

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):

- Population PK analysis (FOCE-interaction)**
⇒ individual Bayesian estimates of exposure (PK)
- 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	29.6%
CV% _{σ_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+θ_1) (1+θ_2 (age-40))		
female on CL/F: θ_1	-0.152 (-15.2%)	12.3%
If age < 40 years: θ_2 on CL/F	0.00403	73.2%
If age > 40 years: θ_2 on CL/F	-0.00568	12.9%

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

Derived exposure estimates

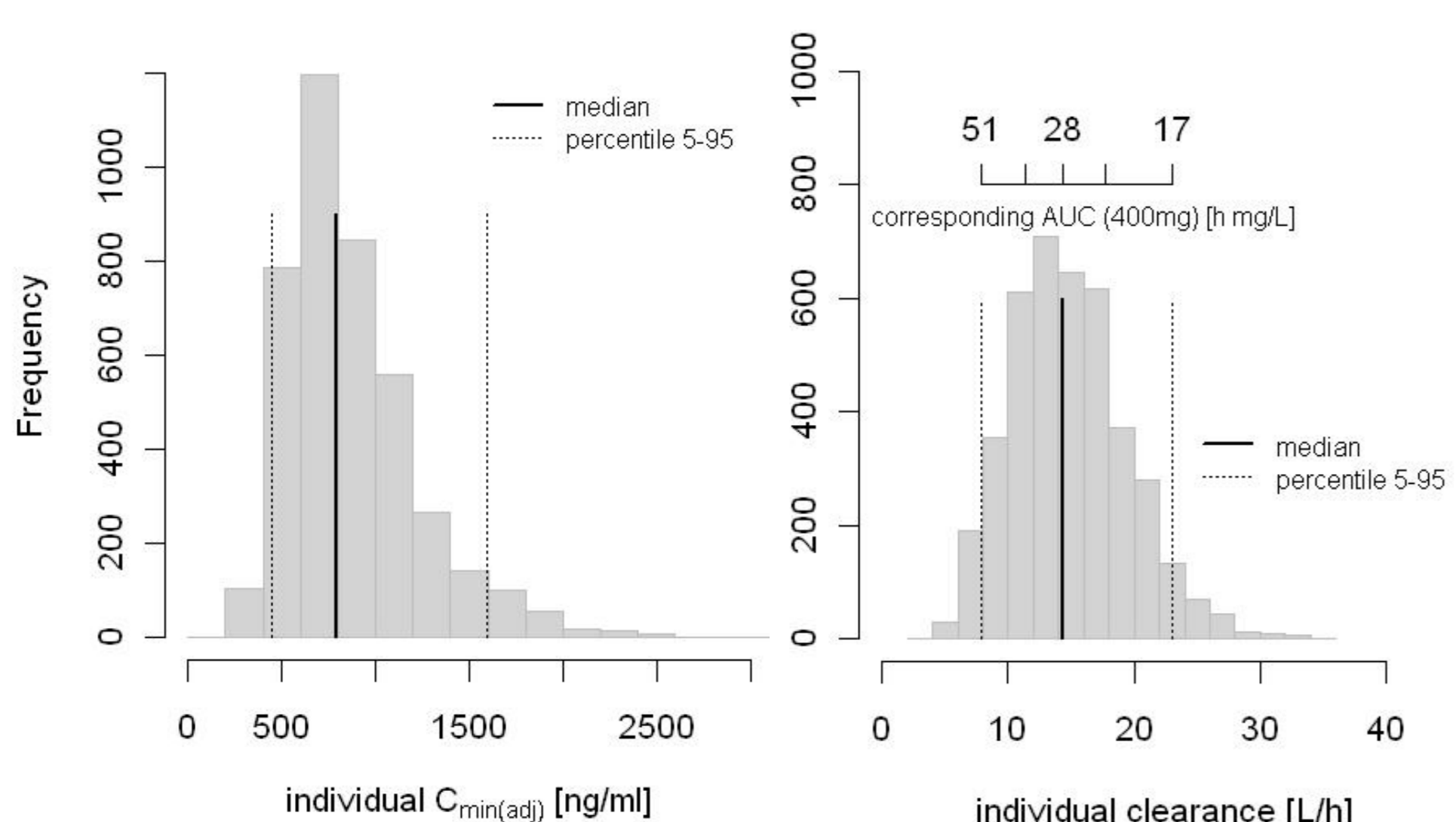


Fig-1: Individual Bayesian estimates of exposure derived from the population PK analysis. Left: Individual C_{min} estimates, adjusted to daily standard dose of 400 mg (C_{min} (adj)), observations >3000 ng/ml not shown (n=2). Right: Individual clearance estimates (CL/F) together with corresponding estimates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

Mixed-effect logistic regression

- Univariate analysis: CL, $\log-C_{min}$, 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 $\log-C_{min}$ ($p = 0.34$) 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	-0.037 (0.014)	59.9% : 46.9%
8.0 L/h : 22.2 L/h (percentile 5 : 95)		
η (BSV variability)	1.34 (0.6)	+/- η : 22.5-80.9% +/- 1.96 η : 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

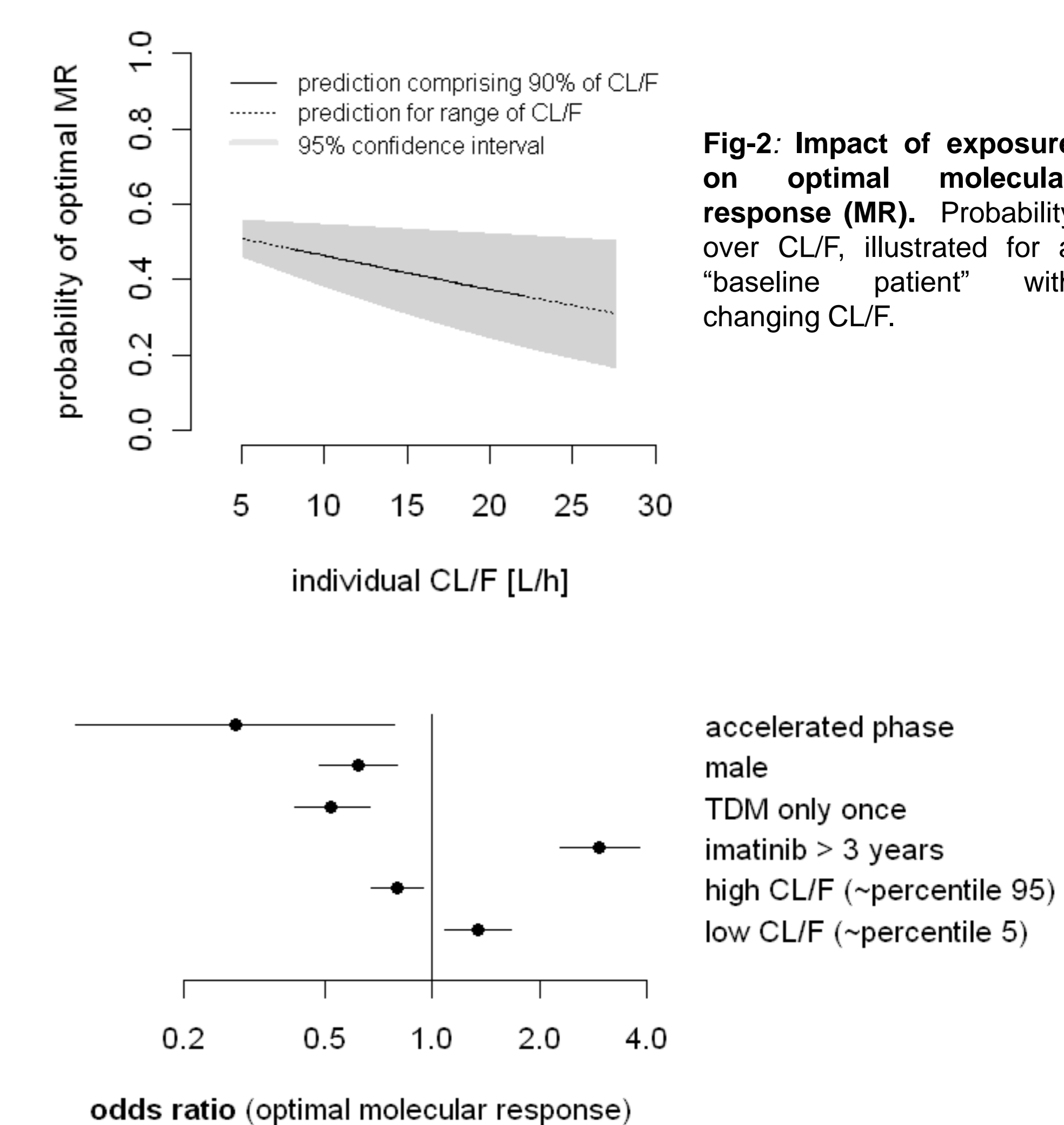


Fig-2: Impact of exposure on optimal molecular response (MR). Probability over CL/F, illustrated for a "baseline patient" with changing CL/F.
Fig-3: Impact of other patient-related factors on optimal molecular response (MR) and comparison with impact of CL/F. Estimated odds ratios with 95% confidence 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

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References

- [1] Picard, S., K. Titier, et al. (2007)
- [2] Larson, R. A., B. J. Druker, et al. (2008)

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