A Combined Biological and Mathematical Approach for Modeling the PK-PD of the Anticancer Drug Irinotecan - Focus on Acquired Resistance and Circadian Rhythms at the Cell Population Scale

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15th December 2008

Irinotecan is an anticancer drug which is currently in use for chemotherapy against colorectal cancer. Here we are interested in the molecular mechanisms occuring within a cell population after Irinotecan exposure. We attempt to mechanistically model Irinotecan Pharmacokinetics(PK),which is what the cells do to the drug (e.g. metabolization, transport), and Pharmacodynamics(PD), which is what the drug does to the cells (e.g. DNA damage).

Experiments on Caco-2 cells (human epithelial colorectal adenocarcinoma cells) have been performed in order to jointly study the influence of acquired resistance and circadian rhythms on Irinotecan Pharmacokinetics-Pharmacodynamics. At the same time, we have built a deterministic ODE-based mathematical model which parameters are fitted to the experimental data obtained on Caco-2 cells.

The experiments have shown evidence for a decrease in the intracellular accumulation of Irinotecan over time: the intracellular concentration increases until 12 hours of exposure and then decreases until 48 hours of exposure. We are currently investigating the hypothesis of an increased drug efflux due to the induction of ATP-Binding-Cassette(ABC) transporters (in particular Pgp).

The PK-PD of Irinotecan is also largely influenced by the circadian rhythms of proteins (in particular those of the drug target Topoisomerase I and of the deactivation enzyme UGT1A1), whose mRNA level (and probably protein amount and activity) vary over a 24-hour period both in vivo and in cultured cells.

Taking into account the possible resistance and the circadian control of relevant pharmacologic pathways, we use the mathematical modeling to theoritically optimize the schedule of cell exposure to Irinotecan.

This study at the cell population scale may then be integrated into a Whole-Body approach leading to potential improvements in the administration of Irinotecan to patients.