PK/PD model of indisulam in combination with capecitabine

a time-dependent pharmacokinetic interaction contributes to excessive hematological toxicity

Anthe Zandvliet, Wandena Siegel-Lakhai, Jan Schellens, William Copalu, Gerard Milano, Jos Beijnen, Alwin Huitema
Outline

• Clinical study
• Hypothesis
• Aims
• Model development
• Simulation studies
• Conclusions
• Clinical recommendation
Clinical study

• Phase I dose escalation study of indisulam in combination with capecitabine
• 1-hour infusion indisulam day 1 and oral capecitabine BID on days 1-14
• Dose escalation: 350 -800 mg/m² indisulam / 1000 –1250 mg/m² capecitabine BID
Clinical study

- Cycle 1 was well tolerated
- Severe side effects at cycle 2
- Increased exposure to indisulam at cycle 2
Increased exposure to indisulam

- **Cycle 1**
- **Cycle 2**

The graph shows the Indisulam plasma concentration (mg/L) over time after dose (h), with two cycles indicated.
Hypothesis

• Time-dependent drug-drug interaction?
• (A metabolite of) capecitabine may inhibit the synthesis of CYP2C9
Hematological toxicity

- Major toxicity of indisulam

indisulam → hematological toxicity

metabolite of capecitabine
Aims

1) to develop a population PK/PD model for the combination of capecitabine and indisulam
2) to evaluate the role of capecitabine in the induction of hematological toxicity
3) to estimate the impact of a pharmacokinetic interaction on the safety of various dose levels
4) to determine a safe dose of the combination
PK/PD model

PK model
indisulam

enzyme turnover model

capecitabine

PD model
hematological toxicity
PK model indisulam

PK model 
indisulam

enzyme 
turnover 
model

Transit 1 → Transit 2 → …… → Transit n

complete inhibition during capecitabine treatment

PK model indisulam

bound

bound

bound

bound

free

free

free

ISF

plasma

RBC

linear elimination (CL)
saturable elimination (Vmax, Km)

bound lin.
tissue

bound sat.

active enzyme
Enzyme turnover model

Capecitabine administration:

Input into first transit compartment:

ON
OFF

Transit 1

Transit 2

……

Transit n

week 1

week 2

week 3

week 1

week 2

week 3

time

time
Time profile of metabolic activity

Turnover time = 9.2 days (± 2.1 days)
### Indisulam exposure (AUC g*h/L)

<table>
<thead>
<tr>
<th>dose level (mg/m²)</th>
<th>Combination therapy</th>
<th>First cycle</th>
<th>Subsequent cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td></td>
<td>1.2</td>
<td>1.8</td>
</tr>
<tr>
<td>550</td>
<td></td>
<td>1.4</td>
<td>2.1</td>
</tr>
<tr>
<td>600</td>
<td></td>
<td>1.7</td>
<td>2.5</td>
</tr>
<tr>
<td>650</td>
<td></td>
<td>2.0</td>
<td>2.8</td>
</tr>
<tr>
<td>700</td>
<td></td>
<td>2.3</td>
<td>3.2</td>
</tr>
</tbody>
</table>
Pharmacodynamic model

\[ k_{\text{prol}} \]

\[ E_{\text{indisulam}} \]

\[ E_{\text{capecitabine}} \]

Feedback = \( \frac{\text{ANC}_{\text{base}}}{\text{ANC}_t} \)^\gamma
Feedback = \( \frac{\text{TC}_{\text{base}}}{\text{TC}_t} \)^\gamma

\[ k_{\text{tr}} \]

Proliferation \[ \rightarrow \] Transit 1 \[ \rightarrow \] Transit 2 \[ \rightarrow \] Transit 3 \[ \rightarrow \] Circulation

MTT

\[ k_{\text{circ}} (= k_{\text{tr}}) \]

Friberg et al. JCO 2002; van Kesteren et al. Invest. New Drugs 2005
Pharmacodynamic model

\[ E_{\text{indisulam}} = \text{slope}_{\text{indisulam}} \cdot \text{plasma concentration} \]

\[ E_{\text{capecitabine}} = \text{slope}_{\text{capecitabine}} \cdot \text{dose} \]
# Pharmacodynamic parameters

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Interindividual variability</th>
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</thead>
<tbody>
<tr>
<td><strong>Absolute neutrophil count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTT (h)</td>
<td>134</td>
<td>24%</td>
</tr>
<tr>
<td>Gamma</td>
<td>0.0834</td>
<td>74%</td>
</tr>
<tr>
<td>Slope indisulam (L/mg)</td>
<td>0.0206</td>
<td>39%</td>
</tr>
<tr>
<td>Slope capecitabine (mg⁻¹)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Proportional residual error (%)</td>
<td>57.5</td>
<td></td>
</tr>
<tr>
<td><strong>Thrombocyte count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTT (h)</td>
<td>88.8</td>
<td>19%</td>
</tr>
<tr>
<td>Gamma</td>
<td>0.0731</td>
<td>68%</td>
</tr>
<tr>
<td>Slope indisulam (L/mg)</td>
<td>0.0113</td>
<td>50%</td>
</tr>
<tr>
<td>Slope capecitabine (mg⁻¹)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Proportional residual error (%)</td>
<td>58.2</td>
<td></td>
</tr>
</tbody>
</table>
Hematological toxicity

indisulam

metabolite of capecitabine

hematological toxicity
Time profile neutrophil count

Abs. neutrophil count ($10^9$/L) vs. Cycle
Time profile neutrophil count

Abs. neutrophil count ($\cdot 10^9/L$)

Time (weeks)
Simulation studies

- Risk of dose limiting neutropenia
  - CTC grade 4 neutropenia during >7 days

- Groups of 10,000 patients
  - various doses of indisulam (500-700 mg/m²)
  - standard dose of capecitabine (1250 mg/m² BID)
Risk of dose limiting neutropenia

- 700 - 1250
- 650 - 1250
- 600 - 1250
- 550 - 1250
- 500 - 1250

Cycle
Risk of dose limiting neutropenia

Risk of dose limiting neutropenia

Cycle

Risk of dose limiting neutropenia

1 2 3 4

700 - 1250
650 - 1250
600 - 1250
550 - 1250
500 - 1250
700 monotherapy
Conclusions

• co-administration of capecitabine caused a time-dependent inhibition of the saturable elimination pathway of indisulam

• the pharmacokinetic interaction explains the excessive hematological toxicity

• the risk of dose limiting neutropenia is acceptable at a dose level of indisulam 550 mg/m² + capecitabine 1250 mg/m² BID
Clinical recommendation

• The dose level 500/1250 was safe in a limited number of patients in the clinical study

• This study strongly supports that the dose level 550/1250 is recommended for future studies
Acknowledgment

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