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Zanubrutinib plus Ixazomib & Dexamethasone in newly diagnosed symptomatic Waldenström macroglobulinemia:a phase II study

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Abstract

Waldenström macroglobulinemia (WM) is a rare type of lymphoma, with no optimal treatment. BTK inhibitor have shown promising outcomes, yet achieving deep remission remains challenging and time-limited therapy has not been studied. We conducted a phase 2 clinical trial (NCT04463953) to evaluate the efficacy and safety of combining zanubrutinib, ixazomib, and dexamethasone (ZID) in newly diagnosed symptomatic WM patients. Patients received ZID induction therapy for up to six 28-day cycles, followed by consolidation therapy up to total 24 cycles. The primary endpoint was the deep remission rate. Overall, 24 of 27 enrolled patients completed induction treatment. One patient (4.2%) achieved CR, 10 patients (41.6%) achieved VGPR, 12 patients (50%) attained PR. The overall, major and deep remission rates were 100%, 95.8% and 45.8%, respectively. The median time to response was 2 months (range, 1-5). Five of 22 patients had *CXCR4* mutation, with no disparity in the deep remission between the patients with/without *CXCR4* mutation (40% vs 50%, P=0.594). The median abnormal lymphocyte (7.6% vs 1.6%, P =0.0019) and plasma cells (0.28% to 0.02%, P =0.0306) were significantly reduced after treatment. The immune TME dysfunction exists in WM patients and is associated with IgM levels and deep response. The level of IgM was positively associated with the percentage of NK cells (R=0.54, P=0.0096) and negatively associated with the percentage of CD3 T cells (R= -0.49, P=0.021) and CD4 T cells (R= -0.63 P=0.0023). Furthermore, the deep response rate was positively associated with the proportion of CD4 helper T cells (P=0.0039). After treatment, the immune function had partially recovered, with a significant increase in the proportion of CD4 helper T cells (39% vs 48%, P=0.0115), CD8 cytotoxic T cells (18% vs 25%, P=0.0252) . With a median follow-up of 30.9 months (range, 15-42), 5 patients progressed. The median PFS and OS were 40 months (95% CI:35.5-44.5) and not reached, respectively, with no difference in patients with/without *CXCR4* mutations. The most common AE was hematological toxicity. SAEs were infection (12.5%) and

thrombocytopenia (8.3%). Overall, ZID regimen offered significant deep remission and provided a time-limited BTKi therarpy in WM patients with manageable AEs.