A pharmacometrical framework for dose individualisation of sunitinib in GIST

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Sunitinib therapy in Gastro-Intestinal Stromal Tumors (GIST)

- **Sunitinib** is a Tyrosine-kinase inhibitor
Sunitinib therapy in Gastro-Intestinal Stromal Tumors (GIST)

- Various biomarkers have been suggested for dose-individualisation:

  - **Therapeutic Drug Monitoring**
    - • $\text{Css, min Sunitinib} + \text{SU12662}$
  - **Toxicity-Adjusted Dosing**
    - • Neutropenia
    - • Hypertension
  - **sVEGFR-3 based dosing**
    - • sVEGFR-3 changes

Hansson et al., 2013, *CPT: Pharmacometrics and Syst Pharmacology*
Lankheet et al., 2014, *Br J Cancer*
Sabanathan et al., 2017, *Cancer Chemother Pharmacol.*
Models can be useful…

\[ Y_{ij} = f(x_{ij}, \theta_i) + \epsilon_{ij} \]

**Pharmacokinetic models**

- Estimate PK parameters
- Explore alternative dosing regimens
- Evaluate covariates and drug-drug interaction

**Pharmacodynamic (exposure-response) models**

- Define therapeutic window
- Detect robust biomarkers

Box et al., 1967, Journal of the American Statistical Association
Pharmacometric Framework: concept

- **Dose, regimen changes**
  - Dose
    - Pharmacokinetic model
      - $C_{\text{trough}}$, AUC, concentration(t)
    - Adverse effects PKPD model
      - $\Delta_{\text{baseline}}$, circ(t)
    - Biomarker response PKPD model
      - AUC, biomarker(t)
    - Tumor response PKPD model
      - TSR, tumor(t), TTG, $K_{\text{grow}}$
    - Survival model

Pharmacometric framework

Adverse Events

- Fatigue
- Hand Foot Syndrome
- Neutropenia
- Diastolic Hypertension

Overall survival

Tumor size

Yu et al.

Dose

sVEGFR-3

AUC

Hansson et al., 2013a, CPT: Pharmacometrics and Systems Pharmacology
Hansson et al., 2013b, CPT: Pharmacometrics and Systems Pharmacology
Pharmacometric framework

Adverse Events
- Fatigue
- Hand Foot Syndrome
- Neutropenia
- Diastolic Hypertension

Tumor size
Overall survival

Yu et al.
Dose
AUC

Hansson et al., 2013a, CPT: Pharmacometrics and Systems Pharmacology
Hansson et al., 2013b, CPT: Pharmacometrics and Systems Pharmacology
Biomarker-based dose adaptations

- Therapeutic Drug Monitoring
- Toxicity-Adjusted Dosing
- sVEGFR-3 based dosing

PK — PD
Schedule for dose individualisation

Dose adjustments:

- **All:** ↓ Grade 2/3 toxicities
  - ↓ CSS, min > 75 ng/ml
  - ↑ dBP < 7.5%
  - ↑ ANC > -27%
  - ↑ sVEGFR-3 > -45%

**Schedule for dose individualisation**

- **Fixed Dosing Regimen**
- **Therapeutic Drug Monitoring**
- **Toxicity-Adjusted Dosing**
- **sVEGFR-3 based dosing**

Weeks after initiation of sunitinib therapy:

- Weeks 2, 4, 8
Comparison of biomarkers: adverse events

TDM = therapeutic drug monitoring, TAD = toxicity-adjusted dosing

Daily observations of adverse events

Simulation with 1000 individuals

1 cycle = 6 weeks of sunitinib therapy
Comparison of biomarkers

Overall Survival

Adverse Events

- Fatigue ≥ Grade 3
- HFS ≥ Grade 2
- Neutropenia ≥ Grade 3
- dBP ≥ Grade 3

TDM = therapeutic drug monitoring, TAD = toxicity-adjusted dosing
Comparison of biomarkers

Overall Survival

Adverse Events

TDM = therapeutic drug monitoring, sVEGFR-3 = sVEGFR-3 based dosing
Model-based dose individualisation

- Neutropenia
- Diastolic Blood Pressure
- sVEGFR-3
Schedule for dose individualisation

**Fixed Dosing Regimen**

**Therapeutic Drug Monitoring**

**Toxicity-Adjusted Dosing**

sVEGFR-3 based dosing

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**Dose adjustments:**

- $\uparrow$ Css,min < 37.5 ng/ml
- $\downarrow$ Css,min > 75 ng/ml
- $\uparrow$ dBp < 7.5%
- $\uparrow$ ANC > -27%
- $\uparrow$ sVEGFR-3 > -45%

Weeks after initiation of sunitinib therapy
Schedule for dose individualisation

- **Fixed Dosing Regimen**
- **Therapeutic Drug Monitoring**
- **Toxicity-Adjusted Dosing**
- **sVEGFR-3 based dosing**

**Dose adjustments:**
- $\uparrow$ Css, min < 37.5 ng/ml
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Weeks after initiation of sunitinib therapy:
Accuracy of neutropenia forecasts

Monitoring frequency

<table>
<thead>
<tr>
<th>Monitoring Frequency</th>
<th>Daily</th>
<th>Weekly</th>
<th>Biweekly</th>
</tr>
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</table>

 Accuracy at Week 4:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Accuracy</th>
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<tbody>
<tr>
<td>Daily</td>
<td>85.6%</td>
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<tr>
<td>Weekly</td>
<td>78.4%</td>
</tr>
<tr>
<td>Biweekly</td>
<td>73.5%</td>
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</tbody>
</table>

\[
\Delta ANC = \frac{ANC(t) - 5}{5}
\]

Results are based upon the CD schedule (37.5 mg)

Accuracy = 80-125% true value

ANC = absolute neutrophil count

*ANC = absolute neutrophil count

Netterberg et al., 2017, Cancer Chemother Pharmacol
Accuracy of dBP and sVEGFR-3 forecasts

\[ \Delta \text{dBP} = \frac{\text{dBP}(t) - \text{BASE}_{\text{dBP}}}{\text{BASE}_{\text{dBP}}} \]

\[ \Delta \text{sVEGFR-3} = \frac{\text{sVEGFR-3}(t) - \text{BASE}_{\text{sVEGFR-3}}}{\text{BASE}_{\text{sVEGFR-3}}} \]

- **Daily:** 35.1%
- **Weekly:** 28.5%
- **Biweekly:** 28.4%

**Accuracy at Week 4:**
- **Daily:** 75%
- **Weekly:** 66.8%
- **Biweekly:** 65.2%

\[ \text{dBP} = \text{diastolic blood pressure} \]

\[ \text{sVEGFR-3} = \text{soluble VEGFR-3} \]
1. A pharmacometric framework provides an integrated approach to answer clinically relevant questions:
   1. Gives an overview of multiple relevant outcomes
   2. Enables interaction between outcomes

2. Pharmacodynamic biomarkers for dose individualisation of survival improve overall survival of GIST patients, as compared to Pharmacokinetic ones.

3. Forecasting treatment outcomes based on early clinical measurements can improve treatment outcome by:
   1. Preventing the development of severe side effects
   2. Allowing for early dose-adaptation
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