PopPK to model the time-varying clearance of the PEGylated asparaginase Oncaspar® in children with ALL

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Objectives

The pharmacokinetics of the polyethylene glycol (PEG)-conjugated asparaginase Oncaspar® is characterized by an increase in asparaginase elimination over time.
The focus of our analysis was the better understanding of this time-dependency [1].

Methods

In paediatric **A**cute **L**ymphoblastic **L**eukemia therapy (**ALL**, AIEOP-BFM ALL 2009, www.clinicaltrials.gov, NCT0111744), two administrations of Oncaspar® (2500 U/m² intravenously) in induction phase (14 day interval) and one single administration in reinduction were followed by weekly monitoring of asparaginase activity. Samples indicating immunological inactivation were excluded to describe the pharmacokinetics under standard conditions.

➢ PK Models … with Time-Constant Clearance

- one-compartment models with zero order, linear and/or Michaelis Menten elimination
- linear two-compartment model

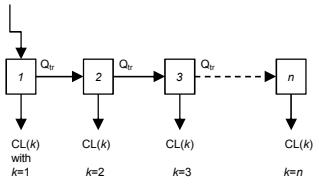
… One-Compartment Models with Time-Varying Clearance

$$CL_{linear} = CL_{initial} + k_{out} \cdot TIME$$
$$CL_{exp} = CL_{initial} \cdot e^{k_{out} \cdot TIME}$$
$$CL_{initial\_exp} = CL_{initial} + CL_{induced} \cdot e^{k_{out} \cdot TIME}$$
$$CL_{concave} = CL_{initial} + CL_{induced} \cdot (1 - e^{-k_{out} \cdot TIME})$$
$$CL_{sig\_Emax} = CL_{initial} + CL_{induced} \cdot \frac{TIME^{\gamma}}{TIME^{\gamma} + t50^{\gamma}}$$
$$CL_{Weibull} = CL_{initial} + CL_{induced} \cdot (1 - e^{-(\lambda \cdot TIME)^{\gamma}})$$

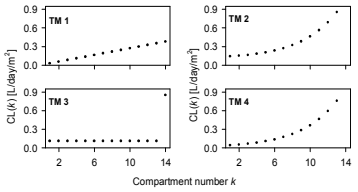
with $CL_{initial}$: clearance at time=0 days; $CL_{induced}$: induced clearance; k_{out}: rate constant for the change in clearance rate; γ: gamma (shape factor); λ: scale parameter of Weibull model; t50: time at which clearance of the CL_{sig_Emax}-model reaches 50 % of its final value; TIME: (i) time after dose or (ii) time after first administration.

… Transit Compartment Models

- In the transit models (TM), an increase in clearance CL(k) over a chain of compartments was modelled.



Schematic view of the transit models.



Increase of clearance CL(k) through the chain of compartments: transit model 1 (TM 1): linear, TM 2 and TM 4: exponential, TM 3: in the last compartment.

Results

➢ Dataset

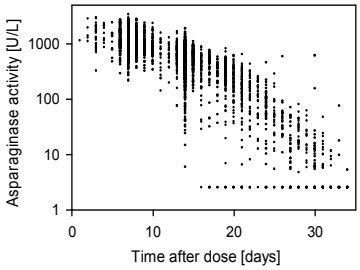
- 1342 patients with 6107 samples were included in the PK analysis.

Baseline characteristics		Median	Range
Age	[years]	5.2	1.0 – 17.9
Body Weight	[kg]	19.6	8.5 - 132
Body surface area	[m²]	0.79	0.41 - 2.65
Oncaspar® dose	[IU]	1950	710 - 5300
	[IU/m²]	2493	1002 - 4882

➢ Asparaginase activities

Oncaspar® administration	Difference to previous administration [days] Median (Range)	
Induction day 12	-	
Induction day 26	14	(11 – 46)
Reinduction day 8	150	(117 - 220)

Right: Asparaginase activities normalized to Oncaspar® dosage of 2500 IU/m² versus time after dose. Activities below lower limit of quantification (LLOQ) were set to 2.5 U/L (= ½ LLOQ).



➢ PK Models … with Time-Constant Clearance

- Models with time-constant CL were not adequate to describe the data.

… One-Compartment Models with Time-Varying Clearance

- Implementing a time-varying clearance improved the fit.
- Modelling
  … an increase of clearance over time after dose (E_{max}- or Weibull-functions, (BIC=72300)) were superior to models with
  … an increase of clearance over time after the first administration (Δ BIC: +206 to +213).

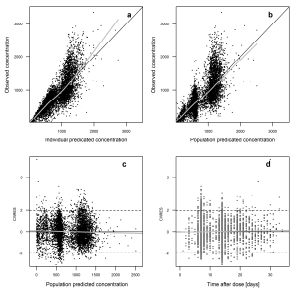
- The observed in vitro hydrolysis of PEG-asparaginase led to the evaluation of transit compartment models.

… Transit Compartment Models

- The empirical transit model 3 was the best structural model (BIC=72156).

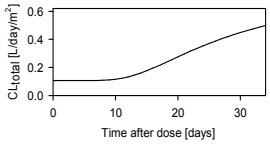
Parameter		Typical value	(% RSE)	Bootstrap Estimate	95 % CI
V	[L/m²]	1.27	(1.6)	1.27	1.23 - 1.31
$CL_{initial}$	[L/day/m²]	0.107	(0.9)	0.107	0.105 - 0.109
$CL_{induced}$	[L/day/m²]	0.740	(10.9)	0.741	0.524 - 0.865
Q_{tr}	[L/day/m²]	0.848	(2.4)	0.852	0.812 - 0.898
F_{BSA}		1.52	(1.8)	1.52	1.47 - 1.58
Prop. residual error	[%]	32.5	(1.5)	32.5	31.4 - 33.5
Add. residual error	[U/L]	4.59	(37.3)	4.75	2.58 - 9.22
IIV $CL_{initial}$	[%]	19.8	(4.8)	19.8	18.1 - 22.1
IIV Q_{tr}	[%]	12.1	(10.7)	12.0	9.3 -14.6

Population pharmacokinetic parameter estimates and nonparametric bootstrap analysis for transit model 3. BSA: body surface area; F_{BSA}: percentage change in $CL_{initial}$, $CL_{induced}$, Q_{tr} and V per m² change from the median BSA of the population; $CL_{initial}$ and $CL_{induced}$: clearance values; IIV: inter-individual variability; Q_{tr}: inter-compartmental clearance; V: central volume of distribution; %RSE: percent relative standard error.



Left: Goodness of fit plots for transit model 3:
a, b: Observed concentration versus individual and population predicted concentrations.
c, d: Conditional weighted residuals (CWRES) versus population predicted concentration and time after dose.

Right: Transit model 3: Increase in total clearance (CL_{total}) over time after dose.



Conclusions

➢ The increase in elimination of PEGylated asparaginase appears to be driven by physicochemical processes that are drug-related.

➢ In Oncaspar®, approximately 69 – 82 PEG-chains are linked to the enzyme by hydrolytically labile ester-bonds [2].
The physicochemical degradation in vitro, represented by a short shelf-life, may also take place in vivo with a direct impact on pharmacokinetics.

➢ The empirical transit model 3 might be interpreted in terms of mimicking de-PEGylation of PEG-asparaginase as a multiple step process through a chain of compartments together with an increase in elimination of the partly de-PEGylated molecules.

References

1: Online published: Würthwein et al, Eur J Drug Metabolism Pharmacokinetics, doi:10.1007/s13318-017-0410-5.
2: EMA. Assessment report Oncaspar: EMEA/H/C/003789/0000. 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/003789/WC500200737.pdf. Accessed 12 May 2017.