IWWM-10 Session 7 (Keynote Lecture): Friday, October 12, 2018, Olszewski

Is there a standard of care for treating treatment naïve WM?

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Waldenström macroglobulinemia (WM) may present with a variety of clinical scenarios, making it impractical to define a single standard first-line therapy. Long lists of acceptable regimens included in the International Workshop on WM and National Comprehensive Cancer Network guidelines, as well as variation of clinical practice seen in observational studies reflect paucity of comparative data. Treatment efficacy in WM is largely established from single-arm studies or subsets of randomized trials enrolling subjects with indolent B-cell lymphomas. Approach should be primarily guided by clinical presentation driving the need for therapy, and differs for patients presenting with high lymphoma burden (cytopenias, splenomegaly), hyperviscosity, auto-immune phenomena, or specific IgM-related complications like neuropathy or amyloidosis. Desired depth and length of remission, balancing treatment intensity and toxicity in the context of patient's age, comorbidities, personal preferences, as well as cost of treatment and emergent molecular characteristics, are all factors to consider when selecting initial therapy. Immunochemotherapy regimens containing an anti-CD20 antibody (rituximab), an alkylating agent (cyclophosphamide or bendamustine), and steroids, offer a limited-duration treatment with response rates of over 90%, median progression-free survival of 3-5 years, and manageable toxicity appropriate for many patients. Regimens substituting a proteasome inhibitor (bortezomib, carfilzomib, ixazomib) for a cytotoxic agent may have comparable efficacy, but their relative advantage remains uncertain pending results of comparative trials. Patients with low burden of disease and presenting with IgM-related autoimmune complications or neuropathy alone, as well as those who do not prioritize deep remissions and long-term disease control, may receive rituximab alone without sacrificing overall survival. Because of IgM flare phenomenon, rituximab monotherapy is not appropriate for patients with, or at risk for, hyperviscosity. Recent results of the iNNOVATE phase 3 trial demonstrate high efficacy of the ibrutinib-rituximab combination with rapid control of monoclonal paraproteinemia, establishing a novel chemotherapy-free approach. Nevertheless, the value of ibrutinib for treatment-naïve patients needs further evaluation considering the requirement for open-ended, continuous therapy, associated cost, and uncertainty about the relative contribution of rituximab. Defining optimal "standards of care" in WM demands more comparative data from prospective and observational studies.