Should proteasome inhibitors be the standard for frontline treatment of WM?

Jorge Castillo, MD, Dana-Farber Cancer Institute, Boston, MA USA

Waldenström macroglobulinemia (WM) is an indolent B-cell lymphoma, which is considered incurable with current standard treatment options. There have been a number of clinical trials evaluating drugs with distinct mechanisms of action in patients with WM. Proteasome inhibitors (PIs) have shown to be safe as well as highly effective in the frontline treatment of patients with WM. In an initial study, the combination of twice-weekly intravenous bortezomib with dexamethasone and rituximab showed an overall response rate (ORR) of 96% although with over 60% drug discontinuation rate due to neuropathy (Treon J ClinOncol 2009). A recent update of this study showed a median progression-free survival of 5.5 years (Treon ASH 2015). Another study evaluated weekly bortezomib with dexamethasone and rituximab and showed an ORR of 85% with a discontinuation rate due to neuropathy of <10% (Dimopoulos Blood 2013). A study evaluated weekly bortezomib with rituximab (without dexamethasone) and reported an ORR of 88% with no grade 3 or 4 neuropathy (Ghobrial Am J Hematol 2011). Carfilzomib, a second generation PI, was combined with rituximab and dexamethasone and elicited an ORR of 87% with neuropathy rates below 5% but with hypogammaglobulinemia, hyperlipasemia and neutropenia (Treon Blood 2014). A study evaluating the oral PI ixazomib in combination with dexamethasone and rituximab is ongoing and already showing promising results with an acceptable toxicity rate (Castillo IWWM-9). In summary, PIs in combination with rituximab appear highly effective in the frontline treatment of patients with WM, with a manageable toxicity profile. Additional benefits of PI-based therapy are the lack of stem cell toxicity as well as no increased risk of secondary malignancies. Therefore, PI-based therapy should be considered as one of the standards for the frontline treatment of patients with WM.