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

Tim Cardilin1,2, Astrid Zimmermann3, Mats Jirstrand4, Joachim Almquist1,2, Samer El Bawab3, and Johan Gabrielson4
1Chalmers University of Technology, Gothenburg, Sweden, 2Fraunhoer-Chalmers Centre, Gothenburg, Sweden, 3Merck, Darmstadt, Germany, 4Swedish University of Agricultural Sciences, Uppsala, Sweden

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. 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](image)

The corresponding system of differential equations reads

\[
\begin{align*}
dV_1 &= k_3V_1 - k_kS_1(C)V_1 - k_{IR}R(D)S_2(C)V_1 \\
dV_2 &= k_kS_1(C)V_1 + k_{IR}R(D)S_2(C)V_1 - k_kV_2 \\
dV_3 &= k_kV_2 - k_kV_3 \\
\end{align*}
\]

with

\[
S_1(C) = 1 + aC, \quad S_2(C) = 1 + bC.
\]

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

![Exposed profiles](image)

Results

Sample of fit for each treatment arm

![Sample of fit](image)

**Estimated parameter values**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>BSV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k_g) (day(^{-1}))</td>
<td>0.17</td>
<td>2.8</td>
</tr>
<tr>
<td>(k_k) (day(^{-1}))</td>
<td>0.032</td>
<td>-</td>
</tr>
<tr>
<td>(V_0) (mm(^3))</td>
<td>88</td>
<td>16</td>
</tr>
<tr>
<td>(k_m) (Gy(^{-1}) · day(^{-1}))</td>
<td>0.12</td>
<td>-</td>
</tr>
<tr>
<td>(a) (mL · mg(^{-1}))</td>
<td>0.56</td>
<td>-</td>
</tr>
<tr>
<td>(b) (mL · mg(^{-1}))</td>
<td>0.12</td>
<td>64</td>
</tr>
<tr>
<td>(x) (%)</td>
<td>25</td>
<td>-</td>
</tr>
</tbody>
</table>

The curve for radiation + drug

![TSC curve](image)

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

Conclusions

- Radiation-modified TGI model successfully captures the data and interaction effect
- Significant synergy between the two treatments – visualized 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