Oral

[O27-4] O27-4: Oncology (2)

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[O27-4-2] Population pharmacokinetic modeling of alemtuzumab in pediatric patients undergoing allogeneic hematopoietic cell transplantation for non-malignant diseases

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Background

Alemtuzumab is a monoclonal antibody binding to CD52 and is a part of a commonly utilized reduced intensity conditioning with fludarabine and melphalan for allogeneic hematopoietic cell transplantation (HCT) for patients with non-malignant disorders. Our group recently recommended an optimal level of 0.2-0.4 g/mL for alemtuzumab on the day of transplantation (Day 0). This will minimize the risk of acute graft *vs.* host disease (GVHD) and development of mixed chimerism, and also lead to timely immune reconstitution post-transplant (Marsh *et al., Blood*, 2016). To establish a strategy to control the alemtuzumab concentration, we prospectively examined alemtuzumab pharmacokinetics (PK), and developed a population PK (PPK) model using these PK data.

Methods

Pediatric patients (n=17; 3.0-11.0 years; 16.2-58.9 kg), with non-malignant disorders, were prospectively enrolled in an intensive sampling PK study of alemtuzumab when they received alemtuzumab as a part of their preparative regimen. Alemtuzumab was subcutaneously administered daily for 5 days starting from Day -14 to -10 at a total dose of 1.0 mg/kg. Alemtuzumab plasma concentrations (at pre-dose, 30 minutes, and 8 hours after each dose, followed by daily levels until Day 0) were quantified by validated flow cytometry-based method. PPK analysis was performed using NONMEM. Bayesian estimation was conducted using MW/Pharm.

Results

Alemtuzumab level was highest on Day -8 and the mean terminal half-life was 5.2 days. Pre-transplant absolute lymph counts (ALC) in patients had a significant impact on alemtuzumab level at Day 0. A one-compartment model with first order absorption was found to adequately describe alemtuzumab PK. Model fit was significantly improved by including allometrically scaled body weight on clearance and volume of distribution ($p<0.01$). Bayesian estimation with the developed PPK resulted in well-predicted alemtuzumab concentration-time profiles in each patient.

Conclusions

This is the first study to develop a PPK model of alemtuzumab, after subcutaneous administration in pediatric transplant patients. Pre-transplant ALC was found to be a potential determinant of variability in alemtuzumab PK. The developed PPK model is being used to support the development of an individualized precision dosing strategy for these pediatric patients, which is now being evaluated in a prospective clinical study for

improvement of transplant outcomes.