Leukopenia following high-dose chemotherapy with autologuos stem cell retransfusion in patients with testicular cell cancer

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Background and Objectives

Myelosuppression is one of the most important dose-limiting adverse events in many anticancer regimens. Peripheral blood stem cell retransfusion (PBSCT) and administration of granulocyte-colony stimulating factor (G-CSF) are widely used in high dose chemotherapy (HDCT) to circumvent this adverse event. The objective of the analysis was the description of the leukopenic-time course of HDCT using a semi-mechanistic PK/PD model following a sequential modelling approach.

Methods

Patients

A total of 19 patients with testicular cancer receiving HDCT of carboplatin (C), etoposide (E) and thiotepa (T)/ifosfamid (I) including PBSCT followed by G-CSF treatment were included in the analysis (Tab. 1). Drug and leukocyte concentrations of 17 patients receiving CET at doses up to 1500, 2400, 750 mg/m², respectively and 2 patients receiving 10000 mg/m² ifosfamide instead of thiotepa as well as additional data on PBSCT and G-CSF treatment were available.

Tab. 1: Study population (n=19)

Characteristics	Median (min.–max.)
Age [years]	33.3 (20.7–54.2)
Weight [kg]	80.0 (58.0-105.0)
Height [cm]	177.0 (160.0-190.0)
Creatinine clearance [mL/min]	114.5 (72.6-188.0)
Leukocyte concentration before HDCT [10^9cells/L]	3.97 (1.75–14.75)

All PK and PD modelling and simulation activities were performed using NONMEM™ VI and were based on carboplatin data only, assuming monotherapy. Statistical analysis were performed using R 2.10.

Population PK/PD modelling

Individual PK profiles of unbound platinum were generated using a modified 2-compartment (CMT) model(1) and served as input for the pharmacodynamic data analysis based on a semi-mechanistic model for myelosuppression(2) (Fig.1). The PD model comprised 5 CMT connecting the proliferating progenitor cells ('Prol. Cells') in the bone marrow with the CMT of circulating leukocytes in the blood via 3 transit CMT linked by 1st order rate constants (k_{tr}). An exponential (γ) feedback mechanism which dependent on the leukocyte was concentration in the peripheral blood ($Circ_t$) and the leukocyte concentration before HDCT ($Circ_0$) was acting on the proliferation rate (k_{prol}) of the central CMT. Drug effect was defined as a linear slope PK/PD model, inhibiting k_{prol}.

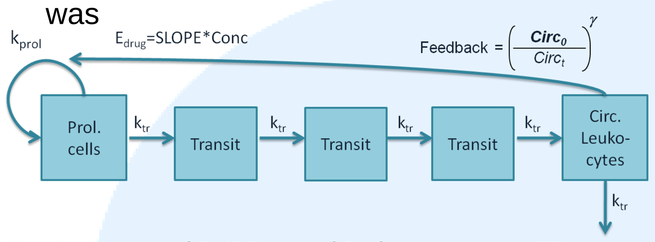

Fig. 1: Structural PKPD model for leukopenia. MTT: mean transit time (= # transits* k_{tr}^{-1}), other abbreviations: see text

Results

Descriptive data analysis

Median nadir concentrations of $0.08x10^9$ cells/L (range $0.02\text{-}0.14x10^9$ cells/L) were reached after 236 h (±39 h), reflecting a grade 4 leukopenia. Recovery to a leukocyte concentration above $3x10^9$ cells/L (grade 1 leukopenia) was observed after a median time of 408 h (±75 h) for patients receiving PBSCT.

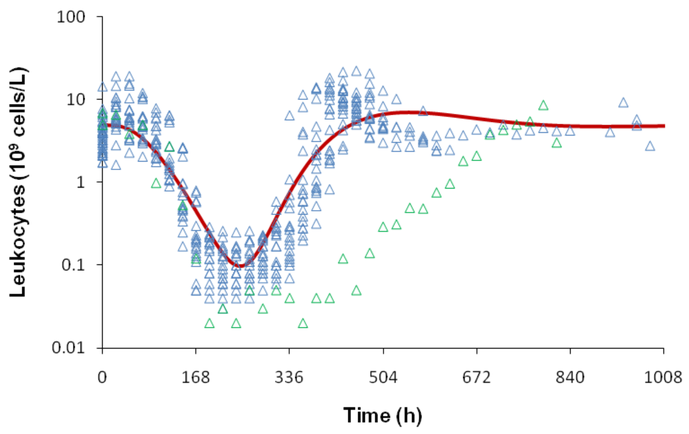

Fig. 2: Leukocyte-time course up to 1008 h: Blue triangles represent observed leukocyte concentrations of IDs receiving PBSCT and G-CSF, green triangles one ID (#7) not receiving the additional myelosupportive treatment. Population prediction for a typical ID is shown as a red line.

In total, a median of $3.5x10^8$ mononuclear cells (range $2.1x10^8$- $3.2x10^{10}$), $2.9x10^6$ CD34+ cells (range 10.00-$1.38x10^7$) and $1.82x10^5$ CFU-GM (range 31.0-$4.49x10^5$) were retransfused.

The most remarkable features observed in the course of leukopenia for this therapy regimen were an increase in leukocyte concentrations during the first days following drug administration and a pronounced rebound after PBSCT and G-CSF administration (Fig. 2).

Population PK/PD modelling

Parameters were estimated with high precision and were well in accordance with previously published values. Creatinine clearance (CRCL) and body weight (BW) were selected as covariates on CL and V_C (exponential relations), respectively (Tab.2).

Tab. 2: Parameter estimates of the final PK model

Parameter	Estimate	RSE, %	Parameter	Estimate	RSE, %
Fixed effects parameters			*Random effects parameters*		
CL [mL/min]	118.0	3.3	*Interindividual variability*		
V_c [L]	22.0	2.8	$\omega_{CL,}$ %CV	13.8	30.9
Q [mL/min]	12.7	5.4			
V_p [L]	30.5	6.3	*Residual error*		
Exponential covariance influence			$\sigma_{additive}$ [mg/L]	0.015	14.0
CRCL on CL	0.63	17.6	$\sigma_{proportional}$,% CV	0.2	8.6
BW on V_C	0.49	35.8			

The 5th and 95th percentiles of the covariates CRCL and BW led to a -25.0%/+36.7% and a -14.7%/+14.4% deviation from CL and VC of a typical patient, respectively.

Tab. 3: Parameter estimates of the current final leukopenia model. SLOPE estimate represents a platinum equivalent for all drugs.

Parameter	Estimate (+ PBSCT,+ G-CSF)	RSE ,% (+ PBSCT,+ G-CSF)	Estimate (- PBSCT, -G-CSF)	RSE ,% (- PBSCT, -G-CSF)	Parameter	Estimate (+ PBSCT,+ G-CSF)	RSE, % (+ PBSCT,+ G-CSF)	Estimate (- PBSCT, -G-CSF)	RSE ,% (- PBSCT, -G-CSF)
Fixed effects parameters					*Random effects parameters*				
					Interindividual variability				
$Circ_0$ [10^9cells/L]	4.91	9.2	4.88	9.9	ω_{circ0} ,%CV	35.9	30.0	36.6	28.7
MTT [h]	94.4	2.5	95.2	2.5	ω_{SLOPE} ,%CV	15.4	64.8	16.6	59.5
γ	0.154	7.4	0.165	4.9	ω_{γ} ,%CV	21.2	59.6	12.3	29.5
SLOPE [L/µmol]	0.234	5.2	0.237	5.5	*Residual error*				
					$\sigma_{proportional}$,%CV	66.4	5.6	64.2	5.6

The generic model of Friberg et al. described the overall time course of the leukocyte concentration in HDCT well (Fig. 4). Although HDCT and myelosupportive features have not yet been incorporated, system-specific parameters were similar to parameter estimates reported for other cytotoxic drugs(2). Exclusion of ID7 had highest influence on ω_{γ}, suggesting that myelosupportive therapy might impact system-specific parameters (Tab. 3).

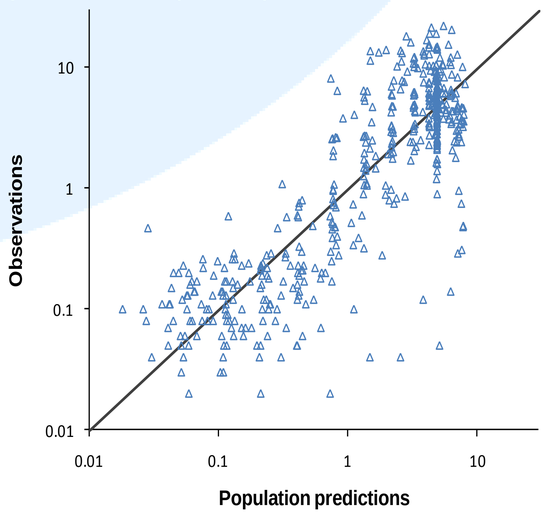

Fig. 4: GOF-plot for the current final PK/PD model

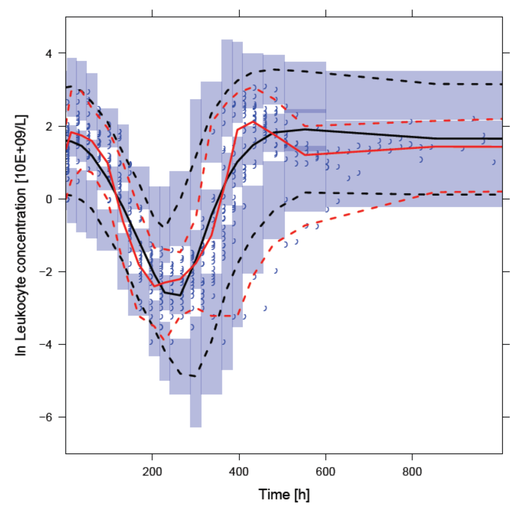

Fig. 5: Visual predictive check (VPC) of the current PK/PD model, based on 1000 simulated datasets: Observed data (dots) with P0.05, P0.5 and P0.95 (red lines) and the corresponding percentiles of the simulated data (black lines) plus the 95% confidence interval (area)

The VPC indicates that the general trend of the data was well captured (Fig. 5), even when ID 7 was excluded (data not shown). However, the two most remarkable time-course features have not been covered. Variability of the PK/PD model was better estimated for the pre-nadir than for the post-nadir phase. Overestimation in variability might result from the additional myelosupportive therapy administered to all patients but one.

References

[1] A Lindauer et al. Ther Drug Monit (2010,Epub ahead of print) [2] LE Friberg et al. J Clin Oncol, 20: 4713 (2002)

Conclusion

The semi-mechanistic PK/PD model was applicable for leukopenia observed in patients undergoing HDCT. Diagnostic plots and Fig. 2 illustrate that two aspects have not yet been accomplished for by the current model appropriately: The initial increase and the pronounced rebound in leukocyte concentrations. The VPC suggests possible improvement for the prediction of the nadir concentrations and of the variability. During PK/PD analysis it was possible to separate k_{prol} from k_{tr} which might allow a mechanistic implementation of the G-CSF effect for future model development. In addition, inclusion of the effect of the remaining drugs, the PBSCT and G-CSF treatment as well as covariates into the model is planned.

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