Proteasome Inhibitors
A Guide to Treatment Options

If you think of a proteasome as the cell's "garbage disposal," a disruption of this normal process with a proteasome inhibitor will cause the unneeded or damaged protein "garbage" to accumulate and "clog" the cell, to the point where this can interfere with cell reproduction and other functions and lead to cell death. Studies have shown that because cancer cells tend to accumulate proteins more quickly, they are more susceptible to the action of proteasome inhibitors than normal cells.

Bortezomib (Velcade)

Bortezomib (Velcade) was the first proteasome inhibitor, developed in 1995 and approved by the FDA in 2003 for the treatment of refractory multiple myeloma. It has since been approved for relapsed mantle cell lymphoma and as first-line therapy for multiple myeloma. It is prescribed off-label for WM.

The Waldenstrom's Macroglobulinemia Clinical Trials Groups studied intravenous bortezomib, dexamethasone, and rituximab (abbreviated BDR) in 23 previously untreated patients, with administration of intravenous bortezomib at 1.3 mg/m^2 and dexamethasone at 40 mg twice a week on days 1, 4, 8, 11, along with rituximab at 375 mg/m^2 on day 11 for 4 cycles as first-line treatment and for 4 more cycles after 3 months as maintenance treatment. The overall response rate and major response rate were 96% and 83%, respectively. Sixty percent of patients discontinued treatment after 4 cycles because of treatment-related peripheral neuropathy. The median progression-free survival was 66 months. (Progression-free survival is the length of time during and after treatment that a patient lives with the disease but does not show signs or symptoms of disease progression.)

Another study of first-line therapy in 59 newly diagnosed symptomatic WM patients used intravenous bortezomib only (1.3 mg/m^2 on days 1, 4, 8, 11) during the first cycle to avoid IgM "flare," which is a transient increase in IgM that has been observed following certain therapies, especially those including rituximab. This was followed by four cycles of weekly bortezomib (1.6 mg/m^2 for 4 weeks) with rituximab and dexamethasone in cycles 2 and 5. Peripheral neuropathy was observed in 46% of the patients, and 8% discontinued treatment due to neuropathy.
According to the NCCN® Guidelines, the combination of bortezomib, rituximab, and dexamethasone is one of the preferred treatment options for both first-line and relapsed/refractory WM. However, bortezomib treatment should be avoided in patients with existing disease-related neuropathy. Bortezomib only, bortezomib with dexamethasone, or bortezomib with rituximab can be considered as alternatives for those who are intolerant to rituximab and/or dexamethasone. Plasmapheresis followed by bortezomib therapy is particularly helpful for rapid reduction of serum IgM levels in patients with symptomatic hyperviscosity, symptomatic cryoglobulinemia, symptomatic cold agglutinin disease, amyloidosis, and renal impairment. Treatment responses are prompt, with partial responses occurring at a median of 1.4 months in one study. Another advantage of bortezomib is that it is not toxic to bone marrow stem cells and therefore can be used as treatment for patients who are considering autologous stem cell transplantation as a future option. Long-term follow-up in multiple myeloma patients does not suggest a risk for secondary malignancies.

Because nerve toxicity is a major concern with bortezomib treatment, subcutaneous (under the skin) administration of bortezomib once weekly, rather than intravenous administration, is now the preferred method of administration to reduce the risk of peripheral neuropathy.

Bortezomib treatment is associated with a high rate of herpes zoster (shingles), and prophylactic treatment with an antiviral is strongly recommended during treatment. Bortezomib treatment can decrease normal levels of IgA and IgG, and these levels should be carefully monitored during therapy.

Carfilzomib (Kyprolis)

Carfilzomib is a second-generation proteasome inhibitor associated with a lower risk of nerve toxicity in multiply myeloma patients. It was evaluated in combination with rituximab and dexamethasone (CaRD regimen), mainly in previously untreated WM patients, in a schedule of dosing on days 1, 2, 8, and 9 and in maintenance therapy on days 1 and 2 every 8 weeks for 8 cycles (reduced from typical myeloma dosing). The overall response rate was 87%. Toxicities included elevation of the enzyme lipase, steroid-related hyperglycemia (high blood sugar), neutropenia (low neutrophil count), and reversible cardiomyopathy (disease of the heart muscle) in a patient with multiple cardiac risk factors. No grade 3 or greater neuropathy was observed.

CaRD therapy, while not a preferred regimen for first-line use in the NCCN® Guidelines, is an alternate option in the first-line setting. Prophylactic treatment with an antiviral agent is strongly recommended during treatment to prevent shingles. Carfilzomib-based therapy can rapidly reduce IgA and IgG levels.

Ixazomib (Ninlaro)

This is a newer proteasome inhibitor administered orally that has been approved for treatment of relapsed/refractory multiple myeloma. Ixazomib combined with dexamethasone and rituximab (IDR regimen) is currently being evaluated in a clinical trial for previously untreated WM patients. Initial treatment consisted of eight cycles, with rituximab administered intravenously for one cycle followed by subsequent subcutaneous administration. This is being followed by two years of maintenance rituximab administered subcutaneously. The overall response rate at the completion of eight cycles was 83%, and the most common adverse events were infections. The trial is still in progress.

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About the IWMF

The International Waldenstrom's Macroglobulinemia Foundation (IWMF) is a patient-founded and volunteer-led, nonprofit 501(c)(3) organization with an important mission: to offer mutual support and encouragement to the Waldenstrom's macroglobulinemia community and others with an interest in the disease; to provide information and educational programs that address patients' concerns; and to promote and support research leading to better treatments and ultimately, a cure.

More information about Waldenstrom's macroglobulinemia and the services and support offered by the IWMF and its affiliate organizations can be found on our website, www.iwmf.com.

The IWMF relies on donations to continue its mission, and we welcome your support. The Foundation maintains a Business Office at 6144 Clark Center, Ave., Sarasota, FL 34238. The Office can be contacted by phone at 941-927-4963, by fax at 941-927-4467, or by email at info@iwmf.com.