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Simulation-based systematic review of imatinib population pharmacokinetics and PK-PD relationships in chronic myelogenous leukemia (CML) patients

Introduction

Imatinib is a first-line drug for CML and is characterized by a considerable pharmacokinetic variability.

Population pharmacokinetic (PPK) and pharmacokinetic-pharmacodynamic (PK-PD) studies have been increasingly performed.

Objective

To compare and combine results from

PPK & PK-PD studies of imatinib

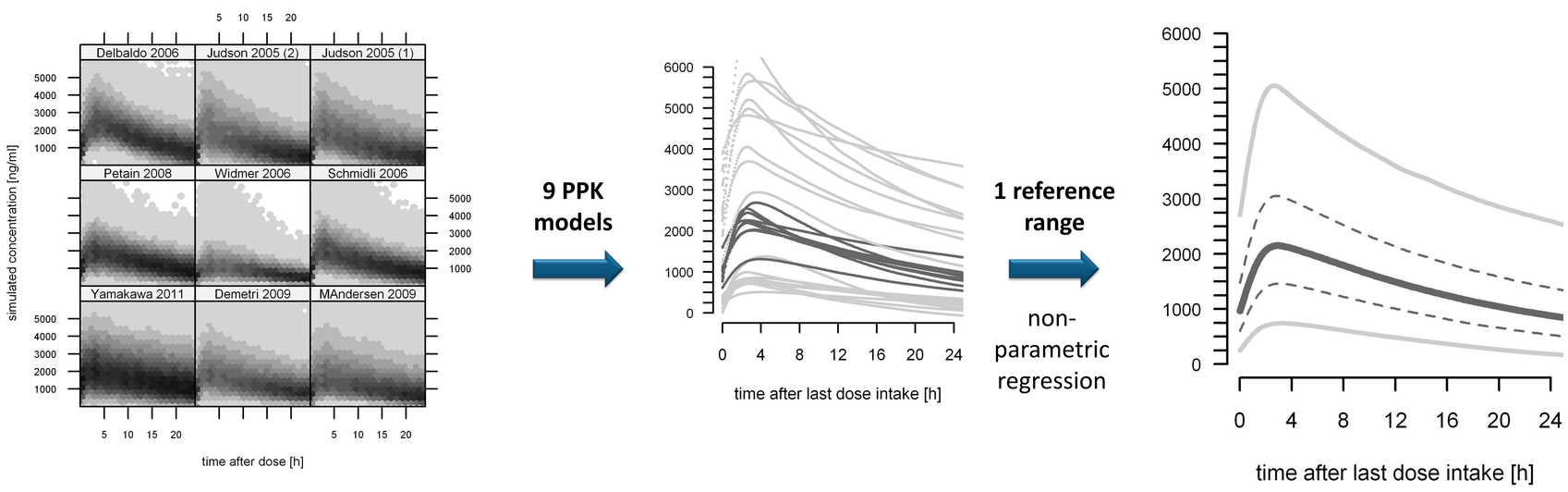
⇨ to improve the interpretation of concentration measurements in the scope of therapeutic drug monitoring.

Methods

- Systematic literature review (MEDLINE) of
  - Imatinib PPK &
  - Imatinib PK-PD relationships
- Simulation-based meta-regression (*without specific study weighting*).

Results

Summary of imatinib population pharmacokinetics ⇨ *expected* concentration range *(=reference range)*



Covariate: reference *(used for simulations)*	**Covariate effect:** Concentration ↓ or ↑ [% change in CL/F; range]
Body weight: 70 kg	105 kg: ↓ [+13 to +72%] 35 kg: ↑ [-16 to -60%]
Age: 50 years	87.5 y: ↑ [-26%] 25 y: ↓ [+18%]
Gender: male	female: ↑ [-18%]
Disease type: CML	GIST: ↑ [-10%]
Albumin: 45 g/L	30 g/L: ↑ [-23 to -49%]
AGP: 0.9 g/L	1.5 g/L: ↑ [-23 to -28%]
White blood cells: 8 G/L	20 G/L: ↑ [-9 to -32%]
Granulocytes: 4.5 G/L	2 G/L: ↓ [+59%]
Hemoglobin: 14 g/L	9 G/L: ↑ [-33%]
ABCG2 (bcrp): wildtype	heterozygous: ↑ [-22%]
Occasion: steady state	day 1: ↑ or ↓ [-25 to +38%]

Table: Reference covariate values used for simulations and summary of covariate effects → altered expected concentration range. AGP: α_1-acid glycoprotein

1) DATA: **Nine population pharmacokinetic (PPK) models were identified and used to simulate concentration-time profiles** of 1000 individuals each. *Black shaded area*: high density of concentrations (→ highly expected). *Grey shaded area*: low density of concentrations (→ concentrations less expected).

Simulated dose: 400 mg/24h (=standard dosage); *Structural kinetic parameters*: D1, CL/F, V/F (standardized to reference covariate values → see Table).

2) COMPARISON: **Median concentration-time profiles** (*black lines*) **and 90% prediction intervals** (*gray lines:* percentiles 5 and 95) of each PPK model, derived from simulations.

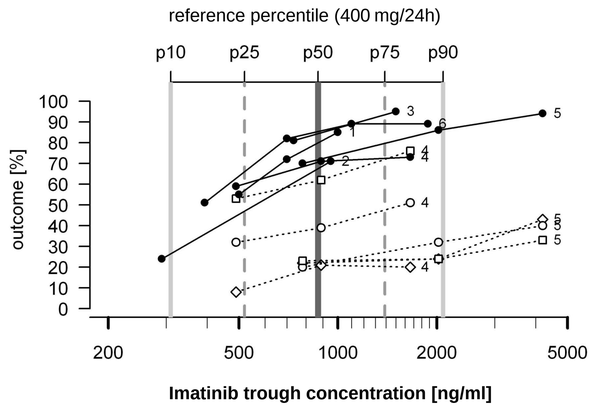
3) COMBINATION: **Reference concentration range, derived from the pooled data from the 9 simulations:** Median concentration-time profile (*black line*) 50% (*dashed lines*) and 90% (*grey lines*) prediction interval. Unexpected high or low concentrations may be partly explained by covariates (→ see Table).

Summary of imatinib PK-PD relationships ⇨ therapeutic *suitability* of C_{trough} (*potential therapeutic range*)

PK measure:
Imatinib trough concentration (C_{trough})

PD outcome:
Proportion [%] with optimal early response & adverse events

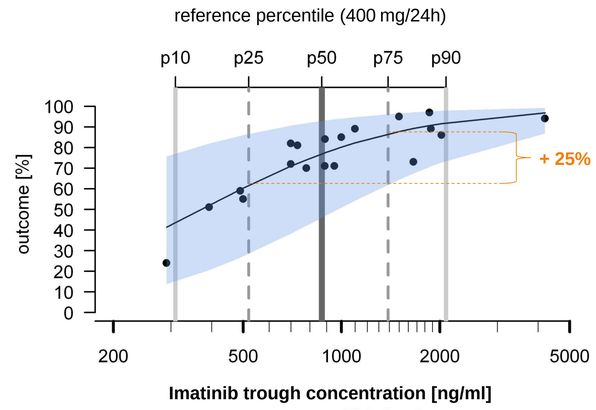
6 PK-PD studies identified



1 summary PK-PD relationship

linear meta-regression

1. Transformation of [%] into log-odds
2. Linear regression model: log-odds ~ C_{min}
3. Transformation of predicted log-odds into [%]



1) DATA: **Six relevant PK-PD studies were identified and proportions** [%] **of PD outcomes ~ C_{min} were used as reported, or simulated** from the distribution reported for responders and non-responders, respectively (3-4 points per study).

Optimal early response is correlated to improved survival and includes complete hematologic response after 1-3 months, and partial or complete cytogenetic response at 6 and 12 months, respectively.

2) COMPARISON: **[%] with PD outcomes ~ C_{min}, plotted for each of the 6 identified studies.**

–●– (*optimal early response*)
···◇··· (*anemia*), ···○··· (*rash*), ···□··· (*fluid retention*)

Studies: 1: Peng 2004; 2: Singh 2009; 3: Sohn 2011; 4: Larson 2008; 5: Guilhot 2012; 6: Picard 2007.

Adverse event reporting was too heterogeneous to perform a meta-regression. The frequency of adverse events increased however consistently with C_{trough}, but less than the response probability in the reference inter-quartile range (IQR) of expected C_{trough} under standard dosage (400 mg/24h)

3) COMBINATION: **The probability to achieve optimal early response was predicted to increase from 62% to 87% (+25%) by increasing C_{trough} from 520 to 1390 ng/mL** (=summary inter-quartile range of C_{trough}, standard dosage of 400mg/24h)**.** Estimated odds ratio for doubling C_{trough}: 2.7. *blue area*: 95% confidence interval.

Conclusions

- **This review represents a first approach to summarize the information generated by the increasing number of population pharmacokinetic analyses for clinical practice.**
- **A single combined range of expected imatinib concentrations can be useful to evaluate adherence & absorption problems, or drug-drug interactions,** especially if no validated in-house model is available.
- **The PK-PD summary can additionally be useful to assist dosage decisions in case of suboptimal response and adverse events.** However, a definite therapeutic range has to be formally validated by a prospective randomized controlled TDM-trial.

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References

Gotta et al. Ther Drug Monit 2013;35(2):150-67