DEVELOPMENT OF A TUMOUR GROWTH INHIBITION MODEL TO ELUCIDATE THE EFFECTS OF RITONAVIR ON INTRATUMOURAL METABOLISM AND ANTI-TUMOUR EFFECT OF DOCETAXEL IN A MOUSE MODEL FOR HEREDITARY BREAST CANCER

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Docetaxel (DOC)

• An anticancer agent for several types of cancer, such as lung, breast, gastric and prostate cancer

• It acts by the inhibition of cell mitosis

• Oral ingestion of docetaxel increases convenience for patients comparing to intravenous administration

• One major limitation for oral docetaxel is its low bioavailability due to its affinity for P-glycoprotein (Pgp) and Cytochrome P450 (CYP) 3A
Docetaxel (DOC)

- An **anticancer agent** for several types of cancer, such as lung, breast, gastric and prostate cancer.
- It acts by the inhibition of **cell mitosis**.
- **Oral ingestion** of docetaxel increases convenience for patients comparing to **intravenous administration**.
- One major limitation for oral docetaxel is its **low bioavailability** due to its affinity for P-glycoprotein (Pgp) and Cytochrome P450 (CYP) 3A.

Ritonavir (RTV)

- An **HIV protease inhibitor** and also a strong **CYP3A4 inhibitor**.
- It has been suggested to have an **anti-cancer effect**.

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Co-administration of docetaxel and ritonavir

• PK: In both mice and humans, co-administration results in an enhanced docetaxel plasma concentration by CYP3A4 inhibition.
Co-administration of docetaxel and ritonavir

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Co-administration of docetaxel and ritonavir

• PK: In both mice and humans, co-administration results in an enhanced docetaxel plasma concentration by CYP3A4 inhibition.

• PK: Will ritonavir inhibit docetaxel intratumoural metabolism?
• PD: Will co-administration enhance anticancer effect?
Preclinical experiment – study design

Host: Cyp3a knock-out + Tumour: inherent Cyp3a expression

<table>
<thead>
<tr>
<th>Arm</th>
<th>Description</th>
<th>Days</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm1</td>
<td>Control (n=15)</td>
<td>1</td>
<td>8</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Arm2</td>
<td>RTV (p.o.) (n=15)</td>
<td>1</td>
<td>8</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Arm3</td>
<td>DOC (i.v.) (n=20)</td>
<td>1</td>
<td>8</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Arm4</td>
<td>DOC+RTV (n=20)</td>
<td>1</td>
<td>8</td>
<td>15</td>
<td>22</td>
</tr>
</tbody>
</table>
Preclinical experiment – PK data

**Ritonavir tumour concentration (ng/g)**

**Docetaxel plasma concentration (ng/mL)**

**Docetaxel tumour concentration (ng/g)**

<table>
<thead>
<tr>
<th>Arm</th>
<th>2: RTV</th>
<th>3: DOC</th>
<th>4: DOC+RTV</th>
</tr>
</thead>
</table>

**Time (days)**

Hersonissos, 4th June 2015
Preclinical experiment – PD data

![Graph showing tumor volume over time for different experimental arms: control, RTV, DOC, DOC+RTV. The graph illustrates the progression and differentiation of tumor volume across different treatment groups.]
Preclinical experiment – PD data

Days to reach 1500 mm$^3$

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median</th>
<th>Mean ± SD</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>10.8 ± 2.2</td>
</tr>
<tr>
<td>RTV</td>
<td>14</td>
<td>12.4 ± 3.1</td>
</tr>
<tr>
<td>DOC</td>
<td>54</td>
<td>53.6 ± 1.1</td>
</tr>
<tr>
<td>DOC+RTV</td>
<td>66</td>
<td>65.6 ± 8.6</td>
</tr>
</tbody>
</table>
Objectives

• To develop a PK-PD model based on docetaxel concentration and tumour sizes from preclinical study

• To further evaluate and quantify the effects of ritonavir on systemic and intratumoral concentration and anti-tumour effects of docetaxel when co-administered
PK model – ritonavir

PK model – ritonavir

PK model – docetaxel


Hui Xin Yu
PK model – docetaxel

PK model – co-administration of docetaxel and ritonavir

PK model – co-administration of docetaxel and ritonavir

Docetaxel plasma concentration (ng/mL)

Docetaxel tumour concentration (ng/g)

Symbols: • observation, ■ prediction

Tran TH, et al. Drug Metab Dispos. 2002, 30(1)
PK model – conclusions

• In Cyp3a knock-out host, ritonavir slightly decreased docetaxel systemic clearance by 8% when co-administered

• In tumour with inherent Cyp3a expression, ritonavir inhibited docetaxel metabolism resulting in docetaxel tumour AUC 2.5-fold higher when co-treated with ritonavir
PK-PD model – Exponential tumour growth model
PK-PD model – docetaxel-treated tumour growth inhibition (TGI) model

\[ C_{\text{DOC,tumour}}/(\text{EC}_{50,\text{DOC}} + C_{\text{DOC,tumour}}) \]

\[ K_{K_{\text{DOC}}} \]

\[ K_{\text{g0}} \cdot e^{\lambda \cdot t} \]

\( \lambda = 0.061 \text{ week}^{-1} \)
PK-PD model – docetaxel-treated tumour growth inhibition (TGI) model

1: control

2: RTV

3: DOC

Tumor volume (mm³)

Time (days)
PK-PD model – ritonavir co-treated TGI model

\[
C_{\text{DOC,tumour}}/(\text{EC}_{50\text{DOC}} + C_{\text{DOC,tumour}})
\]

DOC anti-tumour effect

Non-perturbed cells

\[K_{K\text{DOC}}\]

\[K_{g0}\]

\[K_g\]
Hypothesis test – TGI model with docetaxel-treated TGI and PK parameters

\[ C_{DOC,tumour} / (EC_{50,DOC} + C_{DOC,tumour}) \]

\[ K_{Ke_{DOC}} \]

\[ K_{Ke_{DOC}} \]

\[ K_{Kg_{DOC}} \]

\[ K_{g_{0}} \]

\[ K_{g} \]
Hypothesis test – TGI model with docetaxel-treated TGI and PK parameters

- Slight underestimation of anti-tumour effect in early phase of treatment
- Underestimation of the time to tumour re-growth
Hypothesis test – estimation of ritonavir anti-tumour effect

\[ \text{RTV, tumour PK} = \frac{\text{EG50}_{\text{DOC}} + C_{\text{DOC, tumour}}}{K_{\text{DOC, tumour}}} \]

\[ K_{\text{Ke}, \text{DOC}} \]

\[ K_{\text{Ke}, \text{RTV}} \]

Non-perturbed cells

DOC anti-tumour effect

RTV anti-tumour effect
Hypothesis test – estimation of ritonavir anti-tumour effect

- Bias in the model prediction of tumour volume in the co-administration disappeared

- Objective function value dropped 59 points comparing to the model estimation without ritonavir anti-tumour effect
Final PK-PD model

Docetaxel PK

Ritonavir PK

TGI
Final PK-PD model – visual predictive check

Arm1: control

Arm2: RTV

Arm3: DOC

Arm4: DOC+RTV
Conclusions

• A PK-PD model has been successfully developed describing the complex interaction between docetaxel and ritonavir when co-administered in a mouse model for hereditary breast cancer.

• We showed that the enhanced tumour growth inhibition observed in the co-administration of docetaxel with ritonavir is mainly caused by boosting the tumour concentration of docetaxel and to a minor extent by a direct tumour growth inhibitory effect of ritonavir.
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