POPULATION MODELING OF TUMOR GROWTH IN UNTREATED XENOGRAFTED MICE

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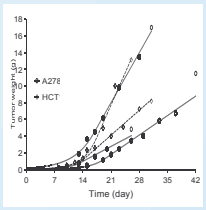
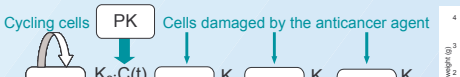
Introduction

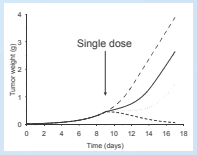
- The in vivo evaluation of the anti-tumor effect is a fundamental step in the preclinical development of anticancer agents. In these experiments tumor cells are inoculated in athymic mice; groups of animals are then randomized to receive placebo (controls) or the active treatments. Tumor volumes are measured at different times and the effect of the active molecule is measured by comparing the average tumor weights in treated and control animals at the end of the experiment.
- We recently developed a minimal pharmacokinetic-pharmacodynamic (PK-PD) model, linking the dosing regimen of a compound to the tumor growth in animals. With this model we were able to analyse successfully a number of data sets obtained after administration of a variety of anticancer agents (Simeoni et al., 2004); the model was also used to prospectively predict the outcome of experiments using different dosing regimens and/or schedules.
- The predictive capabilities of the model could be even more exploited introducing the variability contributions. Since the modeling of the unperturbed tumor growth in controls is a foundamental piece of the PK/PD model and due to the large inter-experiment variability observed, we present here some population analyses aimed at evaluating this aspect.



Tumor growth model

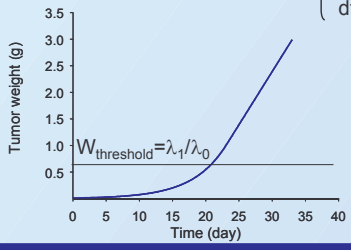


See also Simeoni et al, PAGE 2004)



Tumor growth in controls: exponential + linear growth

$$\begin{cases} \frac{dW}{dt} = \lambda_0 \cdot W(t) & \forall W(t) < W_{threshold} \\ \frac{dW}{dt} = \lambda_1 & \forall W(t) \geq W_{threshold} \end{cases}$$



$$\frac{dW}{dt} = \frac{\lambda_0 \cdot W(t)}{\left[1+\left(\frac{\lambda_0}{\lambda_1}\cdot W(t)\right)^{\psi}\right]^{\frac{1}{\psi}}}$$

$$W(0) = w_0$$

Methods

Female Hsd: Athymic Nude-nu mice, 5-6 weeks of age (20-22 g), were obtained from Harlan, Italy. A2780 human ovarian carcinoma and HCT116 colon carcinoma cell lines (American Type Culture Collection) were used. Tumor fragments were implanted s.c. into the left flank of mice. Mice were clinically evaluated daily and weighed two times weekly. Dimensions of the tumors were measured by caliper timely during the experiments and tumor masses were calculated assuming density ρ = 1 mg/mm^3 for tumor tissue.

$$\text{tumor weight (mg)} = \frac{\text{length (mm)} \cdot \text{width}^2 \text{ (mm}^2\text{)}}{2}\rho$$

A database of 14 experiments with A2780-derived tumors (n=116) and 11 with HCT 116-derived tumors (n=83) was considered. The model for growth of control tumors was implemented in NONMEM (v. V): contributions of variability across cell lines and across experiments were considered, together with the interanimal variability. Different variability models (additive, multiplicative) were considered. Descriptive statistics of post-hoc PD parameters were calculated and the frequency distributions of the various parameters were evaluated.

Conclusions

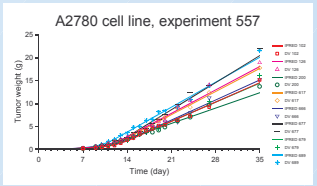
These analyses propted the implementation of the PK-PD model of tumor growth inhibition using NONMEM. The important role of the inter-experiment variability was confirmed and a better comprehension of the meaning of the model parameters was possible: the rate of the exponential growth, likely related to the cell line characteristics, was less variable across experiments than the other parameters, which are likely influenced by the different immunological responses among animals.

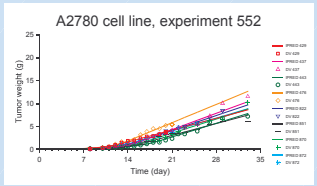
The characterization of the variability of unperturbed tumor growth for a specific cell line will allow a better prediction of the subsequent in vivo studies *via* stochastic simulation techniques.

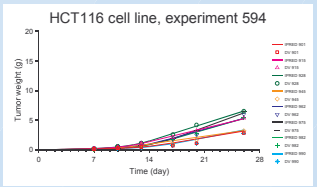
Results

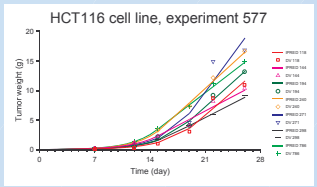
The model fitted well the experimental data. The inter-individual variability of these parameters was well described using a lognormal distribution. The residual variability was described using proportional and additive contributions. Inter-experiment variability was calculated from the individual post-hoc estimates. The specific rate of exponential growth (λ_0) was sensibly less variable across-experiments (CV was 5.0 and 5.8% for A2780 and HCT116 cells, respectively) than the other parameters (λ_1 CV were 20.9 and 54.5% and w_0 CV were 12.3 and 10.5%).

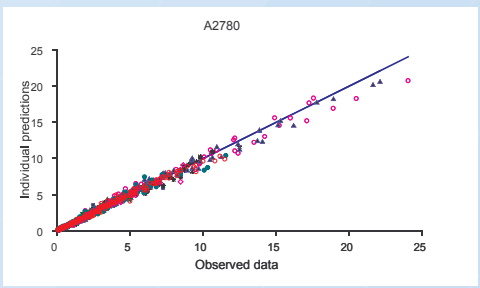
fixed effects		
	mean	CV%
λ_0	0.2920	1.45
λ_1	0.4600	4.00
w0	0.0300	5.83
random effects		
	var	CV%
λ_0	0.0140	20.64
λ_1	0.2260	12.39
w0	0.0823	38.64
σ_1^2	0.0173	14.74
σ_2^2	0.0065	26.84

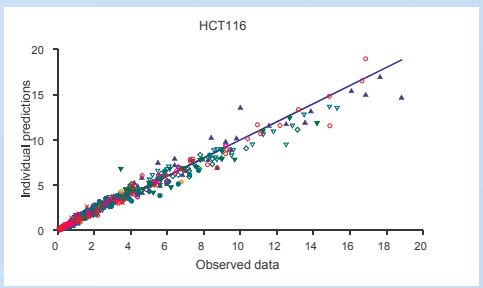












Reference

Simeoni M. et al. Predictive PK-PD modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. Cancer Res. 2004, 64:1094-1101