



Modelling of the effect of Topotecan on B cell subsets in tumor bearing rats

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INTRODUCTION

The number of models developed based on different mechanism to describe the hematotoxic effect of several anticancer drugs have been increased in the last decade (Friberg & Karlsson, 2003).

The idea in this work, was to describe (partly or totally) the time course of mature cells as a function of other intermediate components with the objective, to increase the understanding of the dynamic regulation involved in the hematopoietic alterations after Topotecan (TPT) administration to bearing tumor rats.

METHODS

Experimental Design

Blood samples were withdrawn at different times over the study (see fig.1) to determine: plasma concentrations of TPT lactone form (HPLC) and the different B cell populations, CD90⁺CD45⁺ (immature cells) and CD90⁻CD45⁺ (mature cells) by flow cytometry.

Data Analysis Pharmacokinetic/pharmacodynamic model:

The analysis was performed by NONMEM (VERSION V). A population approach was used to develop the pd model with the pk parameters fixed.

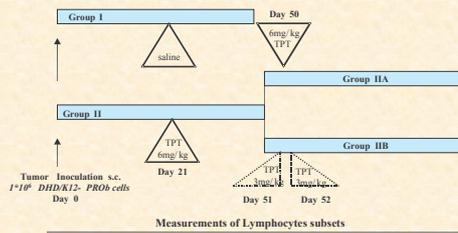


Figure 1: Experimental design for control (group I) and TPT treated groups (IIA and IIB).

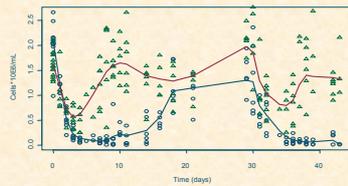


Figure 2: Experimental data, circles and triangles represent immature and mature B cells respectively; dashed and solid lines represent the tendency of the data. Although, the nadir was reached at the same time for both subsets (aprox. 3-4 days), the recovery of mature cells was quicker than for immature cells as it is showed in the graph.

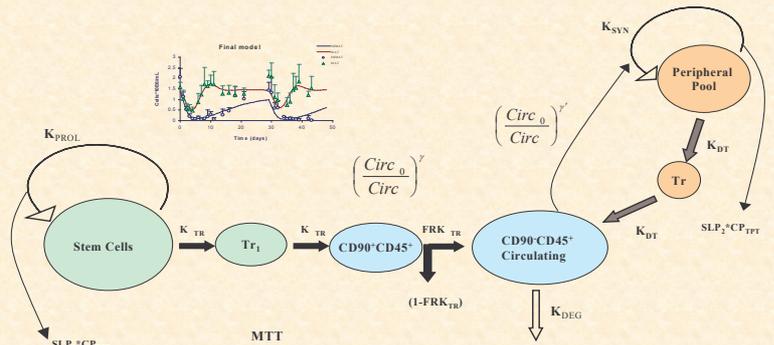


Figure 3: Schematic representation of the pd model developed. K_{PROL} , K_{TR} , K_{DT} , K_{DEG} and K_{SYN} first order rate constants of: initial precursors formation in stem cell; release of cells in peripheral tissues, γ and γ' slopes of rebound effect on immature and mature cells, respectively. SLP₁ and SLP₂ the effect of TPT on precursors of B cells central and peripheral compartments. A representation of mean (\pm SD) data and model predictions (solid lines) is showed on the top of the figure.

Model assumes that the effect of TPT is predominantly located in the stem cells (bone marrow) since the immature cells subset is the main population affected. In addition, the treatment of TPT seems to affect in different way to mature cells subset probably due to its low capacity of the renewal and because the presence of a peripheral pool (like lymphoid tissues) can release B-mature cells (Kroese et al., 1995; Dammers et al., 1999).

RESULTS

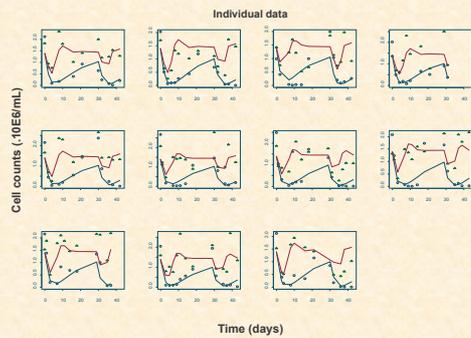


Figure 4: Time course of the two B-cells populations in each animal. Circles and triangles represent the observed immature and mature B cells, respectively. Dashed and solid lines represent the individual model predictions for both subsets.

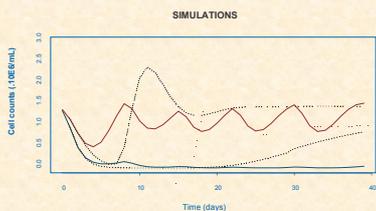


Figure 6: Simulations of the effects described by the final model after two treatment of TPT: 1) solid lines represent the profiles after 5 consecutives doses of TPT in a month for both subsets and; 2) after one dose of TPT per week during a month for both subsets again.

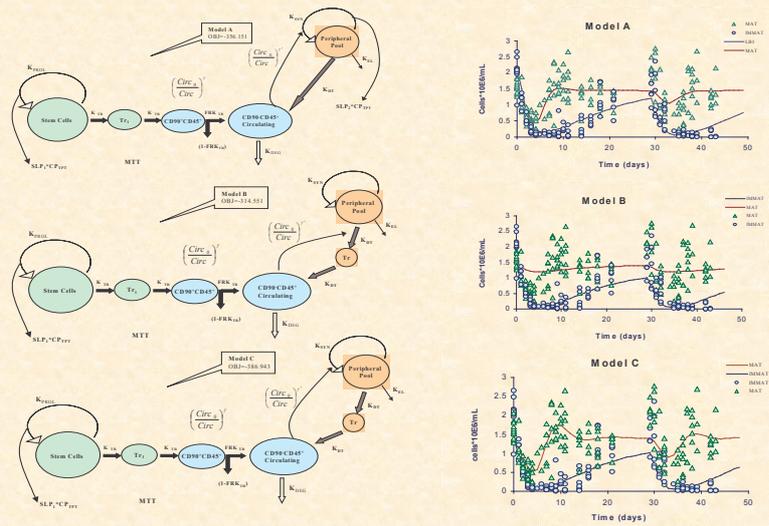


Figure 5: Evaluation of some alternative models was carried out by visual inspection, minimum value of the objective function (OBJ) and the precision of the parameter estimates

CONCLUSIONS

- A physiological-based model could successfully describe simultaneously the effect of TPT on two cycles of chemotherapy in tumor bearing rats.
- This experimental study provides interesting information about the recovery of the hematopoietic precursors and the differences in the homeostatic regulation for mature and immature B-cells after chemotherapy.

References
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