

A population pharmacokinetic model of methotrexate in Korean patients with hematologic malignancy

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Abstract

Aim: This study was conducted to develop a population pharmacokinetic (PK) model of methotrexate in Korean patients with hematologic malignancy, identify factors affecting methotrexate PK, and propose optimal dosage regimen for the Korean population. **Methods:** Data were retrospectively collected from 188 patients with acute leukemia or non-Hodgkin's lymphoma who were admitted to Severance Hospital for the period from 2005 to 2015. Using demographic factors and laboratory results as potential covariates for PK parameters, model development was performed using NONMEM and optimal dosing regimens were developed using the final PK model. **Results:** A two-compartment model incorporating body weight via allometry best described the data, yielding typical parameter values of 25.99L for central volume of distribution (V_{1}), 18.76L for peripheral volume of distribution (V_{2}), 12.9L/h for clearance (CL) and 0.646L/h for inter-compartmental clearance. Covariate analyses showed that, at the weight of 50kg, CL decreased by 0.11 L/h for each one-year increase in age above 14 years old and decreased to 0.8-fold when serum creatinine level doubled, indicating the importance of age-specific dose individualization in methotrexate treatment. Volume of distribution at steady state derived from PK parameters ($=V_{1}+V_{2}$) was 0.90L/kg, which was similar to those in the Western or Chinese population. Optimal doses simulated from the final model successfully produced the PK measures close to the target chosen. **Conclusion:** The population PK model and optimal dosage regimens developed in this study can be used as a basis to achieve precision dosing in Korean patients with hematologic malignancy.

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