Modelling and Analysis of Tumor Growth Inhibition for Combination Therapy using Tumor Static Concentration Curves

Tim Cardilin[1,5], Alexandre Sostelly[2], Johan Gabrielsson[3], Samer El Bawab[2], Christiane Amendt[4] and Mats Jirstrand[5]

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

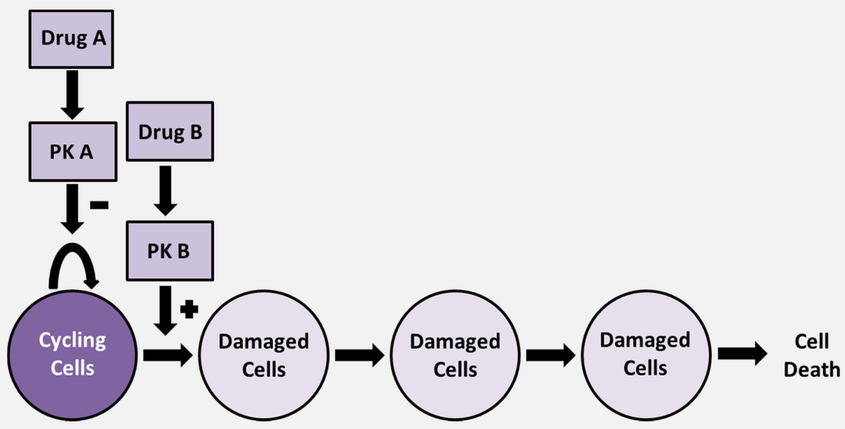
Introduction

Tumor Growth Inhibition (TGI) models provide a simple way to model tumor volume. Drugs can either inhibit cell proliferation or promote cell death. When two drugs are given together the Tumor Static Concentration (TSC) curve may be used as a graphical tool to determine the benefits of the combination.

Methods

Patient-Derived xenograft (PDx) data on an Erbitux-Cisplatin combination experiment with four treatment arms: Vehicle, Erbitux, Cisplatin and Erbitux-Cisplatin combination therapy. Drug exposure profiles were generated based on literature data [1,2].

A TGI model was proposed, where proliferating cancer cells go through three stages of damage before leaving the system. Drug A (Erbitux) inhibits cell proliferation while drug B (Cisplatin) stimulates the kill process.



The system of differential equations becomes

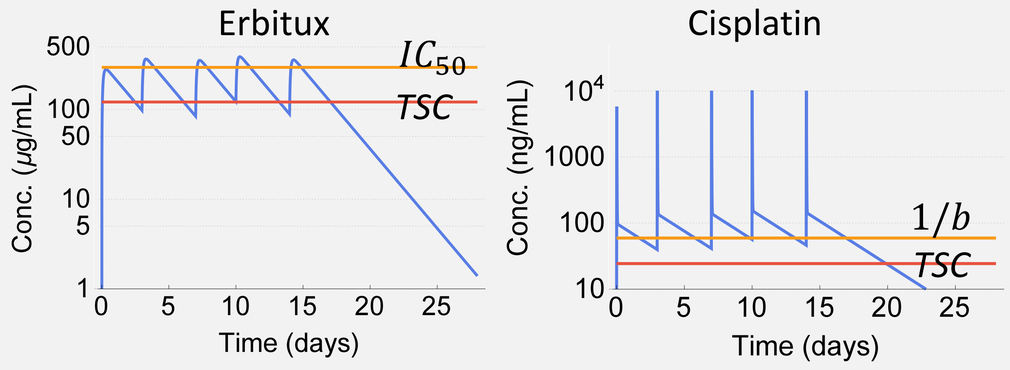
$$\begin{aligned}
\frac{dV_1}{dt} &= k_{growth} I(C_A) V_1 - k_{kill} S(C_B) V_1, & V_1(0) &= V_0,\\
\frac{dV_2}{dt} &= k_{kill} S(C_B) V_1 - k_{kill} V_2, & V_2(0) &= 0,\\
\frac{dV_3}{dt} &= k_{kill}(V_2 - V_3), & V_3(0) &= 0,\\
\frac{dV_4}{dt} &= k_{kill}(V_3 - V_4), & V_4(0) &= 0.
\end{aligned}$$

where the inhibitory and stimulatory functions are given by

$$I(C_A) = 1 - \frac{I_{max,A}\, C_A}{IC_{50,A} + C_A}, \qquad S(C_B) = 1 + b\, C_B.$$

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

Exposure profiles



Tumor static concentrations (TSC)

Consider steady-state conditions

$$\frac{dV_1}{dt} = 0 \Rightarrow k_{growth}\, I(C_A) - k_{kill} S(C_B) = 0,$$

which for the given choice of *I* and *S* becomes

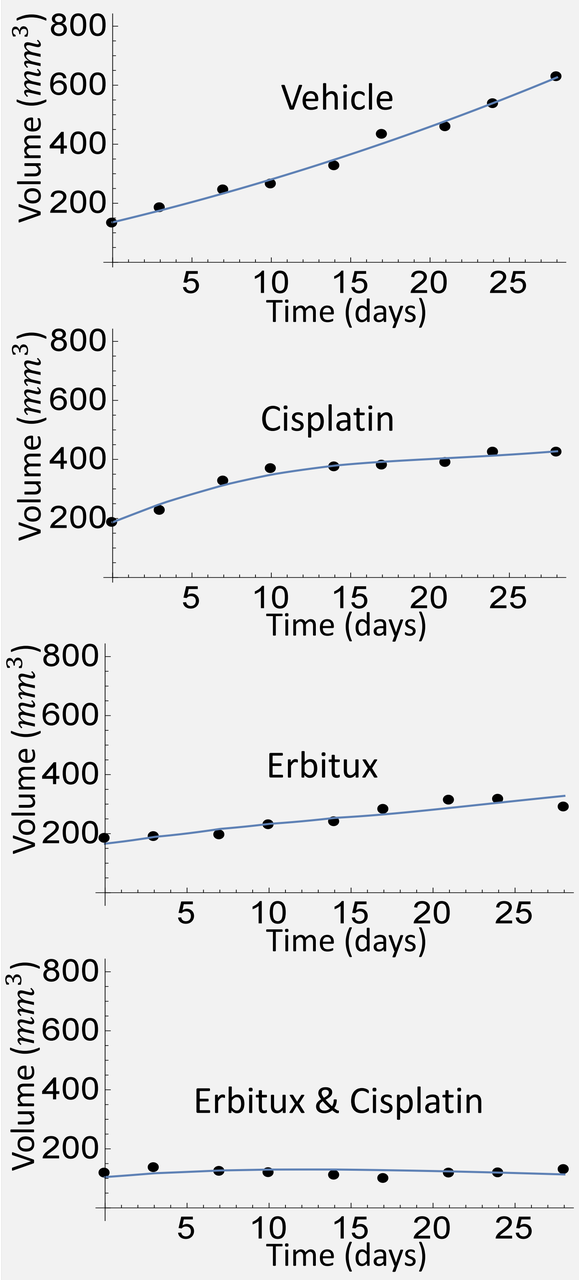
$$k_{kill} b C_A C_B + \big(k_{kill} - (1 - I_{max,A}) k_{growth}\big) C_A + k_{kill} b IC_{50,A} C_B = IC_{50,A}\big(k_{growth} - k_{kill}\big).$$

This equation provides a set of concentration pairs (C_A, C_B) all of which give tumor stasis.

Individual TSC values, *i.e.*, when a drug is given as single-agent

$$TSC_A = \frac{IC_{50,A}(k_{growth} - k_{kill})}{k_{kill} - (1 - I_{max,A}) k_{growth}}, \qquad TSC_B = \frac{k_{growth} - k_{kill}}{b\, k_{kill}}.$$

Results

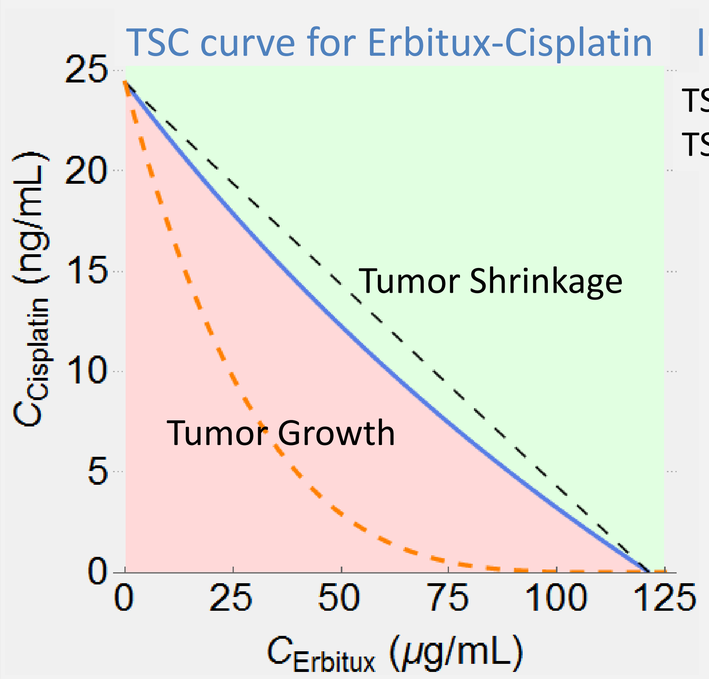


Final parameter values

Parameter	Estimate	RSE (%)
$k_{growth}(days^{-1})$	0.098	9
$k_{kill}(days^{-1})$	0.069	9
$V_0\ (mm^3)$	120	5
$IC_{50,A}\ (\mu g/mL)$	295	23
$I_{max,A}$	1	fixed
$b\ (mL/ng)$	0.017	20
$s\ (mm^3)$	29	4
ω_{11}	0.26	18
ω_{22}	0.30	13

- Parameters were estimated with good precision
- Independent drug action was able to adequately describe the data
- Attempts to incorporate an interaction term did not result in a better fit

TSC curve for Erbitux-Cisplatin



Individual TSC values

$$TSC_{Erbitux} = 121\ (\mu g/mL),$$
$$TSC_{Cisplatin} = 24\ (ng/mL)$$

TSC curve (blue) exhibits minor benefits of combination therapy. Larger curvature (orange) reveals increased benefits.

Conclusions

- TGI model describes single-compound and combinations
- TSC curve highlights concentrations for tumor shrinkage/growth
- TSC curve is a valuable tool for evaluating combinations

References

[1] Johnsson et al. Pharmacokinetics and tissue distribution of cisplatin in nude mice: platinum levels and cisplatin-DNA adducts. *Cancer Chemother. Pharmacol.*, **37**: 23-31, 1995

[2] Lou *et al.* Prediction of Active Drug Plasma Concentrations Achieved in Cancer Patients by Pharmacodynamic Biomarkers Identified from the Geo Human Colon Carcinoma Xenograft model. *Clin. Canc. Res.*, **11(15)**: 5558-5565, 2005