HOMOCYSTEINE AS BIOMARKER IN A SEMI-MECHANISTIC PK/PD MODEL OF METHOTREXATE

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Introduction and Objectives

Elevated homocysteine (HCY) concentrations have been associated with neurotoxic symptoms upon chemotherapy with methotrexate (MTX). Dihydrofolate (DHF) is reduced to tetrahydrofolate (THF) by dihydrofolate reductase (DHF-R). Methionine synthetase (MS) converts HCY to methionine under consumption of THF which is oxidized to DHF. Therefore, HCY concentration may increase when less THF is available following MTX treatment (see Fig. 1).

The aim of this study was to develop a PK/PD model based on plasma MTX and HCY concentrations measured in patients with acute lymphoblastic leukemia (ALL) as a basis for the development of improved dosing regimens with a lower risk of neurotoxicity.

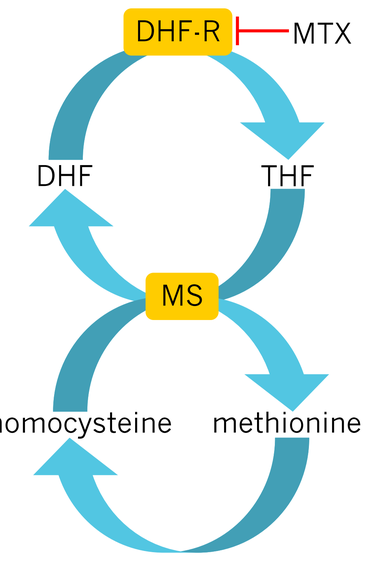

Fig. 1: Influence of MTX on HCY.

Patients and Methods

Patients and schedules: 5381 MTX plasma concentrations from 391 young ALL patients of the Total XV study [1] were determined. The patients received up to 4 cycles of MTX treatment within a consolidation treatment. A subgroup of 290 patients also received lower doses of MTX during an upfront window phase prior to the consolidation phase. During the upfront window phase various infusion regimens were administered. Blood samples were drawn around 6h, 23h and 42h after start of infusion (see table 1 for subgroup and total patients characteristics).

Additionally 1227 HCY plasma concentrations from 212 of those patients were available. To reduce residual error due to co-medication with calcium folinate (Leucovorin®) only HCY concentrations from the upfront window phase and the first cycle of the consolidation phase were considered.

Table 1: Patients characteristics

	upfront window (n=290)		total (n=391)	
	median	range	median	range
Dose [mg]	800.1	398.1–2983.4	1005	398.1–10740.0
Creatinine [mg/dL]	0.4	0.2–1.2	0.4	0.2–1.5
BSA [m2]	0.82	0.40–2.97	0.82	0.40–2.97
Height [cm]	111.6	68.1–194.7	113.4	68.1–194.7
Weight [kg]	19.25	7.8–160.1	20.4	7.8–160.1
Age [years]	5.2	1.0–18.9	5.5	1.0–18.9
Males	161 (55.5%)		218 (55.8%)	
Females	129 (44.5%)		173 (44.2%)	

PK/PD Analysis: Modeling was performed with NONMEM® version 7.1.2 using the first-order conditional estimate (FOCE) method with interaction.

Results

Pharmacokinetic Model: To incorporate an exponential error model, concentrations were log-transformed. A 2-compartment model described the MTX data well, parameterized by CL (total clearance), V1 (volume of the central compartment), Q (intercompartmental clearance) and V2 (volume of the peripheral compartment). As the population represents a wide range of young patients, the parameters were allometrically scaled to a weight of 70 kg with a power of 3/4 or 1 for CL and Q and for V1 and V2, respectively. An interindividual variability (IIV) could be estimated for CL and V1, whereas an IIV of Q and V2 was estimated to be highly correlated with the IIV of V1. An interoccassion variability (IOV) on CL and V1 also significantly improved the OFV ($p < 0.001$) and the exponential residual error was reduced from 0.38 to 0.19. Serum creatinine concentration (C_{CR}) was pre-selected as a covariate on CL and confirmed by backward exclusion ($p < 0.001$).

$$CL_i = \theta_{CL} \cdot \left(\frac{C_{CR,mean}}{C_{CR,i}}\right)^{\theta_{CL,CCR}}$$

Height (HT) was identified as covariate on V1 ($p < 0.001$). Linear and power covariate models were investigated. For both covariate relationships found, the power models exhibited a higher drop in OFV.

$$V1_i = \theta_{V1} \cdot \left(\frac{HT_i}{HT_{median}}\right)^{\theta_{V1,HT}}$$

In case of C_{CR} the mean value was adapted to the age of the patient to account for age-dependent differences [2,3].

Additionally, the parameters were estimated without outliers of more than ±5 mg/L in the conditional weighted residual (CWRES) vs. time plot (Fig. 2). Apart from the residual error no parameter changed more than ±4%, so the outliers were included into the final model.

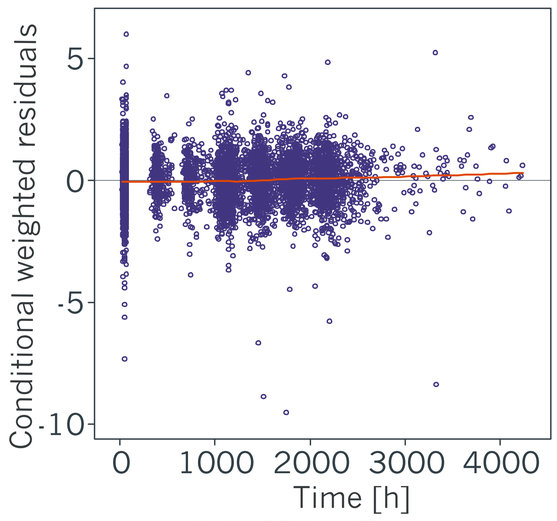

Fig. 2: CWRES vs. Time.

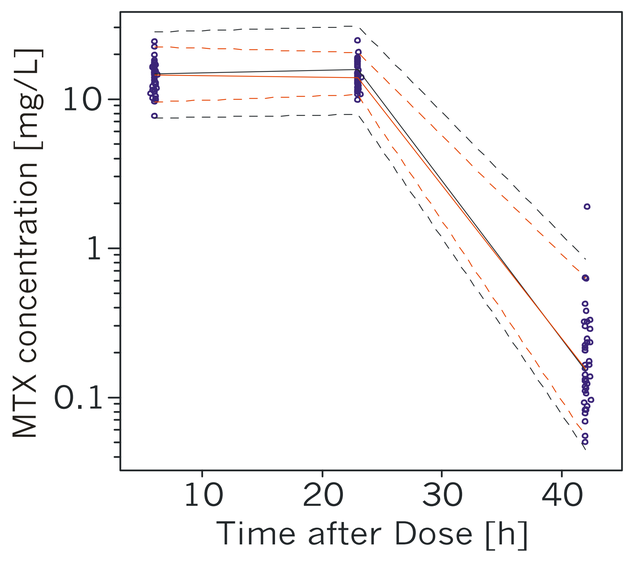

Fig. 3: Visual Predictive Check. Simulation of patients subpopulation with a dose of 1900 mg ±50mg. Observations (○), median (—), 97.5 and 2.5 percentiles (– –) in red and black for observations

Table 2: PK model parameters

	Model estimates	Bootstrap $CI_{90\%}$ (966 of 1000)
θ_{CL} [L/h]	13.47	13.20 – 13.72
θ_{V1} [L]	45.48	43.30 – 47.58
θ_{Q} [L/h]	0.32	0.30 – 0.34
θ_{V2} [L]	7.23	6.84 – 7.71
$\theta_{CL,CCR}$	0.31	0.26 – 0.35
$\theta_{V1,HT}$	-0.50	-0.61 – -0.38
IIV_{CL} [%]	21.19	19.54 – 22.63
IIV_{V1} [%]	23.02	20.90 – 25.26
$\omega_{CL,V1}$	0.04	0.03 – 0.04
IIV-$Ratio_{V1,V2}$	1.98	1.59 – 2.26
IOV_{CL} [%]	12.61	11.83 – 13.42
IOV_{V1} [%]	30.03	27.39 – 32.48
Exp. Error	0.19	0.17 – 0.20

IIV-$Ratio_{V1,V2}$: Ratio of IIV_{V1} to IIV_{V2}

Pharmacodynamic Model: The PD model was built sequentially based on the PK model. An indirect response model [4] with a direct link by an inverse sigmoidal model was chosen (Fig. 4). The parameters HCY_{BL} (HCY baseline concentration), k_{out} (elimination rate constant) and IC_{50} (concentration with 50% inhibition) were estimated. K_{in} (production rate) was calculated according to:

$$k_{in} = \theta_{HCYBL} \bullet \theta_{Kout}$$

IIV was estimated for HCY_{BL} and K_{out}, where IIV_{Kout} was correlated to IIV_{HCYBL} with a ratio of –1. Age was identified as a covariate on HCY_{BL} ($p < 0.001$) with a linear relationship.

$$HCY_{BL,i} = \theta_{HCYBL} + [(Age_i - Age_{median}) \bullet \theta_{HCYBL,Age}]$$

Table 3: PD Model parameters

	Model estimates	Bootstrap CI90% (249 of 250)
θ_{HCYBL} [µM]	4.67	4.50 – 4.84
θ_{Kout} [h^{-1}]	0.03	0.03 – 0.03
θ_{IC50} [µM]	0.24	0.17 – 0.37
$\theta_{HCYBL,Age}$ [µM/y]	0.09	0.06 – 0.12
IIV_{HCYBL} [%]	31.38	25.71 – 34.90
Exp. Error	0.41	0.36 – 0.45

$\theta_{HCYBL,Age}$: Slope (Change in baseline concentration of HCY [µM] per life year [years]).

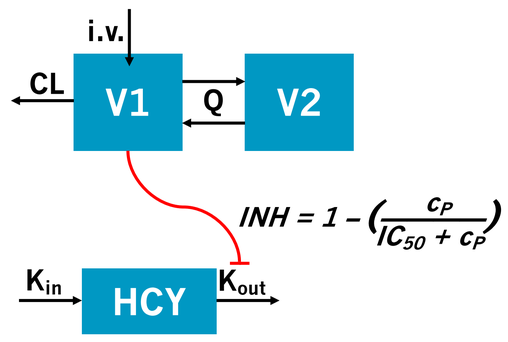

Fig. 4: Full PK/PD Model (c_P: MTX plasma concentration)

Conclusions

- An allometrically scaled 2-compartment model with serum creatinine concentration and height as covariates adequately described the MTX data.
- Increased HCY concentrations could be successfully linked to increased MTX concentrations by using an indirect response PD model.
- Baseline concentrations of HCY concentrations increase with age.
- Future investigations will focus on the link between HCY concentrations and neurotoxicity.

References

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