Poster

[P26-8] P26-8: Oncologic drugs (4): Pharmacokinetics, TDM practice

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[P26-8-9] Population pharmacokinetics analysis of busulfan in Japanese pediatric and adult HCT patients

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Background

Busulfan is the most common chemotherapy agent used in allogeneic hematopoietic cell transplant (HCT) conditioning regimens. As considerable inter-patient variability exists in the effectiveness and toxicity of conditioning regimens including busulfan, personalizing IV busulfan therapy is desirable. Population pharmacokinetic-based approaches have been applied to therapeutic drug monitoring for the purpose of personalizing therapy. Population pharmacokinetic analysis with the objective of personalizing therapy in Japanese patients was conducted by integrating pediatric patient data with adult patient data.

Methods

The data used for analysis was from 54 patients who received four times-daily dosing with IV busulfan in a phase 2 trial and a postmarketing clinical trial. Of the 54 patients, 28 were pediatric patients (median age: 7.2 years, range: 0.3 - 17.7 years).

McCune’s model (Clin Cancer Res; 20, 754, 2014) was used for the analysis. McCune’s model is a 2-compartment model that includes maturation of clearance and allometric scaling of clearance and volume of distribution. To fit C_{max} correctly, lag-time was also included in the model. Since the pediatric data in the dataset for age under 2 years were limited, only key pharmacokinetic parameters were estimated and other parameters were fixed to McCune’s results.

Analysis was performed using the nonlinear mixed-effects modelling software NONMEM VII with ADVAN subroutines and first-order conditional estimation.

Results

The estimated parameters were similar to McCune’s results and no racial differences in busulfan pharmacokinetics were observed. The model could precisely describe the Japanese data. The diagnostic plots, VPC, and nonparametric bootstrap results showed the validity of the analysis. The plasma concentrations for once-daily dosing were simulated using the model, and except for the 4.8 mg/kg dose groups, the predicted busulfan concentrations were within the therapeutic range.

Conclusions

McCune’s model could be successfully applied to the Japanese data. This model would be useful for personalizing IV busulfan therapy in Japanese patients.