New model to Gemcitabin and its metabolites

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INTRODUCTION AND OBJECTIVE

Gemcitabine is a prodrug with proved efficacy in different tumors as lung or pancreas cancer. It is intracellulary actived to bi- and triphosphate metabolites that inhibit processes required for DNA synthesis. Up to now there is not a proper model to fit simultaneously the parent drug and its metabolites. The optimization of this new model could improve clinic therapy with gemcitabine.

METHODS

Analyses were performed with a mixed-effect pk model using NONMEM (Version V, level 1.1). Kinetics of Gemcitabine and its metabolites dFdU and dFdCTP was described using standard compartmental models. The plasma samples were obtained from 64 cancer patients in treatment with fixed-rate infusion of gemcitabine distributed in six cohorts with different times of infusion. Model discrimination was based on the minimum value of the objective function and visual inspection of the goodness of fit plots.

RESULTS

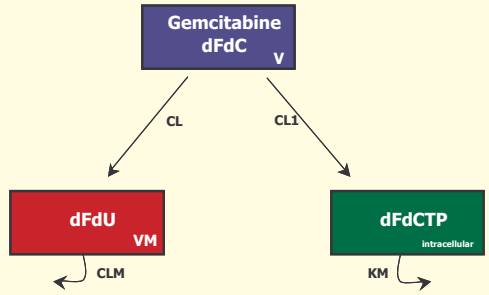
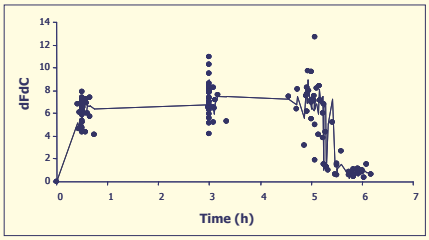


Figure 1. Schematic representation of the pharmacokinetic model developed.

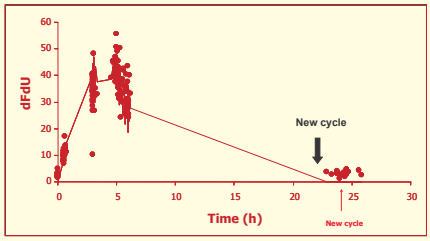
Table I: Population pharmacokinetics parameters of Gemcitabine and its metabolites

V(L)	45
CL (L/h)	100
CL1 (L/h)	150
CL_M (L/h)	25
V_M (L)	37
K_M (mg/L)	10
V_{MAX} (mg/h)	60

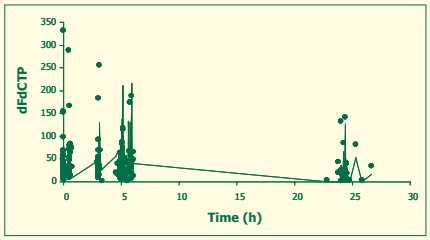
V, apparent volume of distribution of parent drug; CL, first-order rate of formation of dFdU; CLM, first-order rate of elimination of dFdU; VM, apparent volume of distribution of dFdU; CL1, first-order rate of formation of dFdCTP; KM, Michaelis -Menten constant



2a



2b



2c

Figure 2: Concentration-time profiles derived from fitting model for gemcitabine (2a), deoxidifluorouridine(2b) and gemcitabine triphosphate (2c)

CONCLUSIONS

- The monocompartmental model of gemcitabine with Michaelis-Menten kinetics of elimination for thiphosphate metabolite, described above, allows a optimal adjustment of gemcitabine and its two main metabolites concentrations.

- The new model proposed contributes significantly to the optimization of the adjustment of the concentrations of the three compounds relieving the limitations of the traditional model(with first-order kinetics of elimination for dFdU and without considering the triphosphate). Therefore, the application of this new model could be a significant improvement in the clinical managing of this cytostatic drug because a limit step of efficiency of gemcitabine is the saturation in the formation of the dFdCTP metabolite.