

Novel therapies for Waldenstrom's Macroglobulinemia

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The identification of active agents which provide a stem cell sparing approach, and avoidance of long term toxicities such as disease transformation or development of myelodysplasia or acute myelogenous leukemia is a priority in WM. In previous studies, the WMCTG conducted a Phase II study of thalidomide and rituximab, and subsequently lenalidomide and rituximab in WM patients. Neuropathy was an important toxicity at the doses initiated for thalidomide, whilst lenalidomide produced an unexpected acute anemia. Pomalidomide represents a novel derivative of thalidomide, which demonstrates more robust immune stimulatory activity versus both thalidomide and lenalidomide. In early studies in myeloma patients, pomalidomide with dexamethasone showed promising results, and produced responses in patients who had failed thalidomide and lenalidomide. Moreover, fewer neuropathy and myelosuppressive events were observed versus thalidomide and lenalidomide, respectively. As such the combination of pomalidomide, dexamethasone and rituximab (PDR) in the treatment of WM is being contemplated in patients who either are naïve to rituximab or previous showed responsiveness to rituximab. The combination of bortezomib, a proteasome inhibitor, with cyclophosphamide has been investigated in various combination strategies in myeloma patients; as such the WMCTG will be sponsoring a randomized study of CBPR vs. CPR in WM patients, as primary therapy, using a once a week bortezomib dose schedule. In as well, given the success of proteasome inhibition, a novel NEDD8 inhibitor (MLN4924) which demonstrates upstream activity to the proteasome is being considered for WM trials in relapsed/refractory disease. Because of its ubiquitination pattern, MLN 4924 may represent a more neuropathy sparing agent. RAD001 (Everolimus; Afinitor) represents a novel oral therapy recently approved by the FDA for kidney cancer, and has activity in relapsed/refractory WM patients. As such, a Phase II trial examining the upfront activity of this agent as single agent therapy in WM patients who are previously untreated is set to begin later this year. In recent studies, epigenetic modifiers such as the hypomethylating agent Vidaza, and the HDAC-inhibitor Vorinostat have shown activity, particularly in combination preclinical studies in WM. As such a Phase I/II study of Vidaza/Vorinostat has been initiated by the WMCTG in relapsed/refractory WM.