Novel E3 Ligase and Proteasome inhibitors for WM therapy.

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The proteasome inhibitor bortezomib has led to significant improvement in the rates, depth and durability of clinical responses in multiple myeloma (MM). The partially overlapping biological and clinical features of Waldenstrom's macroglobulinemia (WM) and MM raised the notion that proteasome inhibition could also have therapeutic applications in WM. Preclinical studies in the early part of the last decade provided the basis for subsequent clinical studies which showed the notable activity of bortezomib, alone and in combination with rituximab, in WM. Due to its ability to rapidly decrease IgM levels in WM, bortezomib is suitable for management of hyperviscosity-related symptoms and alleviation of rituximab-associated IgM flares. Second generation proteasome inhibitors attempts have been developed with the intent to improve on the clinical activity of bortezomib. Carfilzomib recently received accelerated FDA approval for treatment of MM refractory to bortezomib and to immunomodulatory agents. Other second generation proteasome inhibitors, such as ixazomib (MLN9708) or marizomib (NPI-0052, Salinosporamide A) have also entered clinical trials in MM. This presentation will highlight the overlapping and distinct features of these novel compounds and how these parameters could influence the clinical applications of these agents for MM vs WM. This presentation will also address how bortezomib and 2nd generation proteasome inhibitors compare, vis-à-vis their molecular sequelae and anti-tumor activity, with agents which target the ubiquitin/proteasome pathway at molecular levels 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). Emphasis will also be placed on the opportunities and challenges associated with the preclinical and clinical development of agents targeting E3 ligases in WM and MM