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Probability of achieving optimal molecular response to imatinib treatment in chronic myeloid leukemia (CML) patients

Pharmacokinetic/Pharmacodynamic (PK/PD) relationships observed under field-conditions

Introduction

Background

Imatinib is a first-line drug for CML with considerable pharmacokinetic variability.

Therapeutic drug monitoring (TDM) has been increasingly proposed, as trough concentrations (C_{min}) have been correlated with improved response in prospective trials.[1,2]

Objective

To evaluate the impact of imatinib exposure on optimal molecular response (MR) rates in a large European cohort of patients followed by centralized TDM.

Methods

Study scope

Observational study: Pharmacological Monitoring Project of EUTOS (European Treatment & Outcome Study, 2006-2010)[3].

PK/PD analysis

Sequential PK/PD analysis (NONMEM 7):

1. **Population PK analysis** (*FOCE-interaction)*

   ⇨ individual Bayesian estimates of exposure (PK)

2. **Mixed-effect logistic regression** *(ITS)*

   PD (optimal MR) ~ PK + covariates + η

Covariates considered

PK variables: log-normalized C_{min} (*log-C_{min}*) or clearance (*CL*), adjusted to initial dose

Others: Time on imatinib treatment (stratified at 3 years), sex, CML phase, age, potentially interacting comedication, TDM frequency.

Table 1: Data - patient and sample characteristics

Patients [n]		1299
Gender [n]	male : female	728: 571
Observations [n]		2230
Estimated $C_{min\ (adj)}$ [ng/ml]	median (range)	797 (231-4602)
Estimated CL [L/h]	median (range)	14.4 (5-28)
Age [years]	median (range)	56 (18-92)
Daily dose [mg]	mean (sd)	462 (124)
Months on imatinib	median (range)	45 (18-143)
Comedication [n]	Present : unknown	1682 : 548

$C_{min(adj)}$: trough concentration adjusted to standard (initial) dose of 400mg daily.

Results

Population PK analysis

Table 2: Summary of population PK model	Point estimate	RSE %
Structural parameters (1-compartment, 0-order absorption)		
Duration of absorption (D1)	3.2 h	10.2%
Clearance (CL/F)	17.3 L/h (male)	9.6%
Volume of distribution (V/F)	429 L	10.2%
Between-subject variability		
$CV\%_{CL/F}$	37.7%	12.1%
$CV\%_{V/F}$	51.1%	39.5%
$Correlation_{CL/F-V/F}$	0.75	27.6%
$CV\%_{\sigma 1}$	35.4%	41.8%
Intra-individual (residual) variability		
Proportional part, σ_1 (CV%)	29.1%	4.5%
Additive part, σ_2	84.6 ng/ml	22.8%
Covariate-Model: TVCL = CL (1+θ1) (1+θ2 (age-40))		
female on CL/F: θ1	-0.152 (-15.2%)	12.3%
If age < 40 years: θ2 on CL/F	0.00403	73.2%
If age > 40 years: θ2 on CL/F	-0.00568	12.9%

RSE% relative standard error. **CV:** coefficient of variation.

Derived exposure estimates

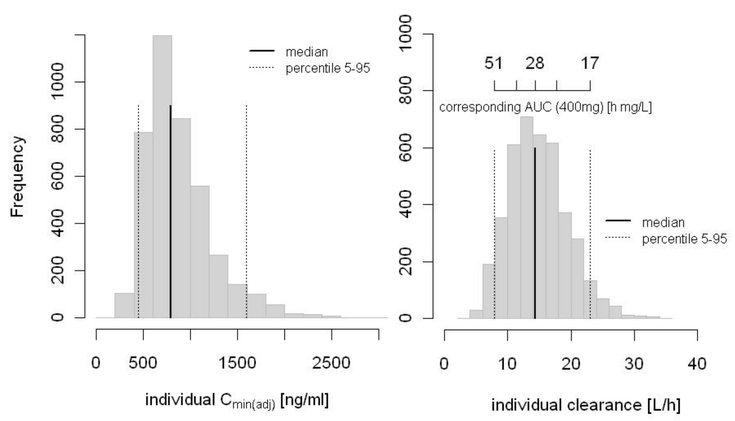

Fig-1: Individual Bayesian estimates of exposure derived from the population PK analysis. *Left:* Individual Cmin estimates, adjusted to daily standard dose of 400 mg ($C_{min(adj)}$), observations >3000 ng/ml not shown (n= 2). *Right*: Individual clearance estimates (CL/F) together with corresponding estimates of dose-adjusted area under the concentration-time curve (AUC_{0-24}).

Mixed-effect logistic regression

- **Univariate analysis:** CL, log-Cmin, time on treatment, TDM frequency, gender (all p<0.01) & CML phase (p=0.02) were significant predictors of the PD outcome.
- **Stepwise multivariate regression:** all but log-Cmin (p=0.34) remained significant.

Table 3: Summary of PK/PD model	Estimate (SE)	BL π [95% CI]
« Baseline patient »: average CL of 16 L/h	0.105 (0.125)	**52.6%** [46.5-58.7%]
Time on imatinib > 3 years	+1.08 (0.130)	**76.6%** [71.7-80.8%]
TDM only once	-0.65 (0.128)	**36.8%** [31.2-42.8]
Male sex	-0.48 (0.127)	**40.9%** [35.0-47.0%]
Accelerated phase	-1.29 (0.534)	**23.4%** [9.7-46.5%]
Individual CL, increase by 1 L/h from 16 L/h **8.0 L/h : 22.2 L/h** (percentile 5 : 95)	-0.037 (0.014)	**59.9% : 46.9%**
η (BSV variability)	1.34 (0.6)	+/- η: 22.5-80.9% +/- 1.96η: 7.5-93.9%

SE: standard error. **BL π:** baseline probability, corresponding to an odds ratio of 1. **CI:** confidence interval. **BSV**: between-subject variability.

PK/PD relationships

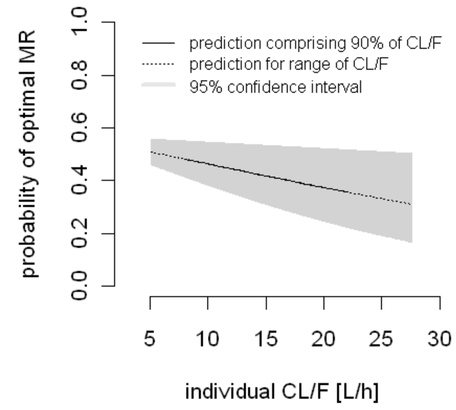

Fig-2*:* **Impact of exposure on optimal molecular response (MR).** Probability over CL/F, illustrated for a "baseline patient" with changing CL/F.

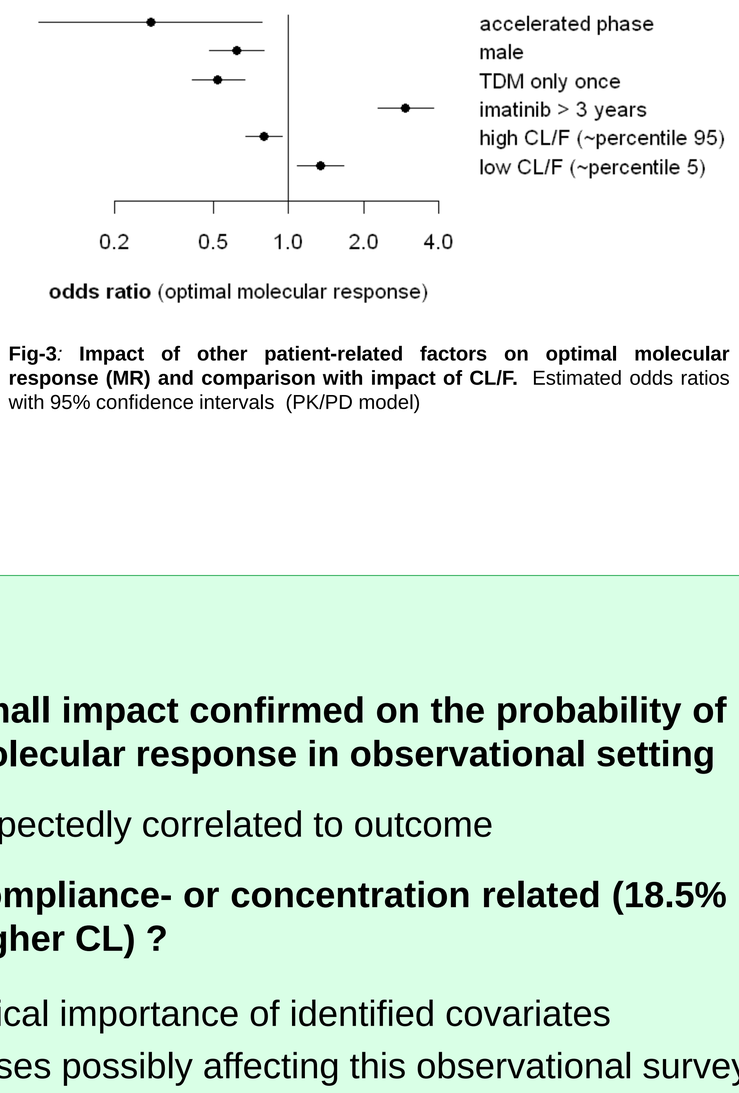

Fig-3: **Impact of other patient-related factors on optimal molecular response (MR) and comparison with impact of CL/F.** Estimated odds ratios with 95% confidence intervals (PK/PD model)

Conclusions

- **Imatinib exposure at treatment initiation** (CL~initial dose/AUC) ⇨ **Small impact confirmed on the probability of molecular response in observational setting**
- CML phase and time on treatment → Expectedly correlated to outcome
- **Male patients: ⇧ increased risk of suboptimal response** ⇨ **Compliance- or concentration related (18.5% higher CL) ?**
- Prospective study needed
  - to confirm clinical importance of identified covariates
  - to exclude biases possibly affecting this observational survey

References

[1] Picard, S., K. Titier, et al. (2007)

[2] Larson, R. A., B. J. Druker, et al. (2008)

Acknowledgements

[3] The EUTOS project is a scientific collaboration between the European Leukemia Net (ELN) and Novartis. The authors thank especially Peter Schuld (Novartis Oncology Region Europe) for logistic support.

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