Modelling the effect of Sunitinib given alone and in combination with CPT-11 on the tumor growth in xenografted mice

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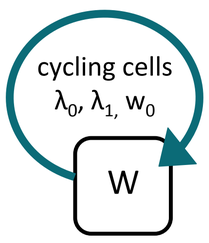
BACKGROUND.

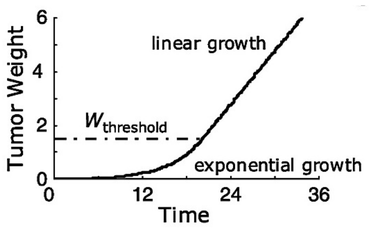
Nowadays anti-angiogenic drugs are considered one of the cornerstone of the anticancer therapy. Limiting oxygen and nutrient supplies to tumor, angiogenesis inhibitors cause tumor stasis but they do not exert a direct tumor cells killing effect. For this reason they are usually administered in combination with chemotherapy. The aim of this work is to study the effects of Sunitinib on tumor growth in xenografted mice both in the case of single drug experiment and in combination regimens with cytotoxic drug (CPT-11) to assess the type and the strength of the interaction.

METHODS.

Data were obtained from CellVax (France) and relate to 2 different experiments both on athymic nu/nu mice xenografted with human colonrectal cancer cells. The treatment started when tumor volume reached 200-300 mm^3.

Tumoral growth in untreated animals was described by an exponential growth phase followed by a linear one.





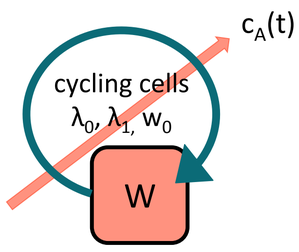
$$\frac{dW(t)}{dt} = \frac{\lambda_0 \cdot W(t)}{\left[1+\left(\frac{\lambda_0}{\lambda_1}\cdot W(t)\right)^{\varphi}\right]^{\frac{1}{\varphi}}}$$

$$W(0) = w_0$$

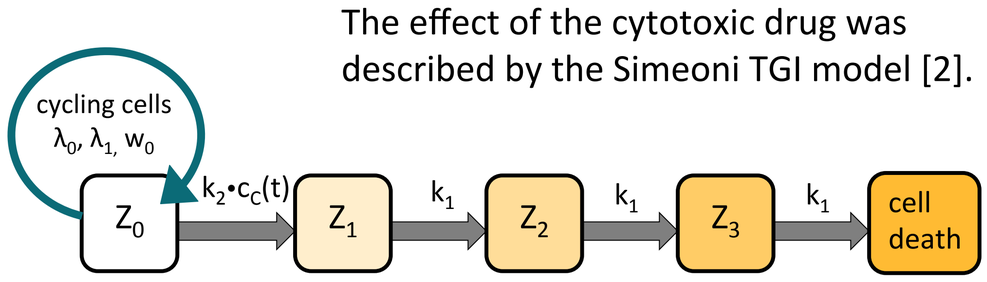
The action of the anti-angiogenic drug was modeled starting from the Rocchetti TGI model [1].

$$\frac{dW(t)}{dt} = \frac{\lambda_0 \cdot W(t)}{\left[1+\left(\frac{\lambda_0}{\lambda_1}\cdot W(t)\right)^{\varphi}\right]^{\frac{1}{\varphi}}} \cdot \left(1 - \frac{c_A(t)}{c_A(t)+IC_{50}}\right)$$

$$W(0) = w_0$$



The effect of the cytotoxic drug was described by the Simeoni TGI model [2].



$$\frac{dZ_0(t)}{dt} = \frac{\lambda_0 \cdot Z_0(t)}{\left[1+\left(\frac{\lambda_0}{\lambda_1}\cdot W(t)\right)^{\varphi}\right]^{\frac{1}{\varphi}}} - k_2 \cdot c_C(t) \cdot Z_0(t)$$

$$\frac{dZ_1(t)}{dt} = k_2 \cdot c_C(t) \cdot Z_0(t) - k_1 \cdot Z_1(t)$$

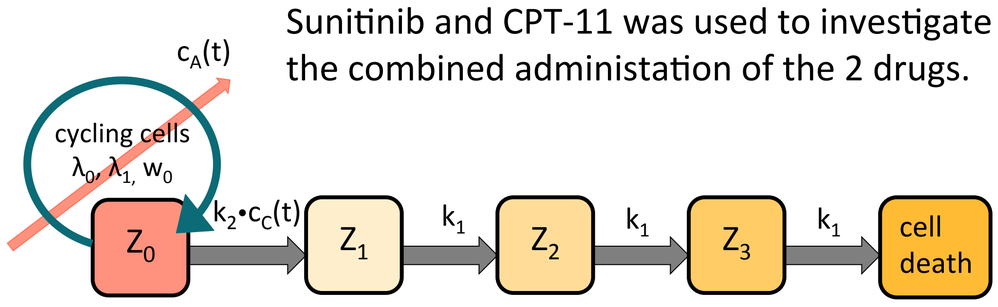
$$\frac{dZ_2(t)}{dt} = k_1 \cdot Z_1(t) - k_1 \cdot Z_2(t)$$

$$\frac{dZ_3(t)}{dt} = k_1 \cdot Z_2(t) - k_1 \cdot Z_3(t)$$

$$Z_0(0) = w_0 \quad Z_{1,2,3}(0) = 0$$

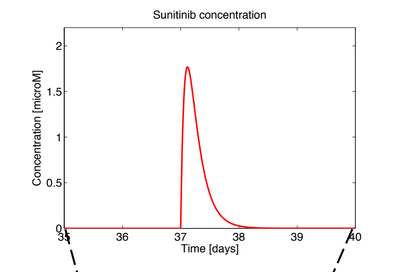
$$W(t) = Z_0(t) + Z_1(t) + Z_2(t) + Z_3(t)$$

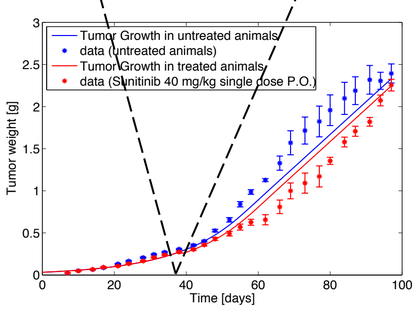
A joint model that integrates the action of Sunitinib and CPT-11 was used to investigate the combined administation of the 2 drugs.



RESULTS.

- <u>Single agent experiment:</u>





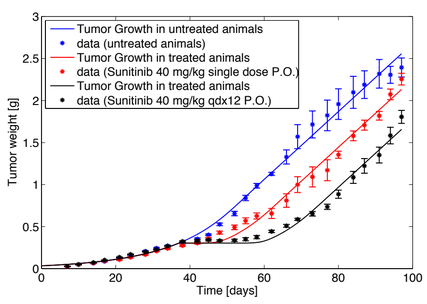
A modified version of the Rocchetti TGI model was proposed to describe the action of Sunitinib. An effect compartment was added to the original model because of the faster PK of Sunitinib compared to Avastin (drug used in [1]). The model successfully describes the experimental data.

$$\frac{dW(t)}{dt} = \frac{\lambda_0 \cdot W(t)}{\left[1+\left(\frac{\lambda_0}{\lambda_1}\cdot W(t)\right)^{\varphi}\right]^{\frac{1}{\varphi}}} \cdot \left(1 - \frac{Z_{eff}(t)}{Z_{eff}(t)+IZ_{50}}\right)$$

$$\frac{dZ_{eff}(t)}{dt} = k_{eff} \cdot \left(c_A(t) - Z_{eff}(t)\right)$$

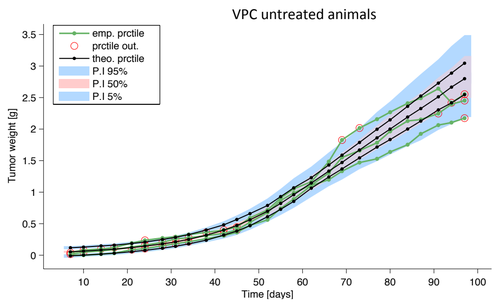
$$W(0) = w_0$$

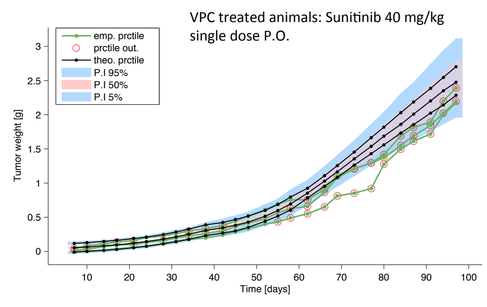
$$Z_{eff}(0) = 0$$

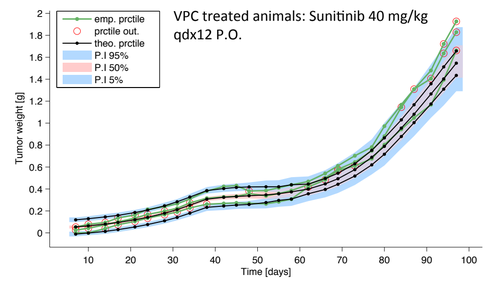


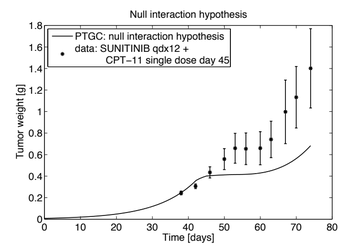
parameter	unit	estimate	CV %
λ_0	$days^{-1}$	0.0596	3.35
λ_1	$g \cdot days^{-1}$	0.0404	2.72
IZ_{50}	µM	0.0001	57.4
k_{eff}	$days^{-1}$	0.7999	1.2e-4
w_0	g	0.0333	7.63

VPCs obtained via population approach





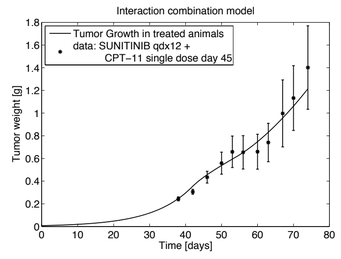




- <u>combination experiment:</u>

$$k_{2,inh} = k_2\left(1 - \frac{Z_{eff}(t)}{Z_{eff}(t)+IZ_{50,combo}}\right)$$

Difference between model PTGC under the null interaction hypothesis and experimental data suggests a negative interaction between Sunitinib and CPT-11.



CONCLUSIONS.

The new TGI model seems to be adequate to describe the action of Sunitinib, while the co-administration with the cytotoxic drug shows a negative interaction.

This work was supported by the DDMoRe project (www.ddmore.eu).

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[2] M. Simeoni, P. Magni, C. Cammia, G. De Nicolao, V. Croci, E. Pesenti, M. Germani, I. Poggesi, M. Rocchetti. Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. Cancer Research 64:1094–1101, 2004