PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS OF GEMCITABINE IN PANCREATIC CANCER IN MICE

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BACKGROUND

Gemcitabine is a nucleoside antimetabolite anticancer pro-drug that shows activity against several solid tumours. It is approved as a single agent in pancreatic cancer. Gemcitabine has been chosen as model drug to build a translational approach from early (preclinical) to advanced (clinical) stages in drug development as a part of pillar 3 of working package I (models in oncology) within the IMI7 founded project, Drug Disease Models Resource (DDMoRe).

The aim of this study is to develop a tumour growth-response model to describe the effects of gemcitabine in a xenograft model of pancreatic cancer.
As a next step, model parameters will be used to establish the translational/multi-scale model.

METHODS

Information related to tumour growth was obtained from eleven studies where Gemcitabine was given as a single agent i.p or p.o to athymic and CD1 nude mice (n=211) inoculated with different human derived pancreatic tumor cell lines (KP4, ASPC1, MIA PACA2, PANC1 and BXPC3). Tumour volume (mm^3) was measured every three or four days.

Tumour volume versus time data were fit using the population approach with NONMEM 7.2

PK parameters were extracted from a PK tricompartimental model developed by Eli Lilly, the metabolite part of the model was not taking into consideration. Typical PK profiles of gemcitabine were used to describe drug response.

PHARMACOKINETICS

Table I. Pharmacokinetics parameters. Eli Lilly Model

PK PARAMETERS					
V (L/kg)	CL (L/day/kg)	V2 (L/kg)	Q2 (L/day/kg)	V3 (L/day/kg)	Q3 (L/day/kg)
0.281	60	0.411	117.6	5.35	18.408

PHARMACODYNAMICS

Table II. Tumour growth studies divided by cell line.

KP4	ASPC1	MIA PACA2	PANC1	BXPC3
Control	Control	Control	Control	Control
Gem IP 15 mg/kg Q3dx4 (days:16,19,22, 25)	Gem P0 15 mg/kg Q3dx4 (days:18,21,24,27)	Gem IP 60 mg/kg Q3dx4 (days:28,31,34,37)	Gem IP 30 mg/kg Q3dx4 (days:28,31,34, 37)	Gem IP 60 mg/kg Q7dx2 (days:33, 40)
Gem IP 30 mg/kg Q3dx4 (days:16,19,22, 25)	Gem IP 30 mg/kg Q3dx4 (days:18,21,24,27)	Gem IP 60 mg/kg Q7dx3 (days:20,27,34)	Gem IP 80 mg/kg (s6) Q3dx4 (days:63,66,69, 72)	
Gem IP 50 mg/kg Q3dx4 (days:15,18,21, 24)		Gem IP 60 mg/kg Q7dx3 (days:24,31,38)		
		Gem IP 200 mg/kg Q7dx4 (days:22,29,36,43)		

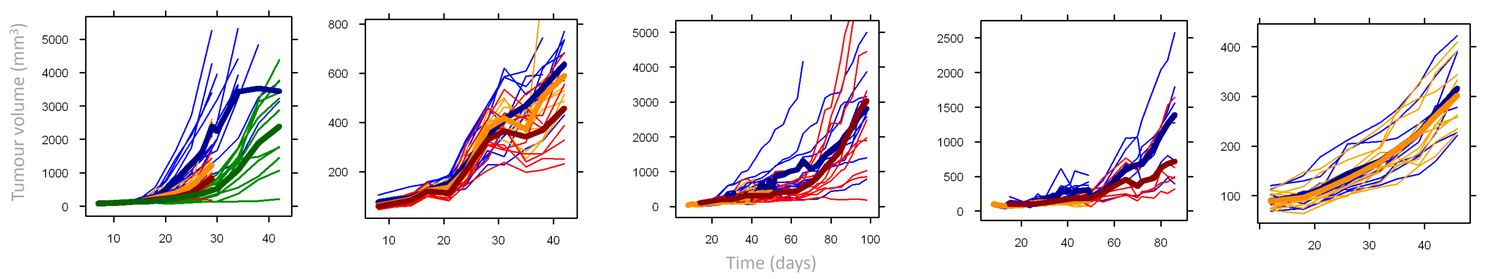


Figure I. Tumour growth by cell line. Individual (thin) and mean profile (thick line)

RESULTS

The model for tumour growth[1] and its corresponding parameters were found to be cell-line specific. Briefly, either nutrients supply or vasculature (K) are needed to allow tumour (T) growth. The cell lines KP4, ASPC1 and PANC1 show a first decrease in their tumour volume, explained by an initial lack of nutrients (lower K_0). Besides, PANC1 cell line has slower and oscillatory growth compared to the other cell lines. The model explains this oscillatory behaviour with the tumour volume/vasculature rate.

Preliminary analysis of data from the active treatment groups reveals that gemcitabine exerts its tumour effects promoting apoptosis as well as decreasing the source of nutrients in all cell lines except in BXPC3, where no drug effect could be quantified. The model well captured the delayed tumour shrinkage observed with respect to time of dosing with transit compartments.

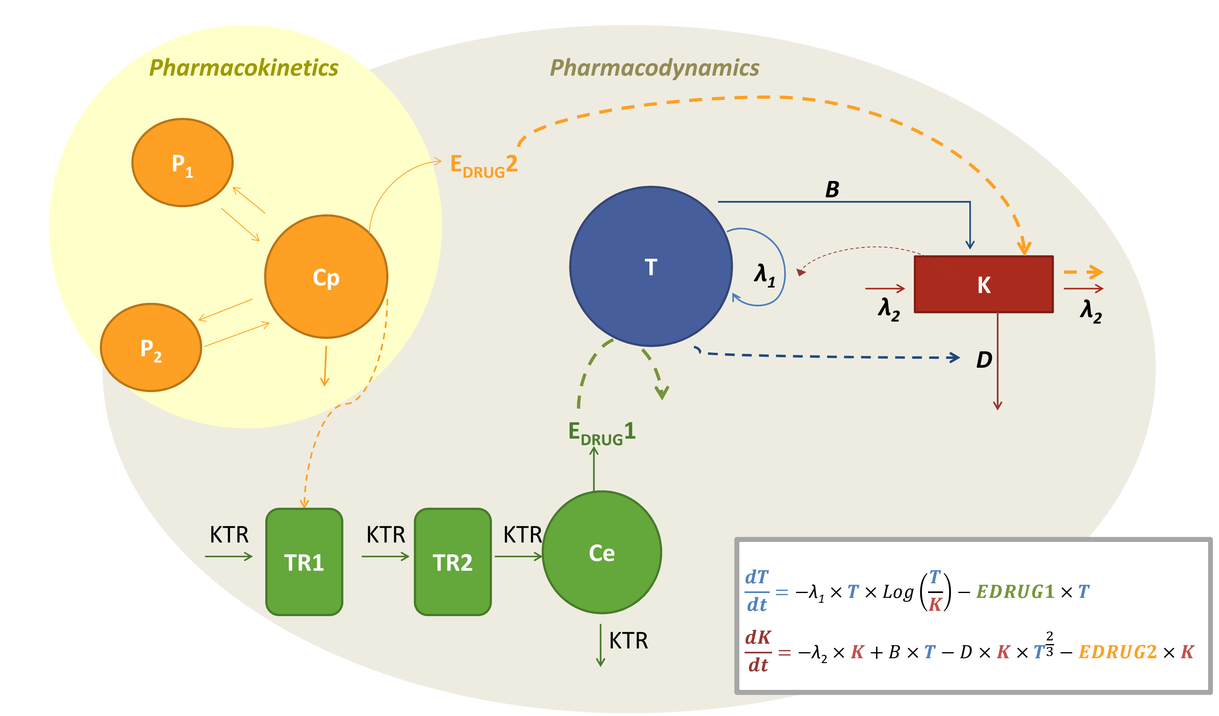


Figure II. Tumour growth PKPD model.
Cp: Plasma concentration. P1 and P2 peripheral compartments. TR1 and TR2, transit compartment between plasma concentration and effective concentration. Ce, effective concentration. T, tumour volume. λ1, tumour proliferation rate. K, carrying capacity or vasculature . λ2, carrying capacity elimination rate constant. B, stimulatory capacity of the tumor upon the inducible vasculature. D, endogenous inhibition of previously generated vasculature. SLOPE, drug effect constant.

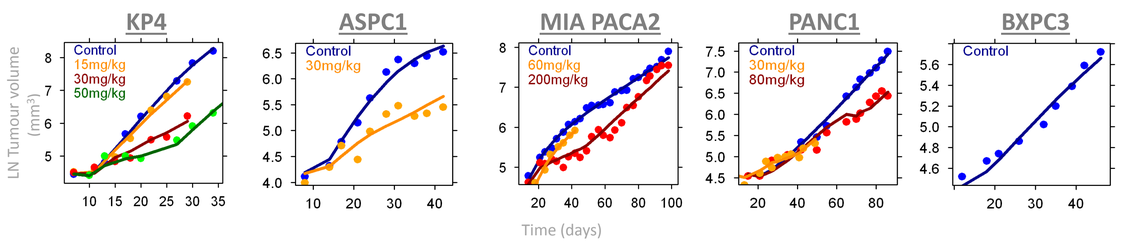
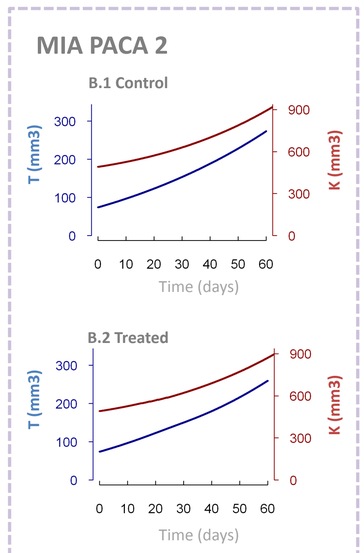
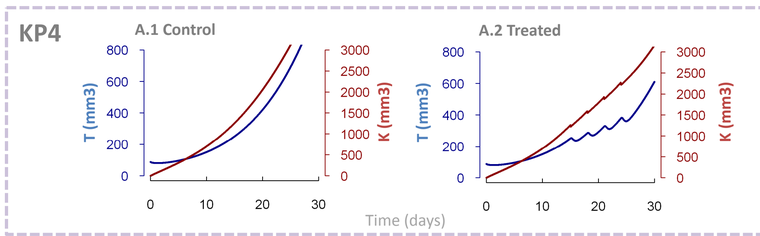


Figure III. Individual Tumour growth profile. Observation VS Prediction

Table III. Estimated model parameters.

PARAMETER	CELL LINE KP4	ASPC1	MIA PACA2	PANC1	BXPC3
T_0 (mm^3)	$8.7x10^2$	$7.47x10^1$	$7.4x10^1$	$9.7x10^1$	$8.42x10^1$
K_0 (mm^3)	$1.13x10^{-2}$	$3.86x10^1$	$4.91x10^2$	$3x10^{-5}$	$8.55x10^1$
λ_1 (day^{-1})	$1.48x10^{-1}$	$1.82x10^{-1}$	$3.45x10^{-2}$	$2.52x10^{-2}$	$2.07x10^{-1}$
B (day^{-1})	$7.73x10^{-1}$	$2.98x10^{-1}$	$1.47x10^{-2}$	$3.08x10^{-1}$	$8.24x10^{-2}$
D ($day^{-1}mm^{-2/3}$)	$1.2x10^{-3}$	$3.1x10^{-3}$	0	0	$8.5x10^{-4}$
λ_2 (day^{-1})	0	0	0	0	0
w(mm^3)	$1.73x10^{-1}$	$1.49x10^{-1}$	$1.81x10^{-1}$	$2.46x10^{-1}$	$1.26x10^{-1}$
IIV_λ_1 (%)	31	35	79	34	88
IIV_T_0 (%)	9	15	44	14	-
IIV_K_0 (%)	14	29	85	20	-
SLOPE (mg/L)	$4.2x10^{-1}$	$1.86x10^{-1}$	$3.26x10^{-2}$	$1.47x10^{-1}$	-
KTR (day-1)	5.02	$1.8x10^{-1}$	$1.93x10^{-1}$	$1.52x10^1$	-
IIV_*SLP* (%)	28	45	28	40	-
IIV_*KTR* (%)	19	10	90	26	-





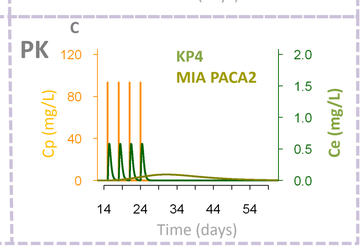


Figure IV. Simulation of Tumour (T) and Carrying capacity (K) growth without perturbation(1) and after receiving 30 mg/kg of Gemcitabine on days 15, 18, 21 and 24 after cell inoculation (2) on KP4(A) and MIA PACA2(B) cell lines . Plot C represents the PK simulation.

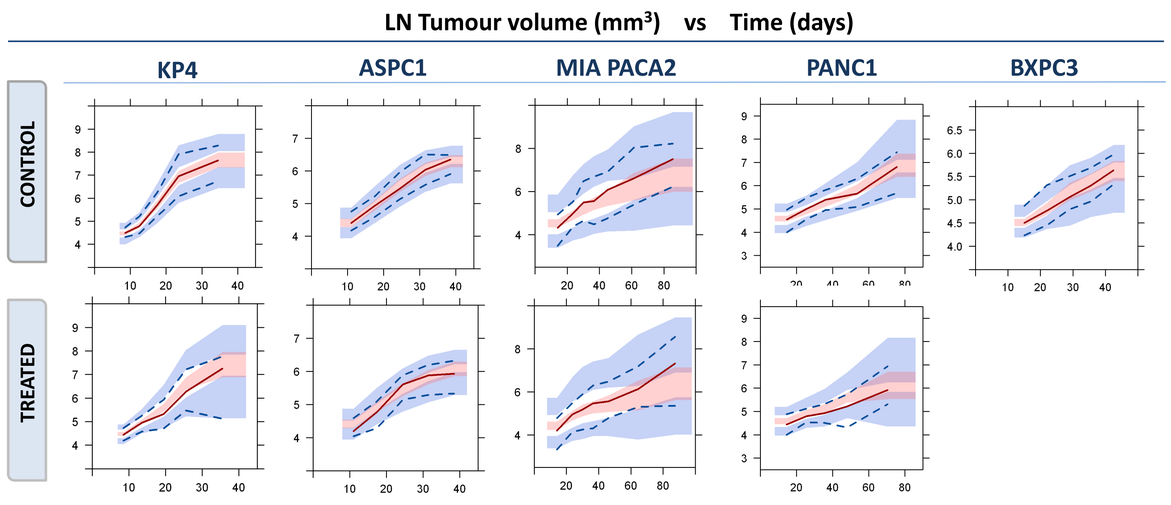


Figure IV. Model evaluation. Prediction corrected Visual Predictive Check.

CONCLUSIONS

A semi-mechanistic PK/PD model for different pancreatic cancer cell lines in xenograft models has been developed. Angiogenesis process was considered in the course of tumour growth. Correlation between parameters is currently being explored.

A modelling/simulation exercise to relate tumour drug response descriptors to the outcome from already performed clinical trials, has been started.

References

[1] Hahnfeldt P et al. Cancer Res 1999; 59(19):4770–5.

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