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Phase II clinical study of Zanubrutinib combined with bendamustine and rituximab (ZBR) for time-limited treatment of Waldenstrom macroglobulinemia

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Introduction: Waldenström macroglobulinemia (WM) is a rare type of lymphoma, with no established optimal treatment. BTK inhibitors and bendamustine-rituximab (BR) are the preferred regimens with promising outcomes. However, continuous therapy and achieving deep remission remain to be improved. We conducted a phase 2 clinical trial (NCT05979948) to evaluate the efficacy and safety of combining zanubrutinib, bendamustine and rituximab (ZBR) in newly diagnosed symptomatic patients with WM.

Methods: Patients with newly diagnosed symptomatic WM received ZBR for 6 cycles. Bendamustine will be given intravenously at 70 mg/m^2 on days 1 and 2 of each cycle. Rituximab will be given on day 1 of each cycle (375 mg/m^2 intravenously), Zanubrutinib will be given orally 160 mg Bid per day, up to 12 months. The participants with WM will also have disease assessment with lymph node ultrasound and abdominal ultrasound each cource, serum IgM, serum protein electrophoresis (SPE), immunofixation (IFA), and viscosity assessments will be measured serially. A bone marrow aspiration and biopsy flow cytometry examination will be done before treatment and at response assessment at cycle 3, 6 and 12. Durability of response will also be assessed every 3 months after treatment.

Results:

25 patients were enrolled. The median age was 63 (33-76), with 10 patients (40%) being 65 years of age or older. The median baseline hemoglobin level was 93 g/L (range, 48–136), and the median baseline IgM was 35.9 g/L (range, 3.46–132). 14 of 25 patients completed induction treatment. After induction treatment, 2 patient achieved CR , 8 patients achieved VGPR, 3 patients achieved PR and 1 patient achieved MR. The overall, major and deep remission rates were 100%, 92.9% and 71.4%, respectively. 7 patients completed maintenance therapy and stopped treatment. The overall, major and deep remission rates were 100%, 85.7% and 71.4%, respectively. Rapid therapeutic response was achieved in all patients treated. The median time to PR was 1 month (1-5) and the median time to best response was 3 months (range, 1-7). Minimal residual disease (MRD) analysis showed that ZBR was effective in removing abnormal cells from the bone marrow. 8 out of 14 (57.1%) patients obtained MRD negativity by FCM. The median abnormal lymphocyte reduced from 10% (range, 1.4-15.4) to 0% (range, 0-0.17) (P<0.0001), and the median abnormal plasma cells were reduced from 0.39% (0.09-4.45) to 0% (0-0.72), P=0.0106. 12 of 14 (85.7%) patients did not detect abnormal tumor cells by bone marrow biopsy. In addition, ZBR was effective in removing large masses. Lymph node enlargement was present in 9 patients, of which 5 patients had complete lymph node remission after treatment. 4 of 9 patients had large masses with a median SPD of 45.9 cm^2 (22-48.9), and the SPD of the patients decreased to 3.08 cm^2 (0-4.2) after treatment. For the enrolled patients, the median follow-up was 8 months (range, 2-16), only one patient died of cerebral hemorrhage at 4 courses of treatment. The most common AE was hematological toxicity. AE (grade ≥3) were neutropenia (28%), infection (28%), thrombocytopenia (12%), rash (8%), fatigue (4.0%) and cerebral hemorrhage (4.0%). No IgM rebound occurred in any of the 7 patients who ended treatment and discontinued the drug.

Conclusion

The ZBR regimen reached significant deep remission rates in newly diagnosed symptomatic WM patients with manageable adverse events. In addition, it can

effectively remove tumor cells and extramedullary masses.