Ibrutinib in previously treated patients with Waldenstrom's Macroglobulinemia.

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Background: $MYD88^{L265P}$ mutation is highly prevalent in Waldenstrom's Macroglobulinemia (WM) and triggers growth via Bruton's Tyrosine Kinase (BTK), a target of Ibrutinib. $CXCR4^{WHIM}$ mutations are common in WM, and confer *in vitro* resistance to ibrutinib. We therefore evaluated ibrutinib monotherapy in previously treated WM patients, and examined MYD88 and CXCR4 mutation status on response outcome.

Methods: Symptomatic patients with $\geq$1 prior therapies were eligible. Intended therapy consisted of 420 mg of ibrutinib by mouth daily until progression, or unacceptable toxicity. MYD88 and CXCR4 status was determined in 63 and 62 patients, respectively.

Results: Sixty-three patients were enrolled. At best response, median serum IgM levels declined from 3,610 to 915 mg/dL; hemoglobin rose from 10.5 to 13.5 g/dL, and bone marrow involvement declined from 60% to 30% ($p<0.001$). Overall and major response rates were 87.3% and 68.3%, and median time to response was 4 weeks. Responses were adversely impacted by $MYD88^{wild\text{-}type}$ and $CXCR4^{WHIM}$ mutation status. With a median follow-up of 48 weeks, 80% of patients remain on treatment without progression. Grade $\geq$2 treatment-related toxicities included neutropenia (25.4%) and thrombocytopenia (14.3%) found more commonly in heavily pre-treated patients; atrial fibrillation in patients with a prior history (4.8%); procedure-related bleeding (3.2%); and recurring epistaxis associated with marine oil supplements (3.2%). IgA and IgG levels remained stable, and no excess infections were observed.

Conclusions Ibrutinib is active and well-tolerated in previously treated WM patients, with rapid improvements in serum IgM and hemoglobin. MYD88 and CXCR4 mutations are determinants of ibrutinib response in WM patients.