Model-informed precision dosing for alemtuzumab in pediatric and young adult patients undergoing allogeneic hematopoietic cell transplantation

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Abstract

Aim: Alemtuzumab is a lymphodepleting monoclonal antibody utilized in conditioning regimens for allogeneic hematopoietic cell transplantation (HCT). A therapeutic range of 0.15-0.6 μg/mL on the day of transplantation is associated with better HCT outcomes. The purpose of this study was to characterize alemtuzumab population pharmacokinetic/pharmacodynamic (PK/PD) and to propose individualized subcutaneous dosing schemes to achieve this optimal level for pediatric patients. Methods: Alemtuzumab concentration and absolute lymphocyte count (ALC) profiles were obtained from 29 patients with non-malignant disorders undergoing HCT. PK/ PD analyses were performed using non-linear mixed effects modeling. Monte Carlo simulation was conducted to evaluate different improved dosing approaches. Results: A one-compartment model with sequential zero- and first-order absorption adequately described subcutaneously administered alemtuzumab PK. Model fit was significantly improved by including allometrically scaled body weight on clearance (0.080 L/h/70kg) and volume of distribution (17.4 L/70kg). ALC reduction following subcutaneous alemtuzumab was swift. An inhibitory Emax model best characterized the relationship between alemtuzumab concentration and ALC. Emax and EC50 were estimated as 1.18*103/μL and 0.045μg/mL, respectively. The currently used per kg dosing was found to cause uneven alemtuzumab exposure across different age and weight cohorts. Simulations indicated target achieving dose as allometry-based of 18 mg*(weight/70)0.75 or body surface area (BSA)-based of 10 mg/m2, divided over 3 days, with a potential individualized top-up dose; both of which yielded similar results. Conclusion: An allometry- or BSA-based starting dosing regimen in combination with individualized Bayesian PK estimation using concentration feedback is proposed for alemtuzumab precision dosing in children undergoing allogeneic HCT.

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