Pharmacokinetics of Flavopiridol Using Bolus or Hybrid Administration Schedules in the Treatment of Acute Leukemias

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Objectives: To characterize the pharmacokinetics of total and unbound flavopiridol administered using either a bolus or a hybrid schedule (bolus followed by a 4-hour infusion); the latter designed to overcome flavopiridol plasma protein binding [1].

Methods: Data from 129 patients enrolled in a Phase 1 (49 patients/hybrid schedule) and two Phase 2 (48 patients/hybrid schedule; 32 patients/bolus schedule) FLAM studies (sequential flavopiridol, ara-C, and mitoxantrone) were used for modeling. Bolus flavopiridol administration consisted of 3 consecutive days of 1 hour IV bolus dosing at 50 mg/m². Hybrid flavopiridol administration consisted of 3 consecutive days of 0.5 hour IV bolus dosing followed by a 4 hour IV infusion with a range of doses explored (mg/m² for bolus:infusion): 20:30, 25:35, 30:40, 30:50, 30:60, and 30:70. Standard population PK methods were used to simultaneously fit the total and unbound flavopiridol concentrations from all 3 studies. A full model approach was used to assess the limited covariate information (body surface area, age, and sex) for explanatory ability.

Results: A 2-compartment model for total flavopiridol with mixed proportional and additive residual variability adequately described the typical and individual profiles. The population estimates of CL, V, Q and V² were 37.8 L/hr, 78.7 L, 9.68 L/hr and 102 L, respectively. A fraction-unbound parameter to account for unbound flavopiridol was estimated to be 11.2%. Plasma binding of flavopiridol was found to be linear/unsaturable. No covariates were found to have a clinically important effect on the PK parameters.

Conclusions: The pharmacokinetics of flavopiridol have been adequately characterized across studies, doses, and administration schedules facilitating future work to assess relationships between exposure and response.

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