Leukopenia following triple high-dose chemotherapy and stem cell rescue

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Background and Objectives

Myelosuppression is one of the most important dose-limiting adverse events in many anticancer regimens. In a clinical study 17 patients received a combination therapy of carboplatin (C), etoposide (E) and thiotepa (T) including a stem cell rescue (SCR) consisting of peripheral blood stem cell retransfusion (PBSCT) and G-CSF treatment. The current data analysis describes the leukopenic effect of all drugs in this combination regimen following a population PK/PD modelling approach. In addition special features of this high-dose chemotherapy (HDTC) regimen were accounted for: an initial increase in leukocyte concentrations and a pronounced rebound after nadir concentrations.

Methods

Patients

Drug and leukocyte concentrations of 17 patients receiving CET at doses up to 1500, 2400, 750 mg/m² body surface area were available. All modelling and simulation activities were performed using FOCE+I in NONMEM™ VI (PK analyses) and VII (PD analysis). Statistical and graphical analyses were performed using R 2.11.1.

Tab. 1: Study population (n=17)

Characteristic	Median (min.-max.)
Age [yr]	34.9 (20.7-54.2)
Height [cm]	178 (160-190)
Weight [kg]	80 (63-105)
Leukocyte concentration before HDCT [10^9 cells/L]	3.70 (1.75-14.5)

Population PK/PD modelling

Population PK models for the 3 drugs were developed and resulting empirical Bayes estimates for the PK parameters were used as input for PD analysis. In addition, data on retransfused CD34⁺ peripheral blood mononuclear cells (PBMC) of PBSCT on day 7 were available. PD analysis was based on a semi-mechanistic model for myelosuppression [1] assuming an additive inhibitory linear effect of the drugs (SLOPE) on the proliferation rate (k_{prol}) of cells in the bone marrow (BM). To account for the observed initial increase in leukocyte concentrations and the PBSCT the model was extended by two CMTs (Fig. 1, green CMTs): (i)'INI', motivated by the initial increase in leukocyte concentrations [6], (ii) 'PBMC' [7] for PBSCT 3 days after the last drug administration. Transfer of cells from PBMC followed a first-order process (k_{IN}) and was explored as an input into all CMTs. Leukopenic potency of each drug in the triple regimen was investigated in the base (model without PBMC and INI) and in the final structural model (including INI and PBMC).

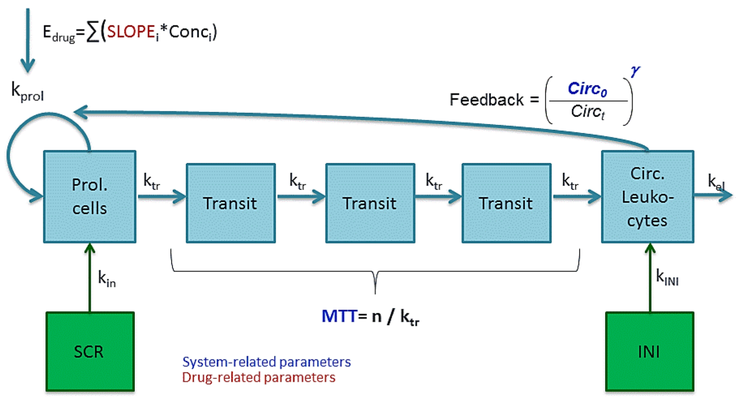

Fig. 1: Final structural PKPD model for leukopenia. MTT: mean transit time (= # transits/k_{tr}), CMT of proliferating progenitor cells ('Prol') in the BM linked with the CMT of circulating leukocytes in the blood ('Circ') via 3 transit CMTs; γ exponential feedback mechanism dependent on ($Circ_t$) and leukocyte concentration before HDCT ($Circ_0$), k_{el} elimination rate constant, 'PBMC' retransfused CD34⁺ PBMCs , 'INI': initial increase, k_{INI}=1/MIT with MIT: mean input time.

Results

Base model

- PK parameter estimates for all drugs were in accordance with previous published ones [2,3,4].
- Contribution of T to the leukopenic effect (SLOPE T) was determined to be negligible (sensitivity analysis). However, for nominal incorporation of T data, SLOPE T was fixed to the estimated value (0.0001 L/µmol) during analyses.

Integration of initial increase in leukocyte concentrations

- Integration of 'INI' resulted in a statistically significant drop of the OFV of 125.8.
- A 23.5% decrease in MTT and an increase of 31.5% in k_{prol} was observed showing the importance of considering the initial increase for estimation of system-related parameters.

Integration of peripheral blood stem cell retransfusion

- Transfer of CD34+ cells from CMT-PBMC to CMT-Prol and not to the transit CMTs resulted in the best description of the data (data not shown) reflecting the proliferating ability of the retansfused PBMCs.
- Estimates of SLOPE were ≤ 60x higher than without PBSCT suggesting that for the setting of HDCT with SCR the clear separation of drug- and system-related parameters of the model is not as obvious anymore (yet, sensitivity of the cells against the drugs should not change due to PBSCT).
- Ranking of the leukopenic effect of C,E,T based on SLOPE estimates was possible with C being more toxic than E and much more than T.

Model evaluation

- Median of simulated and observed data showed that the initial increase in leukocyte concentrations before nadir (Fig. 2) as well as a better representation of the variability for that time interval (Fig. 3) could be described by adding 'INI'.
- In general variability is predicted higher as observed which was probably due to the inclusion of one ID not receiving G-CSF treatment resulting in high estimates of the residual error (Fig. 3).

Tab. 2: Parameter estimates of the base and final structural PK/PD model.

Parameter	Unit	Base model		Final structural model	
		Estimate	RSE, %	Estimate	RSE, %
Fixed-effects parameters					
MTT	[h]	69.3	3.73	73.7	2.84
γ		0.17	8.62	0.19	9.41
k_{prol}	[1/h]	0.04	3.75	0.05	3.69
k_{IN}	[1/h]	-	-	0.02	36.0
INI	[10^9cells/L]	-	-	3.67	28.6
MIT	[h]	-	-	51.3	8.65
SLOPE C	[L/µmol]	0.10	29.8	6.27	121
SLOPE E	[L/µmol]	0.01	71.0	5.46	90.7
SLOPE T	[L/µmol]	0.0001 (FIX)		0.0001 (FIX)	
Random-effects parameters					
ω_{INI}	%CV	-	-	72.2	30.3*
ω_{γ}	%CV	22.5	66.6*	31.0	60.7*
Residual error					
$\sigma_{proportional}$	%CV	76.6	4.67	63.8	4.91

* RSE on variance scale

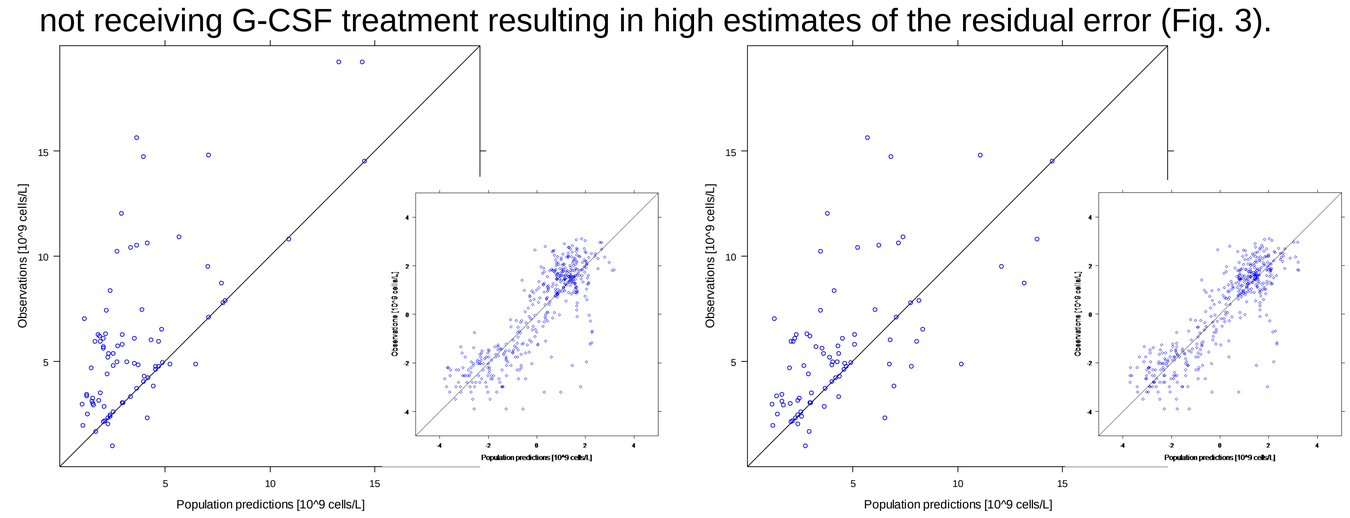

Fig. 3: GOF-plot of the base (left) and the final structural (right) PK/PD model for time points less then 100 h to capture the time interval of the initial increase in leukocyte concentrations. Insets: GOF-plots based on all observations and predictions.

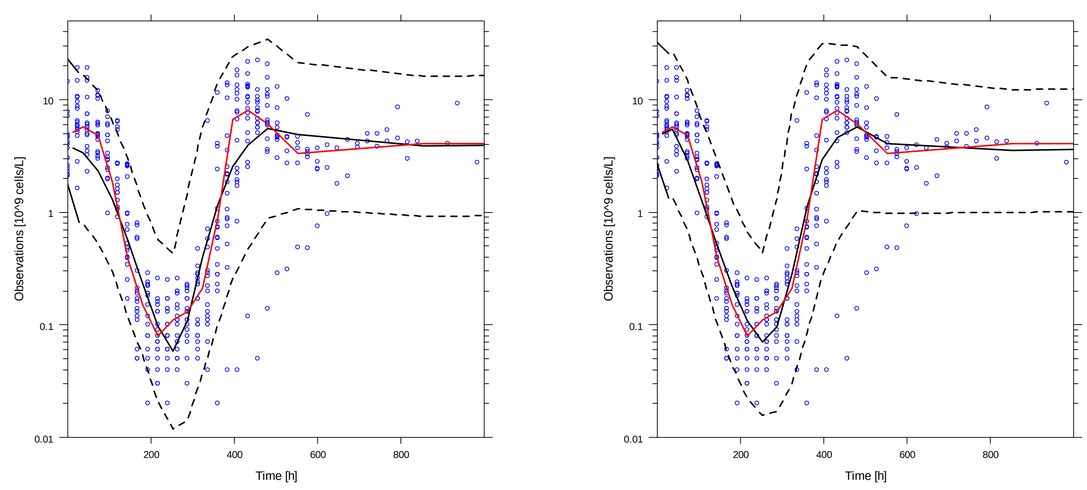

Fig. 2: VPC of the base PK/PD model (left) and the final structural PK/PD model (right), based on 1000 simulated datasets: Observed data (blue dots) with P0.5 (red line) of the observed and P0.05, P0.5 and P0.95 of the simulated data (black lines).

References [1] LE Friberg et al. (2002), [2] A Lindauer et al. (2010), [3] B You et al. (2008), [4] A Huitema et al. (2001), [5] B Jilma et al. (1998), [6] K Ozawa (2007), [7] A Ramon-Lopez (2009)

Conclusions

The PK/PD model for leukopenia allowed the discrimination between and **ranking of the drug effect size** (C>E >> T). Including the peripheral blood stem cell retransfusion resulted in estimates of the drug effects that were ≤ 60x higher than before suggesting that a **clear separation of drug- and system-related parameters** for this special treatment option is **not as obvious anymore**. Adding an **additional CMT (INI)** motivated by the initial increase in leukocyte concentrations **improved the model fit**. Covariate analyses might reveal the influence of G-CSF and dexamethasone on the time course of leukopenia, both having a known effect on leukocyte concentrations and the haematopoietic system. This could result in a more system- and pharmacology-driven model that might help to better understand this dose-limiting toxicity and guide future chemotherapy.

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