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

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Objectives: To characterize the pharmacokinetics and pharmacodynamics of sorafenib in patients with Acute Myelogenous Leukemia (AML) and to optimize the dosing regimen in further clinical trials.

Methods: Sorafenib and its N-oxide metabolite plasma concentration and FLT3/ERK activity from 15 patients with leukemia given 400mg or 600mg BID oral administration of sorafenib were analyzed using sequential PKPD approach in Phoenix NLME v1.4. Sorafenib structural PK model was adopted from a previous publication. Bound and unbound plasma concentrations were modeled simultaneously using an unbound fraction parameter. A one-compartment model of the N-oxide metabolite was added to the parent drug model. The relationship between sorafenib exposure and FLT3/ERK activities were described by Emax model. Different dosing regimens (200mg BID and 400mg BID) were simulated based on the PK/PD relationship.

Results: A one-compartment model with transit absorption compartment and enterohepatic recirculation successfully described the PK profile in leukemia patients. Body weight was modeled as a covariate on both volume of distribution and clearance using an Allometric scaling approach. Sorafenib could inhibit FLT3 activity by 100% with an IC50 of 133.7ng/mL and ERK activity by 90% with an IC50 of 169.6ng/mL.

Conclusions: 200mg BID dosing regimen showed similar FLT3 and ERK inhibitory activity at steady state compared to 400mg BID which is the approved dose for patients with hepatocellular carcinoma or renal cell carcinoma.

References: