Population Pharmacokinetics of Sorafenib in Acute Myelogenous/B-Type Leukemia Patients

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Objectives: To characterize the pharmacokinetics of sorafenib administered using an intermittent dosing regimen, given cyclically to improve the safety and efficacy of patients with Acute Myelogenous Leukemia (AML).

Methods: Data from 15 patients with leukemia given 400mg or 600mg BID oral administration of sorafenib were analyzed using QRPEM algorithm in Phoenix NLME v1.4. Different absorption models were evaluated. Body weight, age, gender, prior therapy and baseline disease status were explored as potential covariates. Bound and unbound plasma concentration were modeled simultaneously using an unbound fraction parameter.

Results: A one-compartment model with transit absorption compartment and enterohepatic re-circulation successfully described the PK profile in leukemia patients. A transit absorption model performed better than a standard lag time model. Body weight was modeled as covariate on both volume of distribution and clearance using an Allometric scaling approach. The pharmacokinetic model parameter estimates for a 70 kg patient were CL/F = 6.4 L/hr, V/F = 166 L and Mean Transit Time (MTT) = 1 hr. The estimated unbound fraction was 1.8 %. No other covariates contributed to the pharmacokinetic variability.

Conclusions: The estimated pharmacokinetic parameters for patients in AML were consistent with those previously published in solid tumor patients and existing knowledge in sorafenib pharmacokinetics. These results will be used to understand the relation between exposure and safety in this new intermittent cyclic regimen in AML patients.

Reference: