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)
  ➢ 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)

1) DATA: Nine population pharmacokinetic (PPK) models were identified and used to simulate concentration-time profiles of 1500 individuals each. Black shaded area: high density of concentrations (agt; highly expected), grey shaded area: low density of concentrations (agt; 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 line) and 30% prediction intervals (grey line: 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 line) and 90% (grey line) 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

1) DATA: Six relevant PK-PD studies were identified and proportions [%] of PD outcomes - C_{trough} were used as reported, or simulated from the model reported for responders and non-responders, respectively (2-4 points per study).

Optimal early response is correlated to improved survival and includes complete hematologic response after 1.5 months, and partial or complete cytogenetic response at 6 and 12 months, respectively.

2) COMPARISON: [%] with PD outcomes - C_{trough} plotted for each of the 6 identified studies.

- O - (optimal early response)
- D - (anemia), C - (citrobacter), A - (fluid retention)


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 interquartile 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 330 to 1300 ng/ml. (simulated interquartile range of C_{trough} standard dosage of 400mg/24h). Estimated odds ratio for doubling C_{trough} 2.7. Blue area: 95% confidence interval.

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References

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Conclusions

- This review represents a first approach to summarize the information generated by the increasing number of population pharmacokinetics 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.