Ibrutinib in rituximab refractory WM patients

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Rituximab and rituximab-based combinations remain the backbone of treatment for patients with symptomatic WM across different disease phases, from the first to second to third line and beyond. However, eventually, a significant proportion of patients will develop resistance to rituximab. Patients with rituximab-refractory disease have limited treatment options and although agents such as proteasome inhibitors, or other targeted therapies may lead to clinical responses, these are shorter in duration and may be associated with significant treatment-related toxicity. Over ≥90% of WM patients have somatic mutations in the MYD88 gene, encoding the mutated MYD88L265P protein, a member of the BCR pathway complex. Mutated MYD88 interacts with BTK leading to constitutive activation of the NF-κB pathway, subsequently supporting survival and proliferation of lymphoplasmacytic cells, as well as additional indirect effects in cytokine balance. Ibrutinib is a first-in-class inhibitor of BTK-dependent signaling. Two clinical studies have proven the efficacy of ibrutinib in patients with relapsed or refractory WM. In the first, pivotal, phase 2 trial, ibrutinib given orally (420 mg/day) until disease progression in 63 previously treated WM patients demonstrated an overall response rate (ORR) of 91% (≥PR in 73%). The estimated 2-year PFS and OS were 69.1% and 95.2%, respectively. In the second study, ibrutinib (420 mg/day) was given in 31 patients with rituximab-refractory disease (open label arm of the iNNOVATE study). With a median number of 4 prior therapies, 42% having high-risk disease per IPSSWM and all being rituximab-refractory, ORR was 90% (≥PR in 71%); estimated 18-month PFS and OS rates were 86% and 97%, respectively. In both studies clinical improvement was rapid, IgM levels decreased rapidly after just 4 weeks, hemoglobin levels increased and bone marrow involvement decreased significantly. In both studies the quality of response was affected by the presence or absence of mutations in MYD88 and in CXCR4, but still response rates remained high. Importantly, toxicity of ibrutinib is rather mild; typically includes mild cytopenias, but also hypertension, diarrhea, bleeding diathesis and atrial fibrillation are reported. Based on these results and the safety profile, ibrutinib is probably the most effective therapy for patients with rituximab–refractory disease and a major treatment option for such patients.