PT-Cy. We show it is a safe regimen, with high engraftment rates, encouraging survival rates and very low grade III-IV aGVHD and extensive cGVHD rates despite relatively high T cell doses. The results from this relatively small number of mostly high-risk patients are encouraging and form basis for testing it in a larger cohort of patients.

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Plasma and Intracellular Population Pharmacokinetic Analysis of Fludarabine in Pediatric Allogeneic Hematopoietic Cell Transplant (alloHCT) Recipients

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Methods: A prospective study was conducted to characterize the pharmacokinetics (PK) of fludarabine plasma (f-ara-A) and intracellular triphosphate (f-ara-ATP) in children undergoing alloHCT and receiving fludarabine with their conditioning regimen. Plasma and peripheral blood mononuclear cells (PBMCs) were collected over the 3–5 days of fludarabine treatment for quantitation of f-ara-A and f-ara-ATP, respectively, using a validated liquid chromatography/tandem mass spectrometry assay. Nonlinear mixed effects modeling was used to develop the population PK model, including identification of covariates that influenced drug disposition.

Results: Fifty-four children (median age 2 years, range 0.25–17) undergoing alloHCT for a variety of malignant and nonmalignant disorders underwent PK assessments. A 2-compartment model with linear elimination best described the PK of f-ara-A while a third compartment representing PBMCs linked f-ara-A to f-ara-ATP. Final parameter estimates and relative standard errors for f-ara-A are as follows: clearance, 5.8 L/h (5.4%), volume of central compartment, 16.6 L (9.0%), volume of peripheral compartment, 16.6 L (5.8%), and intercompartmental clearance, 3.0 L/h (14.1%). Covariates significantly impacting f-ara-A clearance included body weight, age, and creatinine clearance (CrCl). Dose-normalized PK exposure was highest among very small, young children or subjects with renal dysfunction. Predicted f-ara-A clearance was reduced 40% in subjects with CrCl ≤ 50 mL/min compared to those with normal renal function (120 mL/min). Additionally, the rate of f-ara-A into PBMCs and/or transformation to f-ara-ATP (modeled with a first order rate constant) decreased over the course of therapy, resulting in 42% lower intracellular f-ara-ATP exposure following the third versus first dose.

Impact: These results will help inform better dosing strategies for fludarabine, particularly in young infants with small body size or in children with pre-existing renal dysfunction. Re-evaluation of the optimal dosing regimen for fludarabine is warranted given the decrease in intracellular exposure to f-ara-ATP with time.