The use of PKPD-modeling in drug development and for dose individualizing approaches

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Overall survival (OS)  
*Ex, Sunitinib in GIST*

Demetri et al., Lancet 2006

50 mg 4 weeks on 2 weeks off

Kaplan-Meier analysis

50 mg 4 weeks on 2 weeks off

Placebo group on treatment upon progression

How would a changed dose or dosing regimen affect probability of survival?

Are there opportunities for dose individualization?

Figure 4: Kaplan-Meier estimates of overall survival
Results represent central radiology assessment of ITT population and include open-label treatment subsequent to crossover after progression.
Opportunities for PKPD-modeling in oncology

PKPD-modeling in oncology

- Understand the interplay and temporal differences in the time-course of measured variables
- Quantify and explain variability
- Help to pool information from different studies and integrate data across drugs and indications
- Design new studies
Variables for translational PKPD-modeling in Drug development

- Phase 1
- Phase 2
- Phase 3
- Preclinical
- Clinical use

- Drug conc
- Adverse Drug Reactions (ADR)
- Understand trial outcomes
- Study designs
- Individual dose adaptation

- Data from animals
- Imaging
- Biomarkers
- Tumor size
- Survival

- In vitro data
General scheme of PKPD-relationships for evaluation in oncology with common "metrics"

- Dose, regimen changes
- Adverse Effects (AE) PKPD Model
  - PK Metrics: $C_{\text{trough}}$, $AUC$, Concentration(t)
  - AE Metrics: $\Delta$ Baseline, Circ(t)
- Tumor Response PKPD Model
  - Tumor Metrics: TSR, Tumor(t), TTG, $K_{\text{GROW}}$
- Survival Model
  - PFS, OS

Drug-specific
Disease-specific
(Data dependent)
(Purpose)
TUMOR SIZE AS PREDICTOR
Link between tumor size (SLD) and Overall Survival (OS) characterized based on 5-Fluorouracil (FU) data.

Used model to predict survival in Phase III for Capecitabine.
Tumor size as predictor of survival
Colorectal cancer

Fig 3. The 90% prediction interval (light blue area) and observed (line) survival curve for capecitabine in the phase III study. Simulations were performed by using the drug-independent survival model, the week 7 tumor size reduction predicted by the tumor-growth inhibition model, and baseline tumor sizes, as described in Table 3.
### Table 1. Population analyses of clinical tumour SLD response with relation to survival

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Treatment</th>
<th>Model-Based</th>
<th>Other</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>Various chemotherapies</td>
<td>TSR (week 8)</td>
<td>ECOG, tumour SLD&lt;sub&gt;0&lt;/sub&gt;</td>
<td>Wang 2009</td>
</tr>
<tr>
<td>NSCLC</td>
<td>C/P or C/P + Bevacizumab or C/P + Motesanib</td>
<td>TSR (week 8)</td>
<td>ECOG, tumour SLD&lt;sub&gt;0&lt;/sub&gt;</td>
<td>Claret 2012</td>
</tr>
<tr>
<td>CRC</td>
<td>Capecitabine, Fluorouracil</td>
<td>TSR (week 7)</td>
<td>tumour SLD&lt;sub&gt;0&lt;/sub&gt;</td>
<td>Claret 2009</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>Motesanib</td>
<td>TSR (week 8)</td>
<td>ECOG, tumour SLD&lt;sub&gt;0&lt;/sub&gt;</td>
<td>Lu 2010, Claret 2010</td>
</tr>
<tr>
<td>mCRC</td>
<td>Bevacizumab + chemotherapy</td>
<td>TTG</td>
<td>ECOG, number of organs</td>
<td>Claret 2013</td>
</tr>
<tr>
<td>Metastatic breast cancer</td>
<td>Capecitabine + docetaxel</td>
<td>TSR (week 6)</td>
<td>tumour SLD&lt;sub&gt;0&lt;/sub&gt;, ECOG, number of metastasis, study</td>
<td>Bruno 2012</td>
</tr>
</tbody>
</table>

Pharmacometric analyses of OS

Bender et al., Br J Clin Pharmacol, 2015
Metrics of Tumor size as predictor of survival

Should we maximize the wk6 response?

What if we change the dose at wk 9?

Letting the hazard of death be dependent on the full time-course of time-varying predictors is theoretically preferable, i.e. integrate the hazard over time!

- Available information may be limiting

Bender et al., Br J Clin Pharmacol, 2015
Tumor size as predictor

+ Intuitive
+ Related to RECIST criteria, translation

- Sum of Longest Diameters (SLD) a good measure of disease severity?
- Data generally sparse
- Delay in observing treatment response
- Treatment response not always related to shrinkage in SLD
BIOMARKERS AS PREDICTORS
Biomarkers as predictors

Potential for more efficient drug development and drug usage

- Provide an understanding of the mechanism of action
- Facilitate prediction and monitoring of clinical response
- Act as an early indicator of safety issues
- Enable dose optimization & dose individualization
Biomarkers as predictors
Sunitinib in GIST – Data pooled from 4 clinical studies

Dose → AUC → VEGF → sVEGFR-2 → Tumor size → Overall Survival
Dose → AUC → VEGF → sVEGFR-3 → Tumor size → Overall Survival
Dose → AUC → sKIT → Tumor size → Overall Survival

Adverse Drug Reactions

Hansson et al., CPT:PSP 2013
PKPD-modeling of Biomarkers
Sunitinib in GIST

n simulations = 500
- Confidence intervals for the simulated data’s 5th, 50th and 95th percentiles
- 50th percentile of the observed data
- 5th and 95th percentiles of the observed data

Hansson et al., CPT:PSP 2013
Modeling the time-course of biomarkers VEGF, sVEGFR2/3, sKIT in GIST

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>$k_{out}$</td>
</tr>
<tr>
<td>sVEGFR-2</td>
<td>$K_{in}$</td>
</tr>
<tr>
<td>sVEGFR-3</td>
<td>$K_{in}$</td>
</tr>
<tr>
<td>sKIT</td>
<td>Linear</td>
</tr>
<tr>
<td>sKIT DP</td>
<td>Linear</td>
</tr>
<tr>
<td>VEGF DP</td>
<td></td>
</tr>
</tbody>
</table>

$DP = \text{Disease progression}$
Biomarkers related to tumor size

Sunitinib in GIST

Dose \rightarrow AUC(t) \rightarrow s\text{VEGFR-3}_{\text{REL}}(t) \rightarrow Tumor size

Dose \rightarrow AUC(t) \rightarrow s\text{KIT}_{\text{REL}}(t) \rightarrow Tumor size

n simulations = 500

Confidence intervals for the simulated data’s 5th, 50th and 95th percentiles

50th percentile of the observed data

5th and 95th percentiles of the observed data

Biomarkers related to tumor size

Active

Placebo

Hansson et al., CPT:PSP 2013
Time-constant and Time-varying predictors evaluated for Survival
Sunitinib in GIST

What information/biomarkers to collect?

Hansson et al., CPT:PSP 2013, Venkatakrishnan et al. CPT, 2015
Biomarkers related to Survival
Sunitinib in GIST

Parameteric Time-to Event-Model
- Handle changes in dose and time-varying covariates accurately
- Can be used to simulate new scenarios
Modeling framework for Axitinib in mRCC
Learn from Sunitinib in GIST?

Same structural models as for sunitinib in GIST
Standard Uptake Value (SUV) as predictor for sunitinib in GIST
ADVERSE DRUG REACTIONS AS PREDICTORS
Modelling framework
ADRs of sunitinib

- Dose
- AUC
  - VEGF
  - sVEGFR-2
  - sVEGFR-3
  - sKIT
- ADR
  - Fatigue
  - Hand-Foot Syndrome
  - Absolute Neutrophil Counts
  - Blood Pressure
PKPD-Model for blood pressure
Sunitinib in GIST

$K_{in}$  \rightarrow  Blood pressure (BP)  \rightarrow  k_{out}$

AUC(t)  \rightarrow  +

Active

Placebo

n simulations = 500
Confidence intervals based on the simulated data
50th percentile of the observed data
5th and 95th percentiles of the observed data
PKPD-Model for myelosuppression
Sunitinib in GIST

\[ K_{\text{prol}} = K_{\text{tr}} \]

Feedback = \( \left( \frac{\text{ANC}_0}{\text{ANC}} \right)^Y \)

SVEGFR-3_{\text{REL}(t)}

MTT = \( \frac{4}{K_{\text{tr}}} \)

\[ K_{\text{circ}} = \ln(2)/t_{1/2} \]

**Proliferating cells**

\[ \frac{E_{\text{Drug}}}{E_{\text{EC}_{50\text{drug}}} + \text{AUC}} \]

\[ \frac{E_{\text{BM}}}{E_{\text{EC}_{50\text{BM}}} + \text{BM}_{\text{REL}}} \]

Circulating neutrophils

\[ n \text{ simulations} = 500 \]

Confidence intervals based on the simulated data

50th percentile of the observed data

5th and 95th percentiles of the observed data

\[ \text{Active} \]

\[ \text{Placebo} \]
PKPD-Models for categorical AE data
HFS and Fatigue

Probability of current score depends on previous score

Time after start of treatment (weeks)

Grade of HFS

Markov elements to not simulate too many transitions

Hand-Foot-Syndrome (HFS)

Henin et al., Clin Pharmacol Ther, 2009
Models for Fatigue and HFS VPCs for Sunitinib in GIST

- Observed data
- 95% confidence interval based on simulations
- n simulations = 500
- Hand-Foot Syndrome
- Fatigue

Hansson et al. CPT:PSP 2013
ADRs as predictors of Survival
Sunitinib in GIST

Kaplan-Meier plot of observed data
95% confidence intervals based on simulated data

n simulations = 200
Kaplan-Meier plot of observed data
95% confidence intervals based on simulated data

Dose \[ \rightarrow \] AUC(t) \[ \rightarrow \] Absolute Neutrophil Counts
Diastolic Blood Pressure

Overall Survival

Tumor base

ANC(t) \[ \downarrow \] ANC toxicity \[ \uparrow \] h(t) \[ \downarrow \]
BP_{REL}(t) \[ \uparrow \] Blood pressure \[ \uparrow \] h(t) \[ \downarrow \]

Time (weeks after first treatment)
Dose Individualization based on ADR at 4 weeks - Sunitinib in GIST

<table>
<thead>
<tr>
<th>Effect on BP &amp; ANC</th>
<th>Blood pressure $\uparrow &gt; 10%$ &amp; ANC $&lt; 3 \cdot 10^9$ cells/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low effect BP &amp; ANC</td>
<td>Blood pressure $\uparrow &lt; 10%$ &amp; ANC $&gt; 3 \cdot 10^9$ cells/L</td>
</tr>
</tbody>
</table>

50 mg Effect on BP & ANC
75 mg Low effect BP & ANC
62.5 mg Low effect BP & ANC
50 mg Low effect BP & ANC

Graph showing survival over time with different doses of Sunitinib.
Dose Individualization at 4 weeks
Consequence on Other ADR

**Fatigue**

- Grade 1
- Grade 2
- Grade >3

**Hand-Foot Syndrome**

- Grade 1
- Grade 2
- Grade >3

LowADR = Low effect on BP & ANC
Predictor of Survival?
T-DM1 in Breast cancer

Wang et al., Clin Pharmacol Ther, 2014

How would a changed dose affect probability of survival?

Relationship to $C_{\min}$
Tumor growth inhibition model
Prostate-specific antigen (PSA) - Eribulin

LYG = Life years gained
ICER = incremental cost-effectiveness ratio
\( f(\text{Dose}, \text{Duration}_{AE}, \text{Cost}_{dose}, \text{Cost}_{AE}) \)
QALY = quality-adjusted life years
PREDICTION FROM PRECLINICAL DATA
Model-based translation from rats to clinical myelosuppression

System-specific
Species specific

<table>
<thead>
<tr>
<th></th>
<th>$WBC_0$ $\left(\cdot 10^9/L\right)$</th>
<th>MTT $(h)$</th>
<th>$\gamma$</th>
<th>Slope $(L/mg)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>7.12</td>
<td>90.4</td>
<td>0.175</td>
<td>7.91</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>7.21</td>
<td>124</td>
<td>0.239</td>
<td>1.69</td>
</tr>
<tr>
<td>Etoposide</td>
<td>7.07</td>
<td>135</td>
<td>0.189</td>
<td>0.121</td>
</tr>
<tr>
<td>DMDC</td>
<td>7.50</td>
<td>123</td>
<td>0.121</td>
<td>2.76</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>8.10</td>
<td>125</td>
<td>0.147</td>
<td>1.09</td>
</tr>
<tr>
<td>Vinflunine</td>
<td>6.74</td>
<td>112</td>
<td>0.157</td>
<td>0.00347</td>
</tr>
</tbody>
</table>

~7 Similar across species?

Similar drug-related parameters in rats and patients

 Corrections for species differences in
  - protein binding (fu)
  - sensitivity in IC90 in CFU-GM assay

\[ \text{Slope}_{\text{fu,sensitivity}} = \text{Slope}_{\text{rat}} \cdot \left( \frac{\text{fu}_{\text{human}}}{\text{fu}_{\text{rat}}} \right) / \left( \frac{\text{IC90}_{\text{human}}}{\text{IC90}_{\text{mice}}} \right) \]
Scaling the full time-course of myelosuppression

Human system-related parameters:
$WBC_0 = 7 \cdot 10^9/L$  $MTT = 125 \text{ h}$  $\gamma = 0.17$

PK in humans

Proliferative cells
Non-mitotic cells
Mean Transit Time (MTT) = $4/k_{tr}$

Drug concentration
Slope$_{fu,sensitivity}$

Mean Transit Time (MTT) = $4/k_{tr}$

Feedback = $\frac{WBC_0}{WBC(t)}$

Human system-related parameters:
$WBC_0 = 7 \cdot 10^9/L$  $MTT = 125 \text{ h}$  $\gamma = 0.17$

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Drug concentration
Slope$_{fu,sensitivity}$

Mean Transit Time (MTT) = $4/k_{tr}$

Feedback = $\frac{WBC_0}{WBC(t)}$

Friberg et al. Invest New Drugs, 2010
Predictions of the time-course of myelosuppression in patients

System related parameters in patients:
\(WBC_0 = 7 \cdot 10^9/L\), MTT = 125 hours, \(\gamma = 0.17\)

\(\text{Slope}_{\text{patients}} \quad \cdots \quad \text{Slope}_{\text{rats}} \quad \text{Slope}_{\text{fu, sensitivity}}\)

Friberg et al. Invest New Drugs, 2010
IMPROVE STUDY DESIGNS
Finding Maximum Tolerated Dose (MTD) based on PKPD-model

- Simulation of large N patients per dose
- Count DLTs per dose
- Determine MTD as dose level with 1/3 DLTs

**Threshold 33% Tox**

**MTD identified in trial by 3+3 design**

Fouliard et al. (next session), Vong et al., PAGE2014
Prediction of myelosuppression in subsequent studies

Diflomotecan

Soto et al, Invest New Drugs, 2011
Uses of PKPD-modeling

Drug development
- Integrate data and information
  - Desired effects, biomarkers, ADR
- Facilitate translation
- Support trial designs
- Allow for comparison between drugs and indications

Dose individualization
- Identify predictive pre-treatment characteristics
- Feedback dose adjustments
  - Drug concentrations vs. Biomarkers vs. Side effects
Thank you!

Pharmacometrics Research Group at Uppsala University