

POPULATION PHARMACOKINETIC MODELING OF FLAVOPIRIDOL IN CLL PATIENTS

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Flavopiridol, a novel anticancer agent, is currently in phase I/II clinical development for the treatment of a variety of cancer. We utilized pharmacokinetic modeling to develop a 4.5 hr IV infusion strategy with a 30 mg/m² loading dose delivered in the first 0.5 h and an equal or increased dose delivered over the following 4 h to achieve target plasma concentrations of 1.5 to 2.0 µM. This strategy was employed in a phase I study for single agent treatment of CLL. Blood samples were collected from a total of 41 CLL patients at 0.5, 4, 6, 8, 12, 18, 24, 32, and 48 h after initiation of short infusion. Drug concentrations in plasma fractions were quantified using LC/MS/MS analysis developed and validated in our laboratory. Individual pharmacokinetic analysis was performed using WinNonlin. The plasma concentration-time profiles were best described using a two-compartment model with elimination from the central compartment. Population pharmacokinetic analysis was performed by nonlinear mixed-effect modeling using NONMEM to estimate the mean population pharmacokinetic parameters, including clearance and volume, and interindividual variabilities of the pharmacokinetic parameters, and find influences of demographic covariates on them. An error model was constructed using an exponential error model to account for interindividual variability and a proportional residual error model to account for intraindividual. Flavopiridol CL and V were estimated to be 59.2 L/h/m² and 15.7 L/m² with interindividual coefficients of variation (CV) of 32.2% and 16.5%, respectively. The intraindividual CV was estimated at 49.1%. Influence of covariates on the pharmacokinetic parameters (i.e., CL and V) is visualized using Xpose module in S-PLUS, and construction of covariate models is underway.