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A Combined Experimental and Mathematical Approach for Molecular-based Personalization of Irinotecan Circadian Delivery

Irinotecan is an anticancer drug which is currently in use for chemotherapy against colorectal cancer. Its pharmacokinetics (PK- what the cells do to the drug, e.g. metabolization, transport), and pharmacodynamics (PD- what the drug does to the cells, e.g. DNA damage) are largely influenced by 24-hour-period rhythms of certain proteins including the drug target Topoisomerase I, the activation enzymes (Carboxylesterases), the deactivation enzymes (UGT1A1,UGT1A9) and the ABC transporters which are responsible for the efflux of the drug. Indeed circadian rhythms have been described for most of those proteins both in humans and in mice. A chronomodulated scheme of administration for Irinotecan is already used in clinic but recent findings highlight the need of personalized chronotherapeutics delivery pattern according to the patient gender and genetic background ([1]). Within the European project TEMPO, Irinotecan chronotoxicity has been studied in mice and three classes have been determined with regards to Irinotecan best circadian hour of administration (i.e. the hour which induces the minimal toxicity). Our modeling approach aims at identifying molecular biomarkers which could discriminate between the classes and at designing optimal chronomodulated infusion scheme for each of them. A whole body physiologically-based PK-PD model has been built starting from a previous mathematical model designed thanks to a cell culture study ([2]) . Parameters have been estimated for each mouse class by fitting available data on tissular PK for two different circadian hours of administration and on circadian rhythms of relevant proteins. Validation of the mathematical model by comparing its output with independent experimental data is in progress. Then the parameter set will be compared in order to find differences between the classes and optimization algorithms will be applied to the model to design theoretically optimal chronomodulated scheme of administration. This study in mice may give a hint for determining molecular biomarkers which should be measured in patients in order to tailored chronomodulated infusion schemes.

1.Lévi F, Okyar A, Dulong S, Innominato PF, Clairambault J., Circadian timing in cancer treatments, Annu Rev Pharmacol Toxicol. 2010;50:377-421. 2.Ballesta A, Dulong S, Abbara C, Cohen B, Okyar A, Clairambault J et al. A combined biological and mathematical approach to study the anticancer drug Irinotecan molecular pharmacokinetics-pharmacodynamics and their control by the circadian clock, under revision.