Population pharmacodynamics modelling of circulating lymphocyte dynamics in chronic lymphocytic leukemia patients under ibrutinib treatment

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Team 14 « Dose individualization of anti-cancer drugs » - E. Chatelut
Background

➢ **Chronic Lymphocytic leukemia (CLL)**
  - Accumulation of non functional B-cells in lymph nodes and blood
  - Most common form of leukemia in adults

➢ **Ibrutinib**
  - Tyrosine kinase inhibitor targeting the Bruton Tyrosine Kinase (BTK)
  - First line treatment for CLL (FDA, 2016)
  - Highly variable PK (Bioavailability F=3%)

*Fig.1 Ibrutinib inhibits the BTK involved in the B-cell receptor signaling pathway (Herrera et al. 2014)*
Background

➢ Ibrutinib effects on lymphocytes\(^1\)
  - Anti-proliferation
  - Egress from lymph nodes
  - Inhibition of re-homing to lymph nodes
  - Death in blood and lymph nodes

OBJECTIVE: To develop a population PD model describing circulating lymphocyte dynamics in CLL patients under ibrutinib treatment

3 types of lymphocyte dynamics profiles are observed in patients\(^2\)
1. No lymphocytosis
2. Transitory lymphocytosis
3. Prolonged lymphocytosis

\(^2\)Herman SE. et al. Leukemia. 2014 Nov;28(11):2188-96
\(^3\)Brown JR. et al. Leukemia. 2018;32(1):83–91

Fig.2 Various Lymphocyte dynamics profiles observed in patients

Better long term prognosis\(^3\)
Data

➢ 77 CLL patients treated by ibrutinib

➢ Lymphocyte count: **0 to 24 months**

➢ **506** observations
  (2 to 10 observations per patient)

➢ All types of profiles

➢ High **inter-individual variability**

![Fig.3 Lymphocyte counts over time for all patients](image)
Ibrutinib effects on lymphocytes

- Anti-proliferation
- Egress from lymph nodes
- Inhibition of re-homing to lymph nodes
- Death in blood and lymph nodes

Fig. 4 Representation of physio-pharmacological knowledge on CLL cells dynamics and ibrutinib effects
A PK-PD model?

Initial purpose: build a PK-PD model

Fig.4 Representation of physio-pharmacological knowledge on CLL cells dynamics and ibrutinib effects

Fig.5 Final PK model for ibrutinib and its active metabolite
A PK-PD model?

**PK Model (IPP)**

\[
\frac{dA_1}{dt} = K \cdot A_1 \cdot \left(1 - \frac{\text{DRUG}_{\text{BASE2}_{\text{CIRC}}}}{\text{CIRC}}\right) - K \cdot A_1
\]

\[
\frac{dA_2}{dt} = K \cdot A_1 - K \cdot (A_2 - \text{offset})
\]

**DRUG = SLOPE \cdot CONC**

\[
F_1 = \text{BASE1}
F_2 = \text{BASE2}
\]

\[\text{CIRC} = A(2)\]

**No drug concentration in the model**

\[
\frac{dA_1}{dt} = K_p \cdot A_1 - K_{OUT} \cdot A_1
\]

\[
\frac{dA_2}{dt} = K_{OUT} \cdot A_1 - K_{DTH} \cdot (A_2 - \text{offset})
\]

**F1 = BASE1**

**F2 = BASE2**

**MIXTURE (K_{OUT})**

\[
K_p
\]

**PK Model (IPP)**

\[
\frac{dA_1}{dt} = K_p \cdot A_1 - K_{OUT} \cdot A_1
\]

\[
\frac{dA_2}{dt} = K_{OUT} \cdot A_1 - K_{DTH} \cdot (A_2 - \text{offset})
\]

**DRUG = SLOPE \cdot CONC**

\[
F_1 = \text{BASE1}
F_2 = \text{BASE2}
\]

**K_{DTH}**

**K_{OUT}**

**K_{DTH}**

**K_{DTH}**

**F1 = BASE1**

**F2 = BASE2**
A PK-PD model?

Initial purpose: build a PK-PD model

- PK-PD tested models were no better than the PD model without concentration effect
- Ibrutinib effects do not seem to be correlated with the drug concentration level

PK-PD relationship? More complex? How to model it?

**Fig.6** Ibrutinib AUC and Cmax vs. lymphocytosis group
PD model

**PD model without concentration effect**

\[
\frac{dA_1}{dt} = K_p \times A_1 - K_{OUT} \times A_1 - K_{DTH} \times A_1
\]

\[
\frac{dA_2}{dt} = K_{OUT} \times A_1 - K_{DTH} \times (A_2 - off\_set)
\]

**BASE\_BLOOD = BASE** \[1\]

**BASE\_LYMPH = BASE \times (1 + PBASE)**

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**Parameter** | **Estimation (RSE)** | **IIV (RSE) [Shr]**
---|---|---
\(K_p \text{ (day}^{-1}\)) | 0.0557 (13%) | NE
\(K_{OUT} \text{ (day}^{-1}\)) | 0.0085 (24%) | 122% (20%) [14%]
\(K_{DTH} \text{ (day}^{-1}\)) | 0.0586 (11%) | NE
\(off\_set \text{ (G/L)}\) | 2.97 (5%) | 195% (7%) [16%]
\(BASE \text{ (G/L)}\) | 58 (26%) | 257% (11%) [1%]
\(PBASE \text{ (−)}\) | 6.3 (36%) | 381% (13%) [12%]
Proportional residual variability (CV%) | 25.6% (8%) | -

**Tab. 1 Parameter estimates for final PD model**
PD model

PD model without concentration effect

\[
\begin{align*}
\frac{dA_1}{dt} &= K_P \cdot A_1 - K_{OUT} \cdot A_1 - K_{DTH} \cdot A_1 \\
\frac{dA_2}{dt} &= K_{OUT} \cdot A_1 - K_{DTH} \cdot (A_2 - \text{offset})
\end{align*}
\]

\[BASE_{BLOOD} = BASE \quad BASE_{LYMPH} = BASE \cdot (1 + PBASE)\]

Fig. 7 Final PD model

Fig. 8 Goodness-of-fit plots for final PD model
Covariate exploration → biomarkers for response?

\[ \text{BASE}_{\text{BLOOD}} = \text{BASE} \quad \text{BASE}_{\text{LYMPH}} = \text{BASE} \times (1 + PBASE) \]

The parameter \( PBASE \) discriminates between the 3 response groups.

- Tested covariates: Morphology, Biology, Pathology, PK, etc.
- Covariates to be tested: ex-vivo experiments on patients’s CLL cells

Association with clinical outcome

Fig. 9 PBASE parameter vs. lymphocytosis profiles
Discussion

➢ A PK-PD model?
  • Unknown relationship
  • How to model it?

➢ First population PD model to describe lymphocyte count dynamics
  • The model describes the data well
  • But does not totally reflect the physiological reality
  • More data to come: Improve the model? External evaluation?

➢ Aim of the model
  • PBASE parameter: response group classification
  • Covariate exploration: identify response biomarkers?
  • Relationship with clinical outcome
Thank you for your attention

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