

Objectives

The pharmacokinetics of the polyethylene glycol (PEG)-conjugated asparaginase Oncaspar® is characterized by an increase in elimination over time. A transit compartment model was implemented to describe this time-dependency in pharmacokinetics (PK) (1).

Focus of our analyses were:

- to build up a covariate model
 - to account for the marked difference in drug exposure between induction and reinduction
 - test the accuracy of the model
- (based on the PK model, individual drug exposure over the whole asparaginase therapy has to be predicted in order to correlate these data with clinical outcome and toxicity parameters).

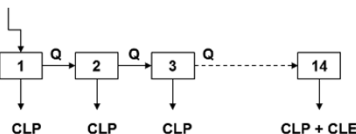
Methods

Study design / Covariates

In paediatric acute lymphoblastic leukemia therapy (AIEOP-BFM ALL 2009; registered at www.clinicaltrials.gov as NCT0111744), two administrations of Oncaspar® (2500 U/m² intravenously) in induction phase (14 days interval) and one single administration in reinduction were followed by weekly monitoring of asparaginase activity. For the purpose of this analysis, the starting model was the previously published non-linear mixed-effects model (1).

1374 patients with 6069 samples were included in the PK analysis.

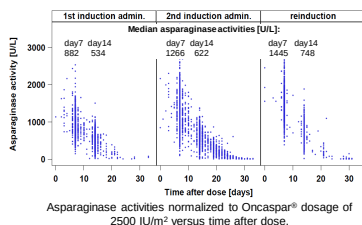
PK Model - covariates



Previously published base transit model (1): a chain of compartments were combined with CLP from each compartment, an inter-compartmental clearance Q and an additional CLE from the last compartment.

Covariates:

- Sex: male: 779 female: 595
- Age [years]: median: 5.2 range: 1.0 – 17.9
- Protocol part: induction vs. reinduction with time difference [days]: median: 150 range: 117–220



Accuracy of the model

Accuracy of the model was tested for:

- single observations of asparaginase activity
- derived PK-parameters: AUC, time over 100, 250, 500 and 1000 U/L

Procedure:

- for patients, where all 6 monitoring samples were available, 1-4 samples were excluded
- estimation step and integration of AUC
- calculation of: (i) Accuracy = Prediction / Observed value
(ii) % of samples with accuracy within ±10% and ±20% error range

Conclusions

- Covariates on CLP and V were best to account for the differences in PK between induction and reinduction:
 - ... CLP might be interpreted in terms of elimination by monocytes and macrophages; lower elimination rates in reinduction seem to be plausible,
 - ... V might reflect the plasma volume; an almost 30% decrease with V of 43 ± 4.6 mL/kg in reinduction is still in the lower range of plasma volume reported for children (2),
- PK model accounts for slight accumulation after subsequent Oncaspar® administrations during induction,
- Test of accuracy demonstrates that derived PK-parameters AUC or time over predefined asparaginase activities are more promising parameters than predictions of individual asparaginase activities for further PK-PD correlations.

Results*

PK model - covariates

Changes of base transit model:

... simplification: CLE = Q

... covariates on CLP and V1 on:

..... induction vs. reinduction (dOFV = -1351)

..... 1st vs. 2nd induction administration (dOFV = -286)

... further covariates on CLP for:

..... age: linear increase of CLP for age > 8 years (dOFV = -24.7)

..... sex (dOFV = -22.9)

Parameter		Typical values (%RSE)		Bootstrap Estimate	95%CI
		Base model	Final model		
V	[L/m ²]	1.30 (1.5)	1.69 (1.5)	1.68	1.61 - 1.76
CLP	[L/day/m ²]	0.11 (0.9)	0.13 (1.4)	0.13	0.12 - 0.13
CLE	[L/day/m ²]	0.79 (7.1)			
Q	[L/day/m ²]	0.87 (2.3)	0.91 (3.1)	0.91	0.84 - 0.98
F _{BSA} ^a		1.50 (1.8)	1.57 (2.1)	1.57	1.50 - 1.64
F _{BSA} ^b			1.43 (2.3)	1.43	1.36 - 1.50
Prop. residual error	[%]	32.4 (1.6)	19.0 (3.1)	19.0	17.5 - 20.5
Add. residual error	[U/L]	8.6 (27.4)	13.2 (41.7)	14.6	5.5 - 30.1
F _V 2nd induction admin.			-0.16 (7.5)	-0.160	-0.184 - -0.134
F _V reinduction			-0.292 (4.1)	-0.291	-0.317 - -0.267
F _{CLP} 2nd induction admin.			-0.113 (13.3)	-0.112	-0.142 - -0.083
F _{CLP} reinduction			-0.433 (3.3)	-0.432	-0.46 - -0.401
F _{age} BP			0.021 (22.2)	0.021	0.011 - 0.031
BP _{age}			8.0 (FIX)	8.0 (FIX)	
F _{sex}			-0.077 (20.3)	-0.076	-0.106 - -0.046
IIV CLP	[%]	20.2 (5.2)	22.7 (5.3)	22.7	20.1 - 25.2
IIV Q	[%]	10.3 (13.6)			
IOV V			13.5 (8.7)	13.5	10.4 - 16.3
IOV CLP			23.1 (4.9)	23.1	20.7 - 25.6

Population pharmacokinetic parameter estimates for base and final model and nonparametric bootstrap.

BP: break point; BSA: body surface area; CLP and CLE: clearance values; F_{age}BP: percentage change in CLP per year for children older than the BP; F_{BSA}: percentage change per m² change from the median BSA of the population; in base model factor (a) for CLP, CLE, Q, V, in final model: factor (a) for V, factor (b) for CLP, Q; F_V 2nd induction admin.: F_V reinduction; F_{CLP} 2nd induction admin.: F_{CLP} reinduction; percentage change in V and CLP at induction 2nd admin. and reinduction; F_{sex}: percentage change in CLP for female; IIV: inter-individual variability; IOV: inter-occasion variability; Q: inter-compartmental clearance; V: central volume of distribution; %RSE: percent relative standard error.

Accuracy of the model

Accuracy of the PK model:

... acceptable for single observations

... superior for AUC and time over 100 U/L, 250 U/L, 500 U/L and 1000 U/L

Run (**)	Samples included for estimation				Accuracy based on posthoc estimates for samples excluded: % of observations and derived PK parameters within ±10 or 20% error range(**)									
	1 st admin.		2 nd admin.		observation		AUC		Time>100 U/L		Time>500 U/L			
	day7	day14	day7	day14	±10	±20	±10	±20	±10	±20	±10	±20		
1	Induction	yes	yes	no	no	28	49	56	85	78	94	62	88	
	Reinduction	no	no	-	-	24	54	70	94	83	96	77	94	
2	Induction	yes	yes	no	no	28	49	55	87	80	94	65	88	
	Reinduction	no	yes	-	-	27	58	91	99	98	100	100	100	
3	Induction	yes	yes	no	no	28	48	55	84	78	95	64	87	
	Reinduction	yes	no	-	-	32	53	88	100	81	97	77	97	
4	Induction	yes	yes	yes	yes									
	Reinduction	no	no	-	-	26	55	69	94	81	96	75	96	
5	Induction	yes	yes	yes	yes									
	Reinduction	no	yes	-	-	29	58	94	100	99	100	100	100	
6	Induction	yes	yes	yes	yes									
	Reinduction	yes	no	-	-	32	57	88	100	82	97	77	97	

(**): Results for other runs and for time over 250 U/L and 1000 U/L not shown

References

- Würthwein et al, Eur J Drug Metabolism Pharmacokinetics, 2017;42:955–63.
- Raes et al, BMC Pediatr. 2006;6:3.

* In the abstract, we reported a PK model with changes in CLP and Q during reinduction; in the meantime we have modelled a change in CLP and V which resulted in an improved fit together with a more plausible interpretation on a pharmacological level.