Modeling of radiation therapy and radiosensitizing agents in tumor xenografts

Tim Cardilin[1,2], Joachim Almquist[1], Mats Jirstrand[1], Floriane Lignet[3], Astrid Zimmermann[4], Samer El Bawab[3], and Johan Gabrielsson[5]

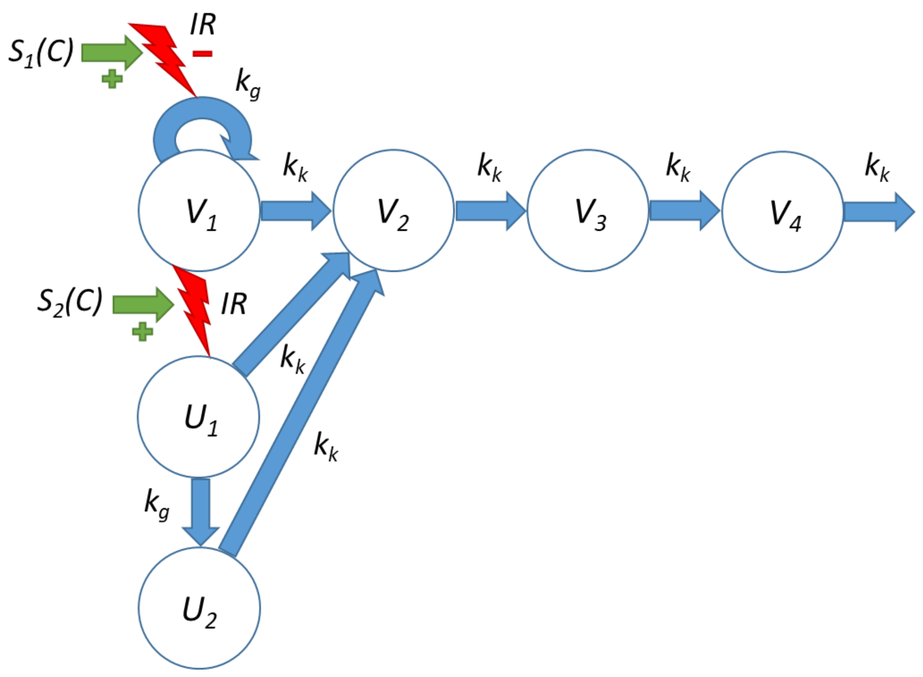
[1]Fraunhofer-Chalmers Centre, Gothenburg, Sweden, [2]Department of Mathematical Sciences, Chalmers University of Technology and Gothenburg University, Gothenburg, Sweden, [3]Merck, Global Early Development – Quantitative Pharmacology, Darmstadt, Germany, [4]Merck, Translation Innovation Platform Oncology, Darmstadt, Germany, [5]Division of Pharmacology and Toxicology, Department of Biomedical Sciences and Veterinary Public Health, Swedish University of Agricultural Sciences, Uppsala, Sweden

Introduction

We introduce a pharmacodynamic model that describes the tumor volume evolution during and after treatment with radiation and radiosensitizing agents. A key contribution is the inclusion of a long-term radiation effect, which allows the model to describe distinct tumor behaviors including tumor eradication and tumor regrowth with different growth rates. The model also accounts for the effects of combining radiation therapy with radiosensitizing treatment. The was model fitted to data from xenograft experiments using a clinically-relevant administration schedule.

Pharmacodynamic Tumor Model

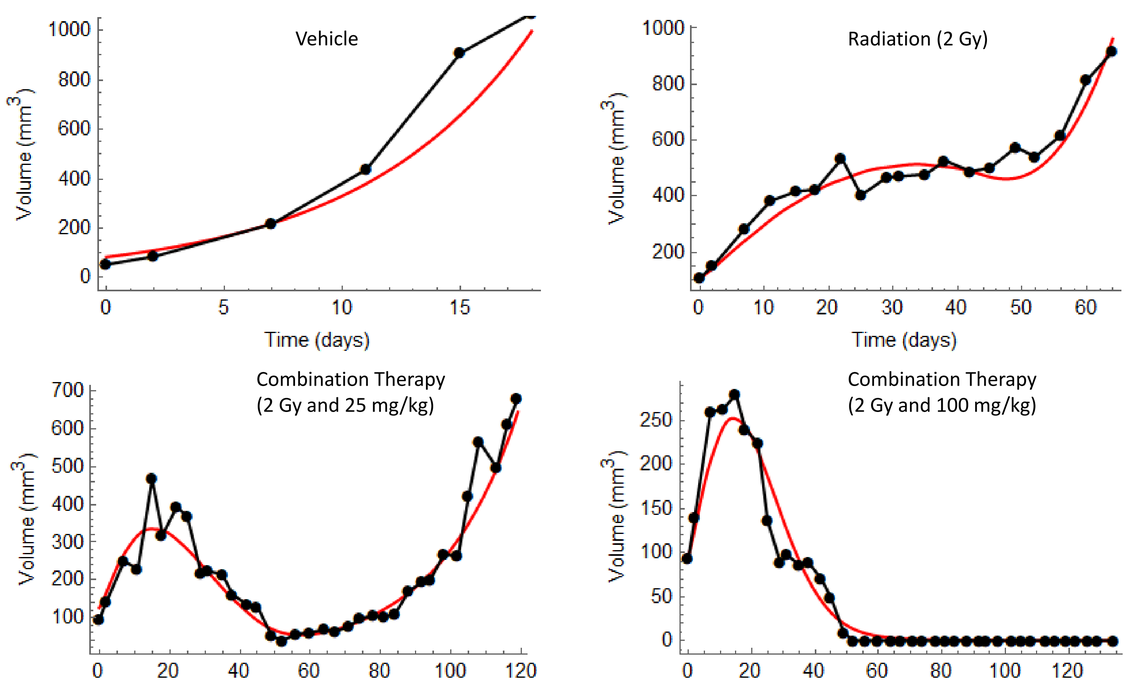
Tumor volume data were generated in FaDu xenograft mouse models. Animals were divided into the following four groups with N = 9 animals per group: vehicle, radiation (2 Gy), and radiation (2 Gy) and radiosensitizer (25 mg/kg or 100 mg/kg). Animals received treatment five days a week for six weeks.



A pharmacodynamic tumor model was adapted from one of our previously-published models [1,2]. A short-term radiation effect is described by allowing lethally irradiated cells up to one more cell division before apoptosis. Long-term radiation effects are described by an irreversible inhibition of the tumor growth rate. The radiosensitizing agent was assumed to stimulate both processes.

Individual Fit

The tumor model was fitted to the data using a mixed-effects approach[3]. Between-subect variability was accounted for in initial tumor volume, and both the short- and long-term radiation effects. Examples of individual fits for each treatment arm are shown below.



The estimated tumor doubling time was 5 days. The model predicts that each fraction of 2 Gy kills 15 % of the proliferating cells. If radiation is preceeded by radiosensitizing treatment (100 mg/kg) 25 % of the proliferating cells are killed.

Model Equations

The model is given by the following system of differential equations

$$\frac{dV_1}{dt} = k_g \exp(-\alpha\, IR_{Tot})\, V_1 - k_k V_1 - \sum F\left(D_{t_i}, C_{t_i}\right) \delta(t - t_i)\; V_1$$
$$\frac{dV_2}{dt} = k_k V_1 + k_k U_1 + k_k U_2 - k_k V_2$$
$$\frac{dV_3}{dt} = k_k V_2 - k_k V_3$$
$$\frac{dV_4}{dt} = k_k V_3 - k_k V_4$$
$$\frac{dU_1}{dt} = \sum F\left(D_{t_i}, C_{t_i}\right) \delta(t - t_i)\; V_1 - k_g U_1 - k_k U_1$$
$$\frac{dU_2}{dt} = 2k_g U_1 - k_k U_2$$
$$\frac{dIR_{Tot}}{dt} = (1 + a\, C) \sum D_{t_i}\, \delta(t - t_i)$$

where k_g is the growth rate, k_k the kill rate, α and β the parameters associated with short- and long-term radiation effects, respectively, and a and b are pharmacodynamics parameters associated with the radiosensitizer. The function F describes the fraction of irradiated cells that are transferred from V_1 to U_1 during each instance of irradiation. F is given by

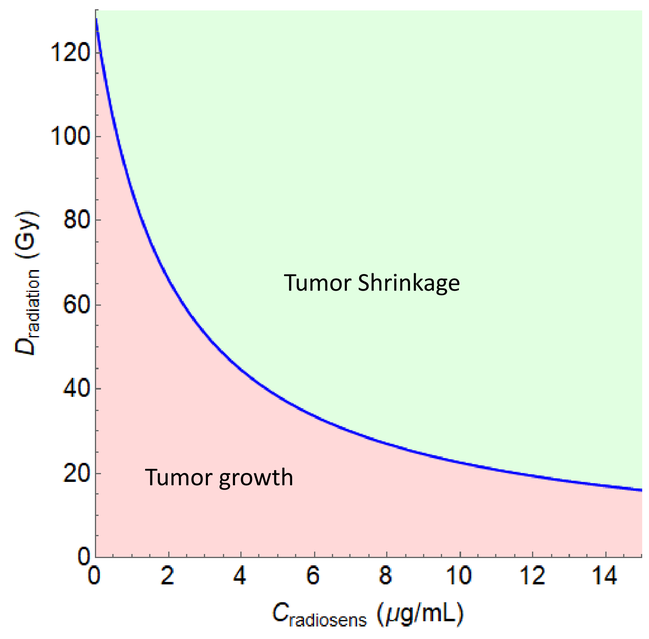
$$F(D, C) = 1 - \exp[-(1 + b\, C)\, \beta D]$$

Tumor Static Exposure

The calibrated tumor model can be used to predict which radiation doses and radiosensitizer exposures that lead to tumor eradication [1,2]. This occurs when the long-term radiation effect inhibits k_g to a value below k_k. The net growth rate $k_g - k_k$ will then be negative and the tumor will shrink. The combinations of total radiation doses and concurrent plasma concentrations of the radiosenstizer that will lead to tumor regression is shown in the figure below (green area).

When radiation therapy is given alone, a total dose of 120 Gy predicted to lead to tumor eradication in a typical individual.

When radiation therapy is preceeded by radiosensitizing treatment (100 mg/kg), the total radiation dose needed for tumor eradication is decreased to 30 Gy.



Summary

A tumor model was developed that:

- Describes the effects of radiation and radiosensitizer treatment on tumor volume
- Captures long-term tumor dynamics including tumor eradication and tumor regrowth with different rates
- Can be used to predict tumor eradication (Tumor Static Exposure)

References

[1] Cardilin T, Almquist J, Jirstrand M, Zimmermann A, El Bawab S, Gabrielsson J. Model-based evaluation of radiation and radiosensitizing agents in oncology. CPT: Pharmacometrics & Syst. Pharmacol. (2017).

[2] Cardilin T, Zimmermann A, Jirstrand M, Almquist J, El Bawab S, Gabrielsson J. Extending the Tumor Static Concentration Curve to average doses – a combination therapy example using radiation therapy. **PAGE 25 (2016) Abstr 5975 [www.page-meeting.org/?abstract=5975]**

[3] Almquist J, Leander J, Jirstrand M. Using sensitivity equations for computing gradients of the FOCE and FOCEI approximations to the population likelihood. J Pharmacokinet Pharmacodyn (2015) 42: 191-209.