A PK/PD model of tumor growth after administration of an anti-angiogenic agent given alone or in combination in xenograft mice

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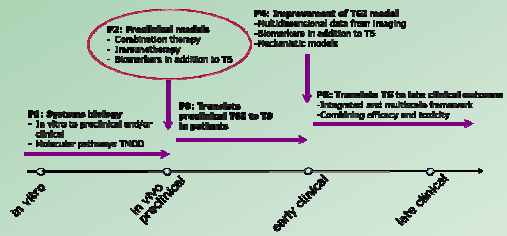
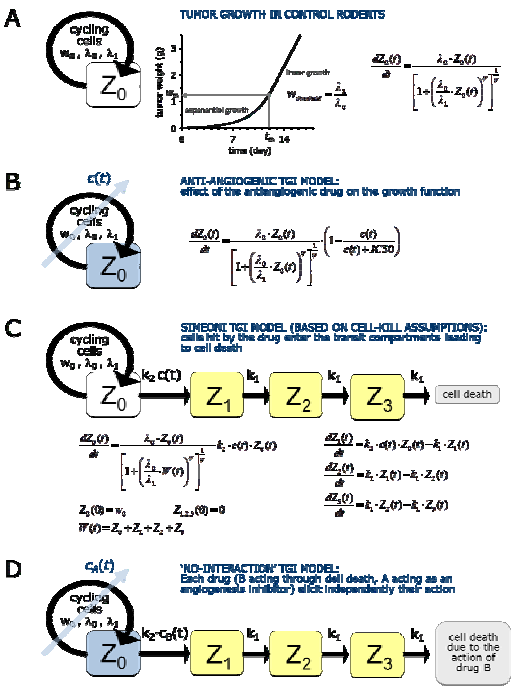
PK/PD models able to predict the action of anticancer compounds in tumor xenografts have an important impact on drug development. Antiangiogenic compounds mainly act on the tumor vascularization without a direct tumor cell kill effect. For this reason, a PK/PD model able to describe the tumor growth modulation following treatment with a cytostatic therapy, as opposed to a cytotoxic treatment, is proposed here.



Pillars for the new model development in the oncology area identified within the DDMoRe project

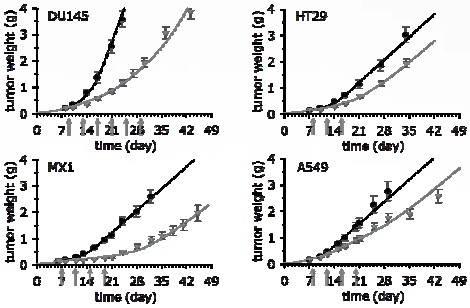
METHODS

- Antitumor efficacy measured in xenograft. Mice were treated with vehicle or Bevacizumab (Avastin ®) given either alone or in combination with NMS-P937, a polo-like kinase 1 (PLK1) inhibitor. Average tumor weights of control and treated groups were considered.
- Untreated tumor growth (TG) was described using an exponential growth phase followed by a linear phase (figure below, panel A).
- In absence of a direct cell-kill effect and assuming a reduced nutrient supply, the action of the anti-angiogenic compound was implemented as an inhibitory effect on the tumor growth related parameters λ_1 and λ_2 (panel B).
- The standard Simeoni TGI model was used for describing the action of the cell-kill anticancer compound (panel C).
- A combination model was also developed under a 'no-interaction' assumption to assess the effect of the combination of bevacizumab with a target-oriented agent (panel D).
- Nonlinear regression techniques were used for estimating the model parameters



RESULTS

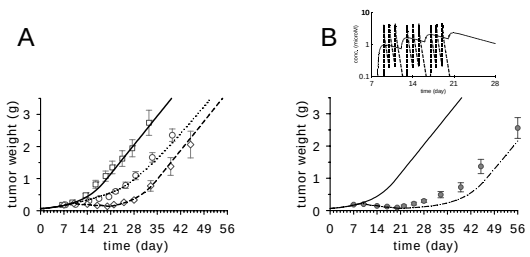
The single-agent bevacizumab: data were analyzed using the anti-angiogenic TGI model (B). The model parameters were identified with good precision (CVs < 16%). Bevacizumab was characterized by an IC_{50} value ranging from 0.88 to 2.4 μM, depending on the cell line. A simultaneous fitting of all the experiments was also successfully performed estimating a single IC_{50}=1.39 μM as a common value (drug-related parameter).



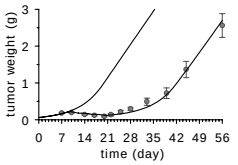
Parameter	Units	Cell lines							
		DU145		HT29		MX1		A549	
		Estimate	CV%	Estimate	CV%	Estimate	CV%	Estimate	CV%
IC_{50}	μM	1.30	9.38	2.32	15.3	0.880	11.2	2.39	12.9
λ_0	1/day	0.212	5.36	0.167	5.43	0.163	7.46	0.202	6.72
λ_1	g/day	0.360	6.63	0.124	7.85	0.120	11.0	0.120	5.41
w_0	g	0.0366	14.2	0.0420	10.8	0.0467	13.6	0.0419	14.1

Combination study: parameters from the single-agent experiments of bevacizumab and NMS-P937 were collected (single-agent fitting in panel A).
The TGI under the 'no-interaction' hypothesis, indicated an effect that is smaller than predicted (testing additivity, panel B).

Parameter	Units	Estimate	CV%
$IC_{50,bevacizumab}$	μM	2.02	13.4
$k_{1,NMS-P937}$	1/day	3.54	55.1
$k_{2,NMS-P937}$	1/(μM day)	0.221	6.29
λ_0	1/day	0.140	5.33
λ_1	g/day	0.129	9.66
w_0	G	0.062	9.27



$$k_{2,inhibited} = k_2 \cdot \left(1 - \frac{C_A(t)}{IC_{50,combo} + C_A(t)}\right)$$

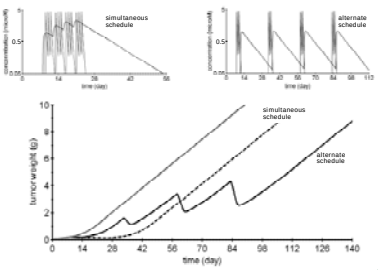


Including an interaction term and fixing all the other parameters to the values obtained in the single-agent experiments was possible to correctly describe the TG after combined treatments (figure on the left).

$IC_{50,combo}$ = 3.6 μM is a measure of the inhibitory effect of bevacizumab on the potency of NMS-P937

CONCLUSIONS

- The single agent anti-angiogenic TGI model was able to accommodate simultaneously data from control and treated animals.
- The 'no interaction' TGI model can provide quantitative indications about possible departures from the TGI expected assuming 'additivity' of the effects.
- Adding specific combination terms, dosing schedules can be explored using simulations to optimize the antitumor effect (in this case the predictions indicate a larger tumor growth delay of the alternate schedule in comparison to the simultaneous schedule).



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