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INTERIM RESULTS OF A PHASE II STUDY OF BLINATUMOMAB PLUS PONATINIB FOR PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

Topic: 02. Acute lymphoblastic leukemia - Clinical

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Background: Ponatinib and blinatumomab both produce high rates of molecular remission in Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). The combination of these two agents may lead to deep and durable responses, thereby reducing the need for allogeneic hematopoietic stem cell transplant (HSCT).

Aims: We evaluated the efficacy and safety of a chemotherapy-free combination of blinatumomab and ponatinib in patients with newly diagnosed (ND) or relapsed/refractory (R/R) Ph+ ALL. For patients with ND Ph+ ALL, the primary endpoint was the complete molecular response (CMR) rate, defined as absence of a quantifiable PCR transcript for *BCR-ABL1*. For patients with R/R Ph+ ALL, the primary endpoint was the overall response rate (defined as the composite of CR/CRi). Secondary endpoints included safety measures, event-free survival (EFS) and overall survival (OS).

Methods: This is a single-arm phase 2 study in adults with ND or R/R Ph+ ALL. Patients were required to have a performance status of ≤2, total bilirubin ≤2x the upper limit of normal (ULN), and alanine aminotransferase and aspartate aminotransferase ≤3x the ULN. Patients with uncontrolled cardiovascular disease or clinically significant central nervous system comorbidities were excluded. Patients received up to 5 cycles of blinatumomab as a continuous infusion at standard doses. Ponatinib 30mg daily was given during cycle 1. Ponatinib was decreased to 15mg daily once CMR was achieved. After completion of blinatumomab, ponatinib was continued for at least 5 years in responding patients. Twelve doses of prophylactic intrathecal chemotherapy were administered.

Results: Between February 2018 and February 2021, 28 patients were treated (19 ND and 9 R/R). The median age for the entire cohort was 59 years (range, 25-83 years); 62 years (range, 34-83 years) and 36 years (range, 25-61 years) in the ND and R/R cohorts, respectively. *BCR-ABL1* transcripts were p190 in 69% of patients in the ND cohort and 100% in the R/R cohort. 44% of patients in the R/R cohort were in salvage 2 or beyond. Overall, 95% of patients responded; the CR/CRi rate was 100% in the ND cohort and 88% in the R/R cohort. No early death within 4 weeks were observed. 86% of responding patients achieved CMR (87% in the ND cohort and 86% in the R/R cohort). The median time to CMR was 1 month (range, 1-13 months). None of the patients in the ND cohort underwent HSCT; 4 patients (44%) in the R/R cohort underwent subsequent HSCT. With a median follow-up of 14 months, the estimated 1-year OS rate was 94% and the EFS rate was 81% for the entire study cohort. In the ND cohort, no patients have relapsed or died, and the 1-year OS and EFS rates were both 100%. In the R/R cohort, 1-year OS and EFS rates were 88% and 55%, respectively. The treatment was well-tolerated, and most side effects were grade 1-2. No patient has discontinued ponatinib due to toxicity. One patient discontinued blinatumomab due to recurrent grade 2 tremor.

Summary/Conclusion: The chemotherapy-free combination of ponatinib and blinatumomab shows encouraging safety and efficacy in Ph+ ALL, with high rates of CMR and durable remissions, particularly when used in the frontline setting. All ND patients remain in remission without HSCT, suggesting that this regimen may obviate the need for HSCT in this setting.

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