Proteasome Inhibitors

Meletios A. Dimopoulos, MD , Evangelos Terpos, MD & Efstathios Kastritis, MD

Department of Clinical Therapeutics, National &Kapodistrian University of Athens, School of Medicine, Athens, Greece
e-mail: mdimop@med.uoa.gr

Proteasome inhibitors (PIs) have proven their efficacy and have contributed significantly in the improvement of survival of patients with multiple myeloma. PIs have also proven their efficacy in patients with WM. Bortezomib is the first in class proteasome inhibitor and as a single agent is associated with responses in ~40% of patients with relapsed or refractory WM, including fludarabine and rituximab refractory patients. Combinations of bortezomib with rituximab(+/- dexamethasone) are very active.In the frontline setting three phase II studies of bortezomib/rituximab combinations, using different schedules of i.v.bortezomib (twice weekly or once weekly), that have included more than 100 patients, showed response rates(≥PR) between 66% to 83% and rapid times to first response (2-3 months). The rapid single agent activity of bortezomibhas been exploited to mitigate “IgM flare”, before initiation of rituximab, as in the EMN study byDimopoulos et al. Bortezomibcombinations are also associated with durable responses. Bortezomib is further evaluated in a large study in France in patients with advanced WM after 1-2 lines of therapy (NCT00777738). Neurotoxicity is the major concern with bortezomib; weekly dosingandsubcutaneous administration may reduce rates and severity of neuropathy. Bortezomibis not stem cell toxic and long-term follow-up in myeloma patients does not suggest a risk for secondary malignancies. Prophylaxis against herpes zoster is strongly recommended.

Carfilzomib, a second generation PI, is associated with a low risk of neurotoxicity. In combination with rituximab and dexamethasone(CaRD), mainly in previously untreated WM patientsoverall response rate was 87% (≥VGPR in 35%). No grade≥3 neuropathy was observed but “IgM flare” occurred in 22%. However, given the potential cardiotoxicity of carfilzomib, this drug should be further studied

in WM patients. Other orally available PIs, such as ixazomib and oprozomib, are under investigation in WM.

Based on the accumulated experience with bortezomib in WM, primary therapy with bortezomib combinations is recommended for patients with high levels of IgM, with symptoms of or, at risk of developing hyperviscosity syndrome, symptomatic cryoglobulinemia or cold agglutinemia, amyloidosis and renal impairment. More data are needed before next generation PIs are recommended over bortezomib.

References

1. TreonSP, Ioakimidis L, Soumerai JD, Patterson CJ, Sheehy P, Nelson M, et al. Primary therapy of Waldenstrommacroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. J ClinOncol. 2009 Aug 10;27(23):3830-5.
2. Ghobrial IM, Xie W, Padmanabhan S, Badros A, Rourke M, Leduc R, et al. hase II trial of weekly bortezomib in combination with rituximab in untreated patients with WaldenstromMacroglobulinemia. Am J Hematol. 2010 Sep;85(9):670-4.
3. Dimopoulos MA, Garcia-Sanz R, Gavriatopoulou M, Morel P, Kyrtsonis MC, Michalis E, et al. Primary therapy of Waldenstrommacroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). Blood. 2013 Nov 7;122(19):3276-82.
4. TreonSP, TripsasCK, Meid K, Kanan S, Sheehy P, Chuma S, et al. Carfilzomib, rituximab and dexamethasone (CaRD) is active and offers a neuropathy-sparing approach for proteasome-inhibitor based therapy in Waldenstrom'smacroglobulinemiaBlood. 2014 [Epub ahead of print]