Schedule Dependence in Tumor Response for 5-Fluorouracil in Colorectal Cancer

Background and Objectives:
The administration schedule that maximizes tumor response for 5-fluorouracil (5-FU) in colorectal cancer is unknown. MTD depends on schedule because 5-FU shows non-linear PK and dose-limiting toxicities are schedule dependent. The aim was to develop a PKPD model for the response rate (RR) and thereby evaluate if RR in colorectal cancer is dependent on administration schedule of 5-FU when its non-linear PK is considered.

Methods:
Data: Observed RR in 39 study arms of 5-FU schedules in colorectal cancer (Table 1 [1]).
PK: The concentration (Cp) -time profiles for each reported schedule were predicted using a PK model with capacity-limited elimination [2].
PD model: A general model for concentration-effect relationships [3] was applied (Fig 1):
1. Cpl is assumed to exert a direct effect (Edir) by a sigmoid Emax-model or a simplification thereof. If the Cp-Edir relationship is 
   Linear: Emax depend on AUC (schedule independent)
   Step-function: Emax depend on time > threshold Cp
   Emax - or sigmoid Emax : Emax depend on relationship in-between extremes above.
2. The area under the curve for the Edir vs. time curve (AUCEdir) is related to the observed effect (Eobs; here RR) by a 2nd sigmoid Emax-model (or a simpler model).
Analysis: Data was analyzed with NONMEM VI. AUCEdir values were normalized to 4 weeks of treatment to compensate for the different cycle lengths in the studies. Sqrt(npatients) was used as weighting factor.

Results:
The predicted RR for different Cpl when a linear, a step-function and an Emax-model for the Cpl-Edir relationship were evaluated is visualized in Fig. 2. The Emax-model fit the data the best, indicating that 5-FU has schedule dependent tumor effect but that the relationship can not be simplified to be described by the time above a threshold concentration.
EC50 was estimated to 0.613 mg/L (RSE 80%). RR was linearly dependent on AUCEdir and an estimated baseline response
RR (%) = 10.5% (RSE 24%) + 0.431(RSE 62%) * AUCEdir
A prolonged infusion results in a higher RR and the relative benefit of a continuous infusion increase with total AUC (Fig. 3).

Conclusions:
5-FU shows schedule dependent RR in colorectal cancer, also when the non-linear PK is accounted for. 5-FU exerts its highest RR when administered as a protracted infusion. There is an increasing benefit of a continuous infusion when total AUC increase.

Table 1. 5-FU schedules in 39 study arms and their response rates in colorectal cancer taken from Sobrero et al. [1]

<table>
<thead>
<tr>
<th>Type of schedule</th>
<th>Number of study arms</th>
<th>Total dose/ 4 weeks (mg/m2)</th>
<th>Patients/ study arm (range)</th>
<th>RR (%) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus daily for 5 days every 3rd-5th week</td>
<td>13</td>
<td>1850-2500</td>
<td>36-110</td>
<td>1-29</td>
</tr>
<tr>
<td>Bolus daily for 3-5 days then once every week</td>
<td>5</td>
<td>1800-3700</td>
<td>19-154</td>
<td>0-33</td>
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<tr>
<td>Bolus once weekly</td>
<td>4</td>
<td>2400-2740</td>
<td>27-72</td>
<td>4-16</td>
</tr>
<tr>
<td>Bolus once every other week</td>
<td>3</td>
<td>2400</td>
<td>34-91</td>
<td>12-17</td>
</tr>
<tr>
<td>Continuous inf over 1-3 days every to every 3rd week</td>
<td>5</td>
<td>5200-12000</td>
<td>39-85</td>
<td>0-30</td>
</tr>
<tr>
<td>Continuous inf over 5-7 days every 3rd-4th week</td>
<td>3</td>
<td>5000-6500</td>
<td>73-88</td>
<td>8-12</td>
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<tr>
<td>Protracted infusion</td>
<td>6</td>
<td>8400</td>
<td>39-87</td>
<td>12-35</td>
</tr>
</tbody>
</table>

References: