Systematic review of population pharmacokinetic analyses of imatinib and relationships with treatment outcomes

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Abstract

Several population pharmacokinetic (PPK) analyses of the anticancer drug imatinib have been performed to investigate different patient populations and covariate effects. The present analysis offers a systematic qualitative and quantitative summary and comparison of those. Its primary objective was to provide useful information for evaluating the expectedness of imatinib plasma concentration measurements in the frame of therapeutic drug monitoring. The secondary objective was to review clinically important concentration-effect relationships to provide help in evaluating the potential suitability of plasma concentration values.

Nine PPK models describing total imatinib plasma concentration were identified. Parameter estimates were standardized to common covariate values whenever possible. Predicted median exposure (C_{min}) was derived by simulations and ranged between models from 555 to 1388 ng/mL (grand median: 870 ng/mL and interquartile “reference” range: 520–1390 ng/mL). Covariates of potential clinical importance (up to 30% change in pharmacokinetic predicted by at least 1 model) included body weight, albumin, α1 acid glycoprotein, and white blood cell count. Various other covariates were included but were statistically not significant or seemed clinically less important or physiologically controversial. Concentration–response relationships had more importance below the average reference range and concentration–toxicity relationships above.

Therapeutic drug monitoring–guided dosage adjustment seems justified for imatinib, but a formal predictive therapeutic range remains difficult to propose in the absence of prospective target concentration intervention trials. To evaluate the expectedness of a drug concentration measurement in practice, this review allows comparison of the measurement either to the average reference range or to a specific range accounting for individual patient characteristics. For future research, external PPK model validation or meta-model development should be considered.

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