# POPULATION MODELING OF TUMOR GROWTH INHIBITION IN VIVO: APPLICATION TO ANTICANCER DRUG DEVELOPMENT.

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## Abstract

The in vivo evaluation of the antitumor efficacy of compounds in animal models is a fundamental step in the development of anticancer drugs. In these experiments, efficacy is expressed as percentage of decrease of the tumor weight in treated animals compared to control animals. We developed a minimal pharmacokinetic-pharmacodynamic model linking the dosing regimen of an anticancer agent to the tumor growth in animal models. The growth of tumors in non-treated animals (unperturbed growth) is described by exponential growth followed by a linear growth phase. The rate of tumor growth in treated animals (perturbed growth) is considered decreased by a factor proportional to both plasma drug concentrations and number of proliferating tumor cells. A transit compartmental system is used to model the delayed process of cell death. The parameters of the pharmacodynamic model are related to the growth characteristics of the tumor, to the drug potency and to the kinetics of the tumor cell death. Since the unperturbed and perturbed growths are measured in different groups of animals and considering that in this model the perturbed growth collapses into the unperturbed one in the absence of treatment, the simultaneous fitting of the two average growth curves was adopted for estimating the model parameters. In this communication we report examples of the use of population approaches for modeling the outcome of these experiments. This would allow estimating the different sources of variability.

## The data

- Anticancer drug, IV bolus administration in mice
- PK and PD estimated in the same animals.
- Paclitaxel

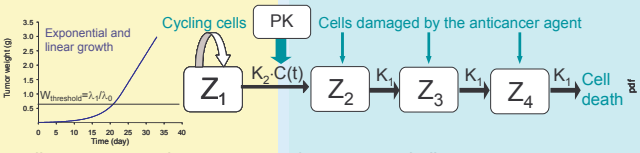
Treatment administered since day 8 every 4 days for 3 times at 20, 30 and 40 mg/kg, 4 mice per dose.

- Drug B

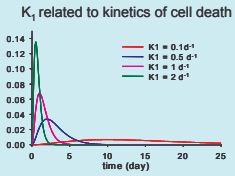
Treatment administered since day 9 every day for 11 days (3 mice), 3 times a day for 1 day (7 mice) and twice a day for 4 days (7 mice) at the same dose of 60 mg/kg.

## THE MODEL

Tumor growth in control animals → Tumor growth in treated animals




$K_1$ related to kinetics of cell death




Differential equations for controls:

$$\frac{dW}{dt} = \lambda_0 \cdot W(t) \quad \forall W(t) < W_{threshold}$$

$$\frac{dW}{dt} = \lambda_1 \quad \forall W(t) \geq W_{threshold}$$

$$\frac{dW}{dt} = \frac{\lambda_0 \cdot W(t)}{\left[1+\left(\frac{\lambda_0}{\lambda_1}\cdot W(t)\right)^{\psi}\right]^{\frac{1}{\psi}}}; \quad W(0) = w_0$$

Overall system of differential equations:

$$\frac{dZ_1(t)}{dt} = \frac{\lambda_0 \cdot Z_1(t)}{\left[1+\left(\frac{\lambda_0}{\lambda_1}\cdot W_1(t)\right)^{\psi}\right]^{\frac{1}{\psi}}} - K_2 \cdot C(t) \cdot Z_1(t)$$

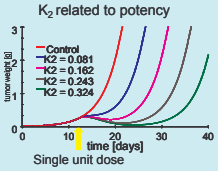
$$\frac{dZ_2(t)}{dt} = K_2 \cdot C(t) \cdot Z_1(t) - K_1 \cdot Z_2(t)$$

$$\frac{dZ_3(t)}{dt} = K_1 \cdot Z_2(t) - K_1 \cdot Z_3(t) \qquad Z_1(0) = w_0$$

$$\frac{dZ_4(t)}{dt} = K_1 \cdot Z_3(t) - K_1 \cdot Z_4(t) \qquad Z_{2,3,4}(0) = 0$$

$$W(t) = Z_1(t) + Z_2(t) + Z_3(t) + Z_4(t)$$

$K_2$ related to potency




## Methods

- Two step analysis: estimation of population PK parameters then estimation of population PD parameters by fixing the individual PK values from the previous step
- Population analyeses carried out with Nonmem version V.
- **PK**:
  - Exponential terms for describing subject-specific random effects.
  - Proportional residual error
  - First-order linearization.
- **PD**:
  - Exponential terms for describing subject-specific random effects.
  - Proportional and additive residual error
  - First-order linearization

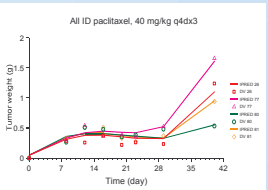
## Results

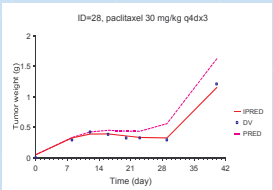
| PACLITAXEL PK PARAMETERS | | |
|---|---|---|
| fixed effects | mean | CV% |
| V (mL kg$^{-1}$) | 501 | 26.15 |
| $K_{10}$ (h$^{-1}$) | 1.18 | 9.83 |
| $K_{12}$ (h$^{-1}$) | 0.099 | 17.30 |
| $K_{21}$ h$^{-1}$) | 0.228 | 10.61 |
| random effects | VAR | |
| V (mL kg$^{-1}$) | 0.456 | 74.78 |
| $K_{10}$ (h$^{-1}$) | 0.061 | 51.40 |
| $K_{12}$ (h$^{-1}$) | 0.000 | |
| $K_{21}$ (h$^{-1}$) | 0.056 | 40.11 |
| sigma$_1$^2 | 0.174 | 16.38 |

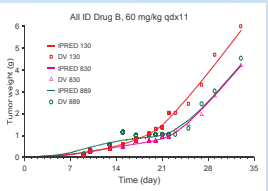
| PACLITAXEL PD PARAMETERS | | |
|---|---|---|
| fixed effects | mean | CV% |
| $K_1$ (day$^{-1}$) | 0.117 | 53.16 |
| $K_2$ (day$^{-1}$ng$^{-1}$mL) | 6.39x10$^{-4}$ | 14.62 |
| $\lambda_0$ (day$^{-1}$) | 0.238 | 15.59 |
| $\lambda_1$ (day$^{-1}$g) | 0.14 | 24.10 |
| $w_0$ (g) | 0.049 | 30.35 |
| random effects | VAR | |
| $K_1$ (day$^{-1}$) | 0.053 | 22.96 |
| $K_2$ (day$^{-1}$ng$^{-1}$mL) | 1.580 | 125.70 |
| $\lambda_0$ (day$^{-1}$) | 0.002 | 4.7 |
| $\lambda_1$ (day$^{-1}$g) | 0.177 | 42.07 |
| $w_0$ (g) | 0.000 | |
| sigma$_1$^2 | 0.019 | 70.16 |
| sigma$_2$^2 | 0.004 | 64.08 |

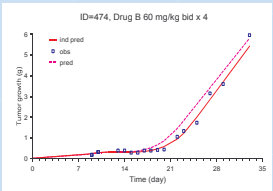
| Drug B PK PARAMETERS | | |
|---|---|---|
| fixed effects | mean | CV% |
| V (mL kg$^{-1}$) | 2110 | 5.45 |
| $K_{10}$ (h$^{-1}$) | 1.500 | 5.03 |
| $K_{12}$ (h$^{-1}$) | 0.526 | 6.44 |
| $K_{21}$ (h$^{-1}$) | 0.279 | 2.41 |
| random effects | VAR | |
| V (mL kg$^{-1}$) | 0.017 | 63.53 |
| $K_{10}$ (h$^{-1}$) | 0.000 | |
| $K_{12}$ (h$^{-1}$) | 0.120 | 25.75 |
| $K_{21}$ (h$^{-1}$) | 0.000 | |
| sigma$_1$^2 | 0.044 | 25.28 |

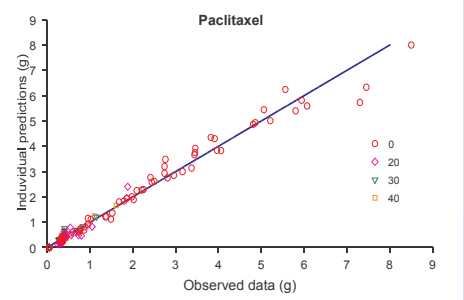
| DRUG B PD PARAMETERS | | |
|---|---|---|
| fixed effects | mean | CV% |
| $K_1$ (day$^{-1}$) | 0.631 | 18.38 |
| $K_2$ (day$^{-1}$ng$^{-1}$mL) | 2.72x10$^{-4}$ | 21.43 |
| $\lambda_0$ (day$^{-1}$) | 0.269 | 7.92 |
| $\lambda_1$ (day$^{-1}$g) | 0.397 | 4.07 |
| $w_0$ (g) | 0.022 | 23.53 |
| random effects | VAR | |
| $K_1$ (day$^{-1}$) | 2.080 | 49.04 |
| $K_2$ (day$^{-1}$ng$^{-1}$mL) | 0.130 | 220.77 |
| $\lambda_0$ (day$^{-1}$) | 0.014 | 40.74 |
| $\lambda_1$ (day$^{-1}$g) | 0.017 | 68.24 |
| $w_0$ (g) | 0.00 | |
| sigma$_1$^2 | 0.014 | 21.63 |
| sigma$_2$^2 | 0.005 | 37.42 |

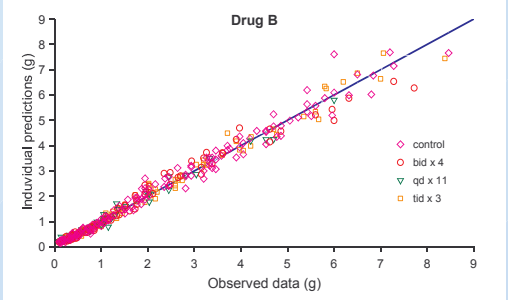



## Conclusions

These analyses demonstrate that the implementation of our PK-PD model is feasible using NONMEM. The use of the population approaches allowed to describe correctly the individual tumor growth-time curves. Using this approach, it was possible to estimate the PK-PD parameters and the corresponding sources of variability (e.g., PK in ancillary groups of animals, PD of unperturbed growth in control animals and drug-related PD parameters in treated animals). The population parameters were in good agreement with the parameters obtained applying the model to the average tumor weight – time data (see paclitaxel and Drug A results, Simeoni et al.).

Since the model was proven effective also in predictive mode, based on the outcome of a preliminary experiment, using population approaches, stochastic simulations can be implemented for a smart and efficient design of the *in vivo* pharmacological studies of a novel anticancer agent.

## Reference

Simeoni M, Magni P, Cammia C, De Nicolao G, Croci W, Pesenti E, Germani M, Poggesi I, Rocchetti M. Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administrations of anticancer agents. CANCER RESEARCH 64, 1094–1101, February 1, 2004

PAGE Uppsala, 17-18 June 2004