Evaluating the Influence of Different Sources of Variability in the PK/PD Tumor Growth Inhibition Model

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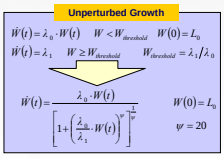
ABSTRACT

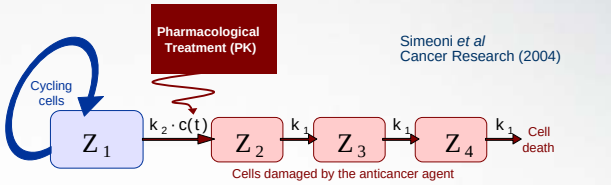
Objectives: Generally, the estimate of the in vivo effect of anticancer compounds is based on the evaluation of the changes in the average tumor growth profiles in treated versus untreated group of 8-10 animals. We recently developed a simple and effective pharmacokinetic-pharmacodynamic model linking the plasma concentrations of anticancer compounds to the effect on the tumor growth [1]. The model has been successfully applied to many different drugs and cell lines, showing also a good predictivity of the expected activity of the tested compounds in the clinics [2]. Essentially, the model describes the system as the interaction of three major processes: the unperturbed tumor growth in untreated animals (representing the biological system), the action of the drug on the tumor growth (representing the pharmacological part of the system) and the pharmacokinetics (PK) of the tested compound. The aim of this communication is to explore and discuss the different sources of variability affecting the response of the system in terms of PD data.

Methods: Different sets of experimental data were considered. For each tested compound the inter-animal variability of the PK and the tumor growth PD parameters was estimated through the variance-covariance matrix of parameters derived from individual fittings. The influence of these different sources of variability was investigated analysing series of simulated tumor growth profiles and comparing them with the observed individual data.

Results and Conclusions: The Monte Carlo simulations based on the PK/PD model, through its parameters, allowed to identify and assess the contribution of the different processes to the overall behavior of the system. The simulated tumor growth profiles in treated animals indicate the biological process (represented by the parameters modeling unperturbed tumor growth) as the major factor influencing the variability of the system response. These analyses are expected to prove particularly useful for the subsequent development of a comprehensive population approach.

MATERIALS AND METHODS





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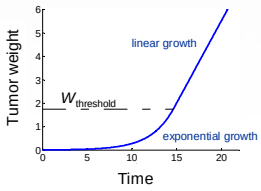
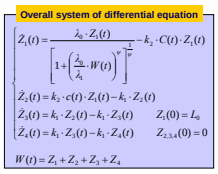




Usually the PK-PD parameters of the TGI model are obtained applying the model to the average tumor growth (TG) curves. For the aim of this study the individual tumor growth observations in the control groups were considered and corresponding $L_{0,i}$, $\lambda_{0,i}$ and $\lambda_{1,i}$ parameters (i = 1,…,8) estimated. Drug effect parameters (k_1 and k_2) were estimated using the standard approach.

Pharmacological experiments testing the activity of two compounds on A2780 tumor-bearing mice were considered: a known anticancer drug (Paclitaxel) given at 30 mg/Kg i.v. bolus q4dx3 and a candidate drug (Drug X) given at 45 mg/kg 10 i.v. bolus daily. Individual PK parameters were derived from ancillary groups of animals (12 for Paclitaxel, 4 for Drug X) using a two comp. open model. A Global Two Stage (GTS) iterative algorithm was applied to obtain the population parameters vector and the covariance matrix for both PD (L_0, λ_0, λ_1) and PK (V, k_{10}, k_{12}, k_{21}) parameters. Based on these variance-covariance matrices, for each compound, fixing the estimated values of k_1 and k_2, 200 tumor growth curves were generated assuming multivariate log-normal distribution of the PK parameters and normal distribution (except L_0) of the PD control parameters. The generated curves were then compared with the observed tumor weights using the 5th and 95th percentiles. In panel A only the PK parameters are randomly extracted, in panel B only the PD control parameters, in panel C both PK and PD control parameters are extracted.

RESULTS

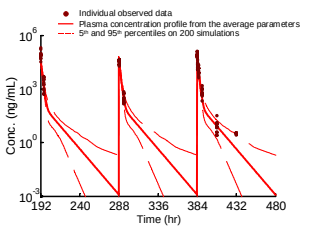
Paclitaxel

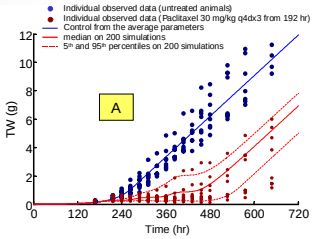
Observed data, median, 5th and 95th percentiles time points derived from 200 Monte Carlo simulations. In the first figure observed plasma concentration data and simulated PK profiles are presented. In panel A, B and C the expected tumor growth curves in control and treated groups are represented.
The pharmacological drug-effect related parameters were previously estimated and fixed at k_1 = 0.0403 1/h and k_2 = 2.62 e-5 mL/ng/h as reported in [1,2].

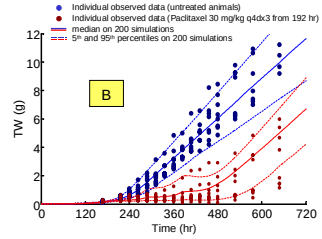
Average and CV% values of the PK and PD control parameters.

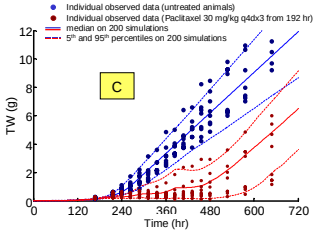
		unit	mean	CV%	mean *	CV% *
PK parametes	V	mL	699.9	32.9	695.7	23.9
	k10	1/h	0.910	16.4	0.853	9.4
	k12	1/h	0.038	109.1	0.022	83.9
	k21	1/h	0.219	231.0	0.144	55.5
PD parameters	λ_0	1/h	0.022	18.9	0.021	16.8
	λ_1	g/h	0.024	16.0	0.024	14.5
	L0	g	0.0049	100.5	0.0049	75.4

(*) Incorporation of the uncertainty of estimation

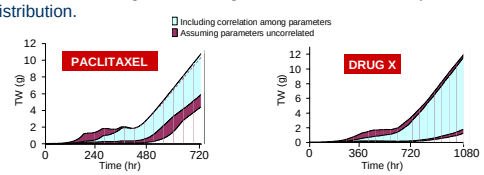






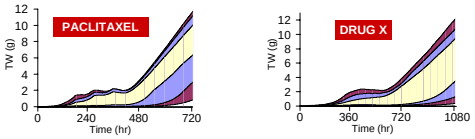


Reduction in the variability of the TG response including the covariance terms in the multivariate distribution. TG curves generated including or excluding these terms in the PD parameter distribution.



Changes in the variability of the TG response considering different CV% values of the PD control parameters (covariance terms were ignored).

parameter	CV%		
Lambda0	10	20	30
Lambda1	10	20	30
L0	25	50	75



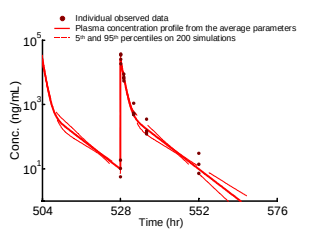
Drug X

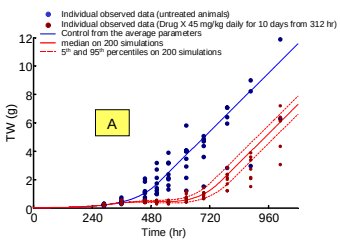
Observed data, median, 5th and 95th percentiles time points derived from 200 Monte Carlo simulations. In the first figure observed plasma concentration data and simulated PK profiles are presented. In panel A, B and C the expected tumor growth curves in control and treated groups are represented.
The pharmacological drug-effect related parameters were fixed at k_1 = 0.0284 1/h and k_2 = 1.03 e-5 mL/ng/h, estimated from the simultaneous fitting of the average control and treated data.

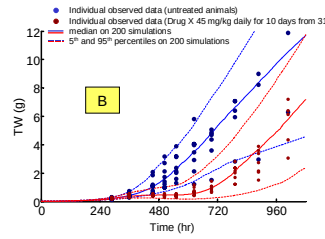
Average and CV% values of the PK and PD control parameters.

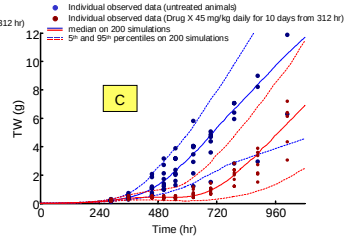
		unit	mean	CV%	mean *	CV% *
PK parametes	V	mL	1537.8	37.5	1672.6	19.1
	k10	1/h	1.22	21.3	1.11	10.6
	k12	1/h	0.223	60.1	0.171	35.8
	k21	1/h	0.230	35.7	0.213	17.6
PD parameters	λ_0	1/h	0.00970	21.2	0.00962	18.4
	λ_1	g/h	0.0181	43.0	0.0172	37.8
	L0	g	0.0145	53.0	0.0143	41.6

(*) Incorporation of the uncertainty of estimation









CONCLUSIONS

The impact of the variability observed in the PK and TG in control animals on the pharmacological response was explored starting from real cases using Monte Carlo simulations based on the TGI PK/PD model. A GTS method was applied to incorporate the uncertainty of estimation in the model parameters in the variance-covariance matrix.
In both the cases presented here (Paclitaxel and Drug X) the major cause of variability observed in the TG in treated animals is due to the biological system.
The covariance terms seem to play a role essentially in the first part of the TG curves during the treatment period.
The simulations performed with different CV% in the PD parameters show that important reductions could be obtained also with changes of 10-25% in the CV values.
The examples reported here are in line with the results observed in other studies with different cell lines and drugs and are indicating that any effort to better standardize the experimental protocol of the biological part of the studies are expected to give clear improvement in the evaluation of the drug efficacy.

REFERENCES

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[2] Rocchetti M, Simeoni M, Pesenti E, De Nicolao G, Poggesi I. Predicting the active doses in humans from animal studies: a novel approach in oncology. European Journal of Cancer, 43, 1862,1868, 2007.