Modeling of acquired resistance under TKI treatment

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1 – Objectives
Most patients under tyrosine kinase inhibitor (TKI) treatment will eventually develop resistance versus TKI drugs [1-3]. We developed a semi-mechanistic PK/PD model describing tumor growth inhibition and resistance under TKI treatment in xenograft mice. Based on model predictions, we aim at optimizing dosing and schedule of administration for patients acquiring resistance.

2a – Methods: In vivo experiments
Tumor growth inhibition (TGI) experiments were conducted in primary patient tumor (LXF A677) bearing mice receiving Erlotinib or Gefitinib treatment. Mice were randomized into treatment groups, control, 6.25mg/kg, 25mg/kg or 100mg/kg for each drug and treatment was daily orally administered for 14 days. Tumor volume was monitored over 30 days and sparse plasma PK data were collected (see Table I).

2b – Methods: Modeling approach
Two semi-mechanistic PK/PD models were developed with and without adaptive resistance and assuming a delay of drug response relative to drug exposure. The performance of the resistance model was compared to a classical TGI model [4]. The classical TGI model assumes a linear effect of plasma exposure on tumor cells, with a delay in disappearance of killed tumor cells as described elsewhere by Simorini et al. [5]. In the acquired resistance model, we distinguish sensitive and acquired resistant cells in terms of sensitivity to treatment and growth rate. Parameter were estimated using Monolix v4.3.2 software [6]. Model discriminations was based on convergence (precision of the parameter estimates) and fitting criteria (residual error, Akaike information criterion and visual predictive checks).

2c – Methods: Simulation analyses
Simulation were performed in Berkeley Madonna v8.3.18 [7]. Developed model was used in a simulation mode to answer following questions from literature [8]:

• How does resistance affect tumor volume under and after treatment?
• What is the optimal dosing protocol to overcome resistance emergence?

3a – Results: Model structure & Parameter estimates

![Figure 1: Classical TGI model (dark blue) and in resistance component (light blue). 'S' refers to sensitive cells and 'R' to resistant cells and 'T' in treated compartments](Image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>a1</td>
<td>0.199 (0.013)</td>
<td>Sensitivity parameter</td>
</tr>
<tr>
<td>a2</td>
<td>0.087 (0.003)</td>
<td>Sensitivity parameter</td>
</tr>
<tr>
<td>b1</td>
<td>0.827 (0.012)</td>
<td>Growth rate parameter</td>
</tr>
<tr>
<td>b2</td>
<td>0.869 (0.013)</td>
<td>Growth rate parameter</td>
</tr>
<tr>
<td>c</td>
<td>0.52 (0.01)</td>
<td>Cell death rate parameter</td>
</tr>
<tr>
<td>d</td>
<td>0.22 (0.01)</td>
<td>Cell death rate parameter</td>
</tr>
</tbody>
</table>

Table: Parameter estimates. RSE is for Relative standard error. A non-linear growth model was used to model the tumor growth.

3b – Diagnostic tools

![Figure II: Observed vs. predicted tumor volume at 100mg/kg (Red), 25mg/kg (Green) and 6.25mg/kg (Blue)](Image)

3c – Results: Simulations

![Figure IV: Simulated tumor volume after daily dose from day 3 to day 43.](Image)

What is the optimal dosing protocol to overcome resistance emergence?

• Resistant cells grow under treatment and total tumor volume increases.
• Faster tumor growth is predicted after treatment due to the faster growing sensitive tumor cells.
• Fraction of resistant cell decreases when treatment stops.

Conclusion
Tumor growth data in xenograft mice were better described with a model assuming adaptive resistance. The proposed resistance model can be used to explain tumor regrowth during and after drug treatment and it allows to simulate impact of dosing regimen on tumor response [9].

The presented modeling results are consistent with findings from Chmielicki et al. [10]:
- Sensitive cells outgrow the resistant cells when treatment stops, leading to a decrease in the fraction of resistant cells. As a result, the tumor becomes again sensitive to TKIs treatment.
- Pulsed treatment can potentially be more beneficial than a continuous treatment, if the resistant cells are sensitive to high plasma drug concentrations. For the presented data set, it was not feasible to identify a killing parameter on the resistant cells. However in this Xenograft model, plasma concentration were still low compared to what is proposed in the pulsed dosing protocol of the ongoing clinical trial [10].

For a thorough evaluation, also safety aspects would need to be considered.

References