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721. CLINICAL ALLOGENEIC TRANSPLANTATION: CONDITIONING REGIMENS, ENGRAFTMENT AND ACUTE TRANSPLANT TOXICITIES: POSTER II | DECEMBER 06, 2014

Pharmacokinetics of Fludarabine in Pediatric Hematopoietic Stem Cell Transplantation

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Abstract

Introduction: Fludarabine is a purine-analog which is effective for leukemic cells with lower toxicity. Thus it has been preferred for preparative regimens of hematopoietic stem cell transplantation (HSCT) recently. However, the pharmacokinetics of fludarabine in pediatric HSCT has not been studied before. This prospective study investigated the pharmacokinetics of fludarabine in children undergoing allogeneic HSCT, and attempted to establish the fludarabine administration in pediatric patients.

Patients and Methods: Forty-three pediatric patients undergoing HSCT were enrolled to the study. The median age was 11.8 years old (range 1.3–17.3), and there were 31 male and 12 female patients. Among the 43 patients, there were 15 acute lymphoblastic leukemia (34.9%), 12 acute myeloid leukemia (27.9%), 3 severe aplastic anemia (7.0%), 3 chronic granulomatous disease (7.0%), and 10 other diseases (23.3%). The preparative regimens included cyclophosphamide with fludarabine, busulfan with fludarabine, busulfan with fludarabine and etoposide, which was selected according to the disease and risk group. Fludarabine was administered as 40 mg/m^2/day i.v. over 30 minutes for 5 to 6 days, and the pharmacokinetic study was carried out at the first and last dose. Blood samplings were taken before administration and 0.5, 1, 3, 5, 8hr after the end of infusion. Fludarabine concentration was analyzed by high performance liquid chromatography-tandem mass spectrometry.

Results: Median (min-max) fludarabine area under the drug concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) of the first day of infusion was 4.64 (2.71-9.52) μg*h/mL, apparent clearance 10.9 (3.28-26.49) L/h, and C_{max} 1,222 (668-1,732) ng/mL. The $AUC_{0-\infty}$ was lower than previously reported $AUC_{0-\infty}$ of the adult study, but the median C_{max} was higher than the result of adult study. In this study, the range of AUC and C_{max} were narrower than those of adult data. When the AUC_{0-8hr} of day 1 and the steady state (day 5 or day 6) was compared, the fludarabine exposure at steady state was 1.21 fold higher than the first day.

In this study, the overall survival was 75.8%, and event-free survival was 60.9%. When grouped by median fludarabine AUC level, the high AUC group and low AUC group showed no significant difference in overall survival or relapse-free survival. Also, there was no significant difference in cumulative incidence of relapse or treatment-related mortality (TRM) between two groups. Neurotoxicity was observed in 5 patients (11.6%) and pulmonary toxicity was observed in 19 patients (44%). These toxicities were not significantly related to the level of fludarabine AUC.

Conclusion: In this study, the fludarabine $AUC_{(0-\infty)}$ and C_{max} was similar with adults, and the range was narrower. Thus fludarabine exposure is considered to be similar with adult, and the recommended dosing for adults can be applied to children. This is the first study to investigate the pharmacokinetics of fludarabine in pediatric HSCT. As fludarabine is being more widely adopted for the pediatric HSCT, this study could provide useful data for the treatment in pediatric patients.

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Disclosures

No relevant conflicts of interest to declare.

Author notes

*Asterisk with author names denotes non-ASH members.

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