Novel Proteasome Inhibitors.

Constantine S. Mitsiades, MD, PhD

Dept. of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA

The introduction of the proteasome inhibitor bortezomib into the therapeutic armamentarium for multiple myeloma (MM) was associated with significant improvement in the rates, depth and durability of clinical responses. The partial overlap in biological and clinical features of Waldenstrom's macroglobulinemia (WM) and MM raised the possibility that the role of proteasome inhibition could be extended to include therapeutic applications in WM. Preclinical studies in the early part of the last decade provided the basis for subsequent clinical studies which showed that bortezomib, alone and in combination with rituximab, exhibits notable activity in WM. Due to its ability to rapidly decrease IgM levels in WM, bortezomib is well suited for the management of hyperviscosity-related symptoms and the alleviation of rituximab-associated IgM flares. The development of 2nd generation proteasome inhibitors attempts to improve on the clinical activity of bortezomib, by capitalizing on the distinct properties of compounds, such as NPI-0052 (salinosporamide A) and carfilzomib, which have entered clinical trials in MM. This presentation will highlight the similarities and differences between each of these novel compounds and bortezomib in terms of their target selectivity (binding to the beta5 subunit of the 20S proteasome core vs. targeting of other sites as well); the reversible or irreversible nature of their binding to the proteasome; the kinetics of interaction with their intended targets; the kinetics of ensuing tumor cell death; as well as the patterns of tissue-specific distribution of these agents. This presentation will also discuss how bortezomib and the 2nd generation proteasome inhibitors compare, in terms of the molecular sequelae and anti-tumor activity, with agents that perturb the ubiquitin/proteasome pathway at different molecular levels situated upstream of the 20S proteasome, e.g. ubiquitin-specific proteases, ubiquitin-ligases or the NEDD8-activating enzyme (NAE), which plays an essential role in regulating the activity of a subset of ubiquitin E3 ligases, the cullin-RING ligases (CRLs). Particular emphasis will be placed on how the distinct features of bortezomib vs. novel proteasome inhibitors vs. investigational upstream inhibitors of the ubiquitin/proteasome pathways can influence the clinical safety and efficacy of these novel agents in ongoing and future studies in WM and MM.