

Pharmacokinetic–Pharmacodynamic Modeling and Treatment Simulation of Maintenance Therapy for Childhood Acute Lymphoblastic Leukemia

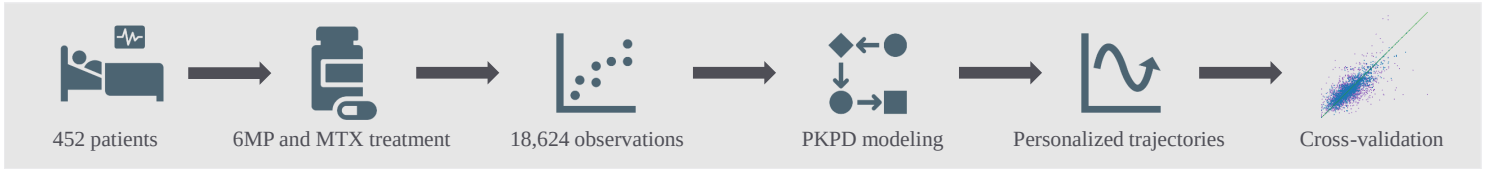


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joint work with Patrick Lilienthal, Markus Metzler, Manfred Rauh, Sebastian Sager, Kjeld Schmiegelow, Linea Natalie Toksvang & Jakob Zierk

Find the paper here:



1 Summary

Acute lymphoblastic leukemia (ALL) is one of the most common pediatric malignancies. During maintenance therapy with low-dose methotrexate (MTX) and 6-mercaptopurine (6MP), treatment aims to keep the absolute neutrophil count (ANC) in the target range of 0.5-2 G/L. With the dose-response relationship varying widely between patients, the developed pharmacokinetic-pharmacodynamic model provides a foundation to explore novel treatment strategies exploiting model features and suggesting a personalized treatment target.

Parameters were estimated with NONMEM 7.5 with a combination of Monte Carlo Importance Sampling Expectation Maximization (IMP) and Stochastic Approximation Expectation Maximization (SAEM). Model analysis and simulation was done with Python 3.10 using CasADI and CVODES.

2 Model

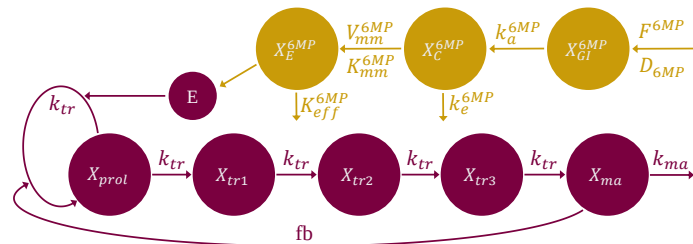


Figure 1: Best performing PKPD model

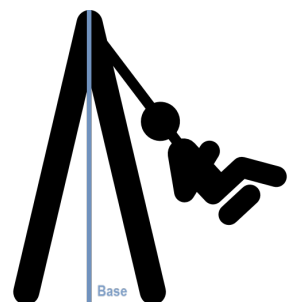
The model links the Erythrocyte-TGN PK submodel with Michaelis-Menten kinetics to the Friberg et al. [1] model by implementing a linear effect function.

Estimated parameters are V_{mm}^{6MP} , K_{mm}^{6MP} , K_{eff}^{6MP} , k_{tr} , $slope^{6mp}$, $base$ and γ with

$$E = slope^{6mp} \cdot X_E^{6MP}$$

$$fb = \left(\frac{base}{X_{ma}} \right)^\gamma$$

3 Simulation - Adaptive Treatment Strategy



Treatment strategy aimed to minimize distance of X_{ma} to $base$:

if $X_{ma}(t + mmt) \geq base$ and $X_{ma}(t + mmt) \geq 0$ then
dose = 75 mg/m²
else
dose = 0 mg/m²
end if

mmt = mean maturation time of the ANC

4 Modeling Results

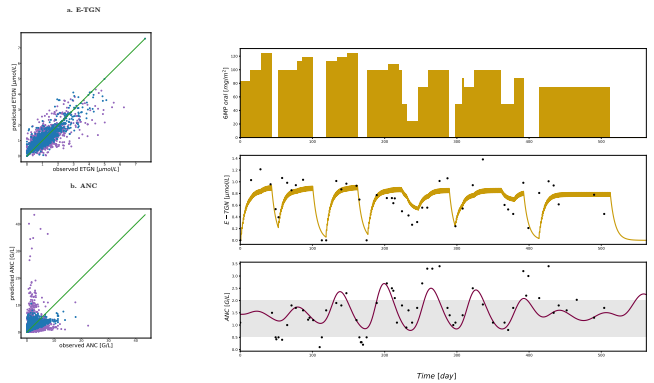


Figure 2: GoF-Plots for E-TGN and ANC

Figure 3: Exemplary E-TGN and ANC trajectories of one patient with 6MP dosing schedule

Main Takeaways:

- Integrating **metabolite measurements** in the model improves results when less data is available (as is often the case in clinical practice)
- base** could function as a **personalized treatment target** replacing the fixed target range for the ANC
- Timing matters**, and modeling might reveal hidden features that allow clinicians to subsequently exploit those

5 Simulation Results

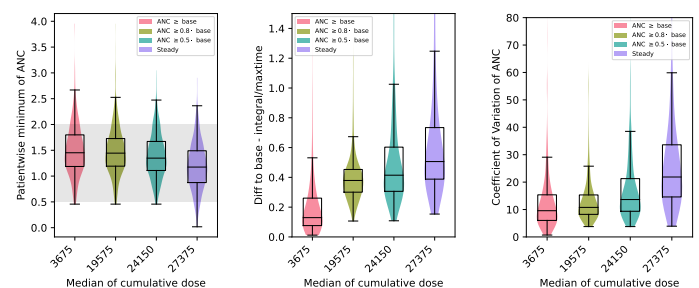


Figure 4: Boxplots of the patientwise median of the ANC, the integral of the absolute difference of the ANC to the individual $base$ and the coefficient of variation of the ANC.

All three novel treatment strategies show fewer minimal ANC values below 0.5 G/L and less variation than steady treatment. The treatment strategy based on $ANC \geq base$ shows trajectories closest to $base$. The treatment strategy based on $ANC \geq 0.5 \cdot base$ has the median cumulative 6MP dose closest to the one of steady treatment.

