Extending the Tumor Static Concentration curve to average doses – a combination therapy example using radiation therapy

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Introduction

A Tumor Growth Inhibition (TGI) model is used to study the impact of ionizing radiation and exposure to a probe compound. The proposed model contains the determinants of synergy between the two provocations. The Tumor Static Concentration (TSC) curve is then generated as a function of radiation dose and probe compound concentration[2]. The curvature of the TSC function demonstrates a significant synergistic effect.

Methods

Xenograft data from a combination therapy experiment where mice were treated with ionizing radiation (IR) and/or a probe compound. Ten mice made up each of the four treatment arms: Vehicle, radiation, compound, and radiation + compound.

The model (Fig. 1) is an extension of the standard TGI model where cells go through damage states before final cell death. IR acts as an instant mass transfer between the healthy state and first damage state. The compound stimulates both the natural- and the IR-induced death processes.

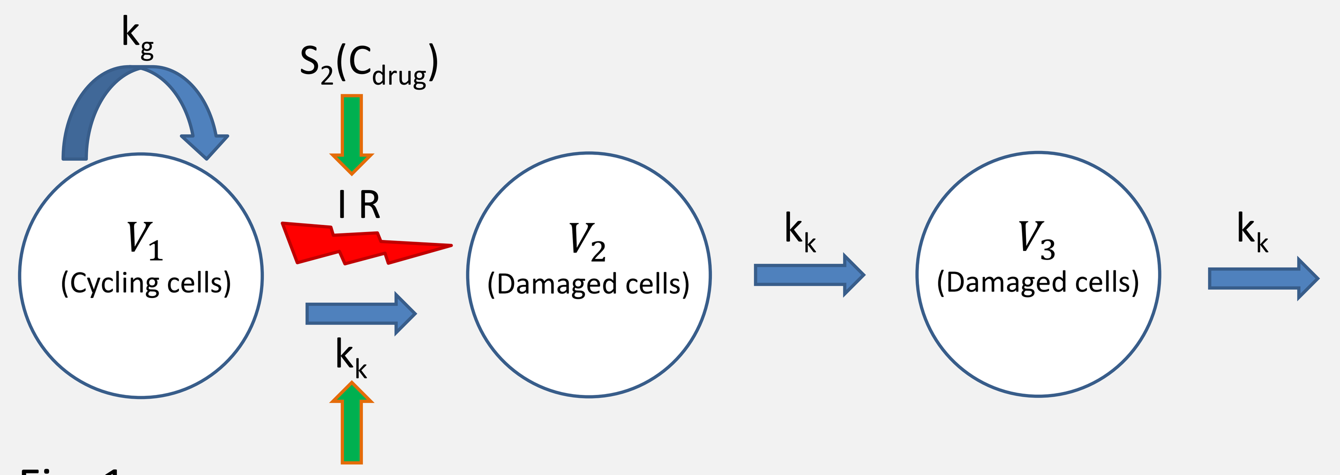

Fig. 1

The corresponding system of differential equations reads

$$\frac{dV_1}{dt} = k_g V_1 - k_k\, S_1(C) V_1 - k_{IR} R(D)\, S_2(C) V_1$$
$$\frac{dV_2}{dt} = k_k\, S_1(C) V_1 + k_{IR} R(D)\, S_2(C) V_1 - k_k V_2$$
$$\frac{dV_3}{dt} = k_k V_2 - k_k V_3$$

with

$$S_1(C) = 1 + a\,C, \qquad S_2(C) = 1 + b\,C$$

A nonlinear mixed-effects approach based on the FOCE algorithm was used to model the population[1].

Exposure profiles

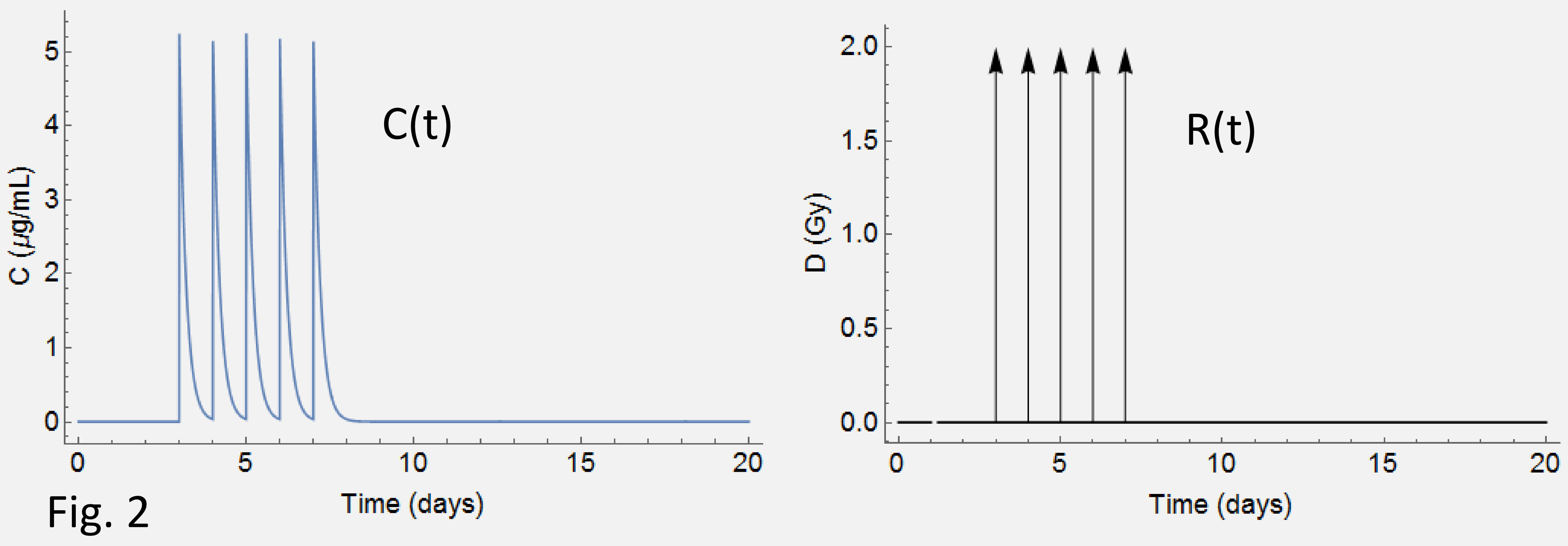

Fig. 2

Results

Sample of fit for each treatment arm

- Compound (green) has little effect when given as single-agent. Radiation (red) has a moderate effect
- Combined (purple) the effect is synergistic

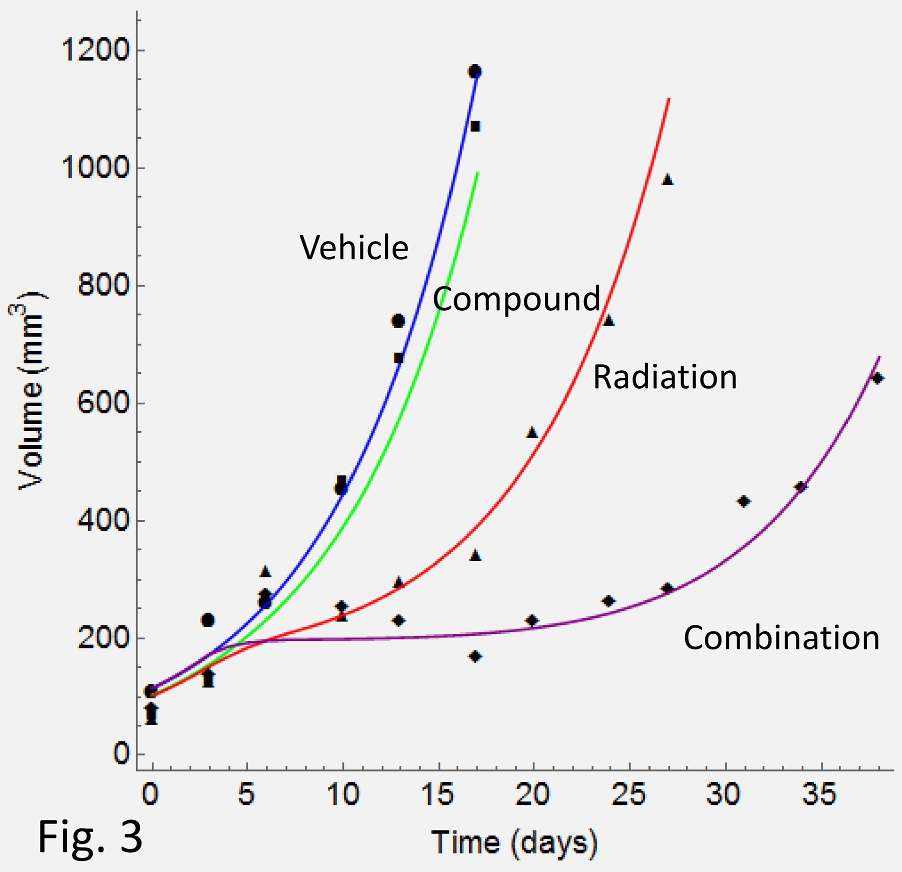

Fig. 3

Estimated parameter values

Parameter	Estimate	BSV (%)
$k_g (day^{-1})$	0.17	2.8
$k_k\ (day^{-1})$	0.032	-
$V_0\ (mm^3)$	88	16
$k_{IR}\ (Gy^{-1} \cdot day^{-1})$	0.12	-
$a\ (mL \cdot \mu g^{-1})$	0.56	-
$b\ (mL \cdot \mu g^{-1})$	0.12	64
s (%)	25	-

- Parameter estimates within biologically reasonable ranges
- Model successfully captured an interaction between radiation and drug exposure
- Interaction (synergy) parameter *b* varies greatly across individuals

TSC curve for radiation + drug

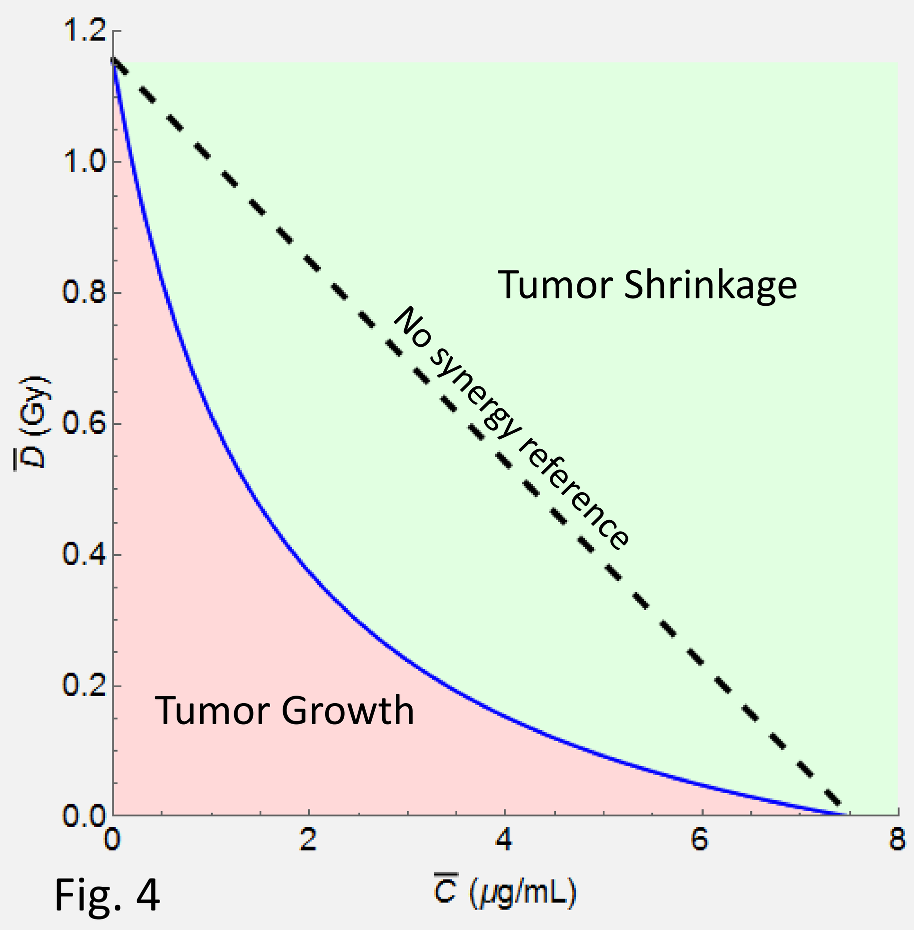

Fig. 4

- TSC curve (blue) shows significant curvature
- Green area represents tumor shrinkage
- Red area represents tumor growth

Extended Tumor Static Concentration curve

Condition for the tumor to be in stasis – the average growth rate of the main compartment is zero

$$\frac{1}{T}\int_0^T k_g - k_k\, S_1(C) - k_{IR}\, R(D)\, S_2(C)\, dt = 0$$

A daily administration schedule gives for the average drug concentration $\bar{C}$ and average radiation dose $\bar{D}$

$$(k_g - k_k) - k_k\, a\, \bar{C} - k_{IR}\, \bar{D} - k_{IR}\, b\, \bar{C}\bar{D} = 0$$

This equation describes a curve in the $\bar{C}\bar{D}$-plane which identifies the necessary concentration-radiation dose pairs for tumor stasis. The larger the curvature, the greater the synergy is between the compounds (Fig 4).

Conclusions

- Radiation-modified TGI model successfully captures the data and interaction effect
- Significant synergy between the two treatments – vizualized by the curvature of the TSC curve
- The TSC concept helps in defining optimal concentration and dose ranges for the two drugs to achieve tumor shrinkage

References

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