A pharmacometric framework for dose individualisation of sunitinib in GIST

Maddalena Centanni, Sreenath M. Krishnan, Lena E. Friberg

Department of Pharmaceutical Biosciences, Uppsala University, Sweden

PAGE 2018 May 30
The pharmacometric framework for sunitinib in GIST

Based on 303 patients

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

Overall survival

Tumor baseline size

sVEGFR-3

AUC

The pharmacometric framework for sunitinib in GIST

Based on 303 patients
Why use a pharmacometric framework?

Modeling

• Integrated understanding of the relationships between drug exposure, plasma biomarkers, adverse events, disease state, and long-term clinical outcome.
  → Valuable for identifying robust pharmacodynamic (PD) biomarkers and guide treatment decisions.

Simulations

• Allows for an interaction between treatment outcomes (e.g. toxicity-induced dose reductions may potentially impact efficacy).
  → Realistic predictions of treatment outcomes under various dosing algorithms.

vvan Hasselt et al. 2015. CPT Pharmacometrics Syst. Pharmacol.
Sunitinib therapy in Gastro-Intestinal Stromal Tumors (GIST)

- **Sunitinib** is a Tyrosine-kinase inhibitor

- Various fixed dosing regimens are followed for GIST:

  - **4/2 (weeks on/off) 50 mg**
  - **2/1 (weeks on/off) 50 mg**
  - **Continuous 37.5 mg**

Demetri et al. 2006. Lancet.
Shen et al 2017. Oncol Ther.
FDA. SUNITINIB: FDA Prescribing Information.
Various biomarkers have been suggested for dose-individualisation:

- **Therapeutic Drug Monitoring**
  - \( \text{Css, min Sunitinib + SU12662} \)

- **Toxicity-Adjusted Dosing**
  - Neutropenia
  - Hypertension

- **sVEGFR-3 based dosing**
  - \( \text{sVEGFR-3 changes} \)

---

Hansson et al., 2013, *CPT: Pharmacometrics and Syst Pharmacology*
Lankheet et al., 2014, *Br J Cancer*
Sabanathan et al., 2017, *Cancer Chemother Pharmacol.*
Objectives

Identify which biomarker could best be utilised for dose individualisation of sunitinib in GIST, to optimize the benefit/risk ratio.
Expansion of the framework

1: popPK model

Yu et al.

Dose

$C_{ss,\text{min}}$

AUC

sVEGFR-3

Adverse Events

Fatigue

Hand Foot Syndrome

Neutropenia

Diastolic Hypertension

Tumor baseline size

Overall survival

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

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

**Weeks after initiation of sunitinib therapy**

- **Dose adjustments:**
  - **All:**
    - \( \uparrow \text{Grade 2/3 toxicities} \)
  - **\( \downarrow \text{Css, min} < 37.5 \text{ ng/ml} \)**
  - **\( \downarrow \text{Css, min} > 75 \text{ ng/ml} \)**
  - **\( \uparrow \text{dBP} < 7.5\% \)**
  - **\( \uparrow \text{ANC} > -27\% \)**
  - **\( \uparrow \text{sVEGFR-3} > -45\% \)**
Comparison of biomarkers: adverse events

- **No Adjustment**
- **TDM**
- **TAD**

**Fatigue ≥ Grade 3**

**HFS ≥ Grade 2**

**Neutropenia ≥ Grade 3**

**dBP ≥ Grade 3**

- **Daily observations of adverse events**
- **Simulation with 1000 individuals**
- **1 cycle = 6 weeks of sunitinib therapy**

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

Overall Survival

Adverse Events

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

Overall Survival

Adverse Events

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

Survival Probability

Time (weeks)

Percent of Individuals

Cycle

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

Neutropenia  Diastolic Blood Pressure  sVEGFR-3
Weeks after initiation of sunitinib therapy

- **Fixed Dosing Regimen**

- **Therapeutic Drug Monitoring**
  - dBP < 7.5%
  - ANC > -27%
  - Css,min < 37.5 ng/ml
  - Css,min > 75 ng/ml

- **Toxicity-Adjusted Dosing**
  - dBP < 7.5%
  - ANC > -27%
  - sVEGFR-3 > -45%

- **sVEGFR-3 based dosing**
  - + model forecasts

**Dose adjustments:**

- + model forecasts

**Schedule for dose individualisation**
Accuracy of neutropenia forecasts

Monitoring frequency

- Daily
- Weekly
- Biweekly

(a) ANC monitored at day 0
(b) ANC monitored up to day 8
(c) ANC monitored up to day 15
(d) ANC monitored up to day 22
(e) ANC monitored up to day 29

Accuracy at Week 4:
- Daily: 86%
- Weekly: 78%
- Biweekly: 74%

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

Results are based upon the CD schedule (37.5 mg)

Accuracy = 80-125% true value

* ANC = absolute neutrophil count

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

\[ dBP = \frac{dBP(t) - BASE_{dBP}}{BASE_{dBP}} \]

\[ sVEGFR-3 = \frac{sVEGFR-3(t) - BASE_{sVEGFR-3}}{BASE_{sVEGFR-3}} \]

**Daily:** 35%

**Weekly:** 28%

**Biweekly:** 28%

**Daily:** 75%

**Weekly:** 67%

**Biweekly:** 65%

**Accuracy at Week 4:**

Based on the CD schedule (37.5 mg)

**dBP** = diastolic blood pressure

**sVEGFR-3** = soluble VEGFR-3
1. A pharmacometric framework including both clinical outcomes and adverse effects provides an integrated approach to answer clinically relevant questions:
   • Provides an overview of the consequences of a dose change on multiple relevant outcomes
   • Enables consideration of interaction between variables

2. For sunitinib in GIST:
   • The suggested algorithm for TDM (concentration) was not predicted to improve OS
   • The suggested algorithm for Toxicity adjusted dosing (TAD) was predicted to improve OS
   • A sVEGFR-3 target was defined which resulted in similar OS and AEs as TAD
   • Next step: Optimize the biomarker cut-off points as well as the sampling schedules
3. Neutrophil counts and sVEGFR-3 appear reliable for forecasting:
   • Early measurements shown to predict later measurements
   • **Next step**: The predictive performance of early measurements to predict individual hazard of death
Acknowledgements

Radboud MC:
- Ingrid Desar
- Nielka van Erp

Metrum Research Group:
- Kyle T. Baron

Funding:
- Swedish Cancer Society
- European University Consortium for Pharmaceutical Sciences