Bench-to-Bedside Translation of Everolimus Efficacy in Hepatocellular Carcinoma Using a Multiscale Quantitative Systems Pharmacological Approach.

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Objectives: Dysregulation of mTOR pathway is common in hepatocellular carcinoma (HCC). A bench-to-bedside quantitative systems pharmacology (QSP), pharmacokinetic (PK) and pharmacodynamic (PD) model dissecting the circuitry of this pathway was developed to predict HCC patients’ response to everolimus, an mTOR inhibitor.

Methods: The time course of key signaling proteins in the mTOR pathway, HCC cells viability, tumor volume (TV) and everolimus plasma and tumor concentrations in xenograft mice, clinical PK of everolimus and progression free survival (PFS) in placebo and everolimus-treated patients were extracted from literature1-3. The final preclinical QSP/PK/PD model integrated indirect response, transduction, minimal physiologically-based PK (PBPK), Gompertz, and cell-cycle specific arrest models. Clinical translation was performed through model-based simulations using a clinical hybrid-PBPK model with everolimus tumor concentrations driving the dynamics of intracellular signaling proteins, which in turn drove the TV time trajectory and PFS. Model fittings and simulations were performed using Monolix and ADAPT5.

Results: The S6-Kinase protein was identified as critical in the mTOR signaling pathway for everolimus efficacy in HCC patients. The net growth rate constant (kg) of HCC cells was estimated at 0.019hr⁻¹ (2.88 %SEM). The partition coefficient of everolimus into the tumor was determined at 0.06 (13.32 %SEM), and kept identical in the clinical hybrid-PBPK model to predict everolimus tumor concentrations in HCC patients. The value of kg in patients was calculated from the doubling time of TV in naturally progressing HCC patients and was 0.004day⁻¹. The model-predicted PFS were in good agreement with observed PFS for placebo and everolimus-treated patients (Fig.1).

Conclusions: A multiscale QSP/PK/PD model for everolimus efficacy in HCC patients was successfully developed and predicted PFS reasonably well compared to observed clinical findings. This model could provide insights into clinical response to everolimus-based therapy and serve as a valuable tool for bench-to-bedside translation of novel small molecule inhibitors.