Pharmacokinetic characterization of flotetuzumab in pediatric patients with refractory /relapsed acute myeloid leukemia

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Background: Acute myeloid leukemia (AML) accounts for about 20% of childhood leukemia cases. The CD123xCD3-targeting bispecific antibody flotetuzumab was studied in the Children's Oncology Group phase I trial in pediatric patients with multiply-relapsed/refractory AML (PEPN1812; NCT04158739; Lamble ASH annual meeting 2022). Two dose levels (DL) of flotetuzumab were explored: 500 ng/kg (DL1; adult recommended phase 2 dose [RP2D]) and 700 ng/kg (DL2). The drug was administered as a continuous infusion for 28 days using a step-up dosing approach during the first week of treatment to minimize known infusion-related reaction and cytokine release syndrome effects (Uy *Blood* 2021).

Methods: Flotetuzumab pharmacokinetics (PK) were characterized by compartmental modeling. Serum concentration-time data were fitted by non-linear least squares regression using the program WINNONLIN (Pharsight). The Akaiki and Schwarz Bayesian criteria were used to select the best-fit model.

Results: Of the 16 patients enrolled in the trial, PK were evaluable for 3/7 patients at DL1 and 8/9 patients at DL2. Reasons for inevaluability included undetectable flotetuzumab serum concentrations (n=1, DL1), insufficient post-infusion serum concentration data (n=2, DL1), missing serum concentration data (n=1, DL1), and patient not treated (n=1, DL2). During DL1 step-up dosing, median flotetuzumab serum concentrations increased from 17.0 pg/mL to 110 pg/mL. The median steady-state concentration (Css), half-life and body weight-adjusted clearance (CL) values were 135 pg/mL, 9.7 hr and 0.16 L/hr/kg, respectively. During DL2 step-up dosing, median flotetuzumab serum concentrations increased from 18.2 pg/mL to 128 pg/mL. The median Css, half-life and CL values were 124 ng/mL, 10.1 hr and 0.18 L/hr/kg, respectively. The median CL values were 0.16 L/hr/kg for females and 0.66 L/hr/kg for males. Patients 12 years and younger had higher median CL compared to older patients (1.06 L/hr/kg, n=5 vs 0.15 L/hr/kg, n=6).

Conclusion: Flotetuzumab showed a low serum clearance and moderate half-life in this small cohort of patients. Css levels did not differ significantly between the two dose levels. Patients 12 years and younger had the highest CL values. Based upon these PK and clinical safety data, a pediatric RP2D of flotetuzumab of 500 ng/kg was selected. Next-generation CD123xCD3 bispecific antibody therapies in patients with relapsed/refractory AML are now under clinical investigation.

Key words: pediatric acute myeloid leukemia, flotetuzumab, bispecific antibody