomib, a second-generation selective proteasome inhibitor, showed a favorable toxicity profile in the myeloma setting. Notably, in a large report on the safety of single-agent carfilzomib in relapsed/refractory myeloma patients, the incidence of PN was low (13.9%), including patients with baseline neuropathy. Treon et al evaluated the efficacy and safety of the combination of carfilzomib, rituximab, and desamethasone (CaRD) in 31 patients with symptomatic WM, naïve to bortezomib and rituximab. ORR was 87.1%, and 36% of patients achieved VGPR/CR. One patient attained a molecular CR (the first observation of molecular CR in WM). The response to CaRD was independent of the presence of the $CXCR4^{WHIM}$ mutation (35.5% of patients in the study). This is of particular interest, given the negative impact on response carried by this mutation.Protocol therapy was interrupted for nonresponse or progression in 10 patients, for progressive IgA/IgG hypogammaglobulinemia with infections in 2 patients, and for cardiomyopathy in 1 patient with multiple risk factors. Concerning treatment-related PN, it should be underlined that only 1 patient suffered grade 2 PN, and no patient needed discontinuation of the CaRD program because of neuropathy. This is of great clinical relevance, given the high incidence of neurologic toxicity usually observed with the proteasome inhibitor bortezomib. These results indicate that the carfilzomib-based CaRD combination represents an advancement in the treatment of WM patients requiring a proteasome inhibitor-based therapy. In fact, the efficacy of the combination, associated with a very low incidence of peripheral nerve toxicity, offers a neuropathy-sparing alternative to bortezomib-based protocols.