Age-Dependent Volume of Distribution of Pegylated Asparaginase (Oncaspar™) in children and adults

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Introduction

Asparaginase (ASNase) is an essential component in most treatment protocols for acute lymphoblastic leukaemia (ALL) and non-Hodgkin's lymphoma (NHL). Pegylated ASNase (PEG-ASNase, Oncaspar™) is an enzyme derived from Escherichia coli and conjugated to polyethylene glycol. This chemical derivatisation causes a reduced clearance of the enzyme, which has practical advantages compared to the native forms.

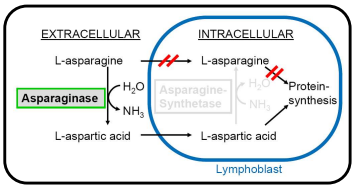

Figure 1 Mechanism of action for Asparaginase

Objectives

A higher volume of distribution normalized to body surface area (V/BSA) was reported for PEG-ASNase in adults [1]. A Population pharmacokinetic (PopPK) analysis for PEG-ASNase in children also identified a trend towards higher V/BSA with increasing age [2]. Therefore, we analysed serum activities from both children and adults to get a better insight into possible age-dependent pharmacokinetics of PEG-ASNase.

Patients

We analysed 2086 serum activity measurements of 446 patients aged 0.8 to 80.6 years (median age 27.1) from the paediatric ALL/NHL-BFM 95 and ALL/NHL-BFM REZ protocol as well as the adult GMALL 07/03 an GMALL Elderly 1/2003 protocol (table 1). Adult patients received PEG-ASNase by protocol as first-line medication whereas the paediatric protocol used PEG-ASNase as second line medication in the case of a hypersensitivity reaction against the first line administered native E. coli ASNase (Asparaginase medac™) preparation.

		All patients	Adults	Children
Patients	[n]	446	312	134
Samples	[n]	2086	1216	870
Dose (Range)	[U/m²]	465 – 2564	500 – 2000	165 – 2564
Activity median range	[U/l]	357,0 2.5 – 3567.0	354,5 2.5 – 2751.0	366.5 2.5 – 3567.0
Age median range	[years]	27.1 0.8 – 80.6	40.5 16.2 – 80.6	6.0 0.8 – 19.0
BSA median range	[m²]	1.79 0.4 – 2.56	1.9 1.35 – 2.56	0.88 0.4 – 2.23
WGT median range	[kg]	32.0 8.7 – 115.0	73.0 50.8 – 115.0	23.5 8.7 – 106.0

Table 1 Patients demographics

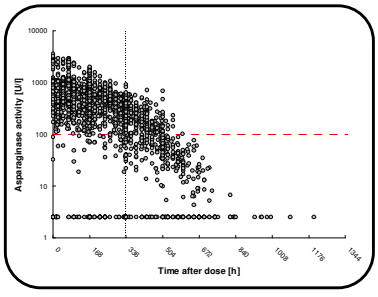

Figure 2 Plot of the raw data (↔ threshold 100 U/l; -- d14)

Methods

The PopPK analysis was performed using NONMEM (version VI) with FOCE and INTERACTION option. Influence of age on V was assessed by fitting a PopPK model with time-dependent Cl developed by Hempel et al [2] to the dataset of children and adults. Cl was considered into the model according to the following formula: $Cl = \theta_1 * e^{(\theta 2 * TAD)}$ where TAD is time after dose, θ_1 is the typical initial Cl and θ_2 is the factor for the exponential increase of Cl with TAD. Age-dependent effect on V was modeled either as categorical or as continuous covariate.

Results

A one-compartment model with time-dependent clearance (CL) including BSA as covariate for CL and V described the data of children and adults sufficiently. Plotting the individual *posthoc* estimates of V normalized to BSA versus the patient's age presented a difference in V/BSA between children and adults (figure 3).

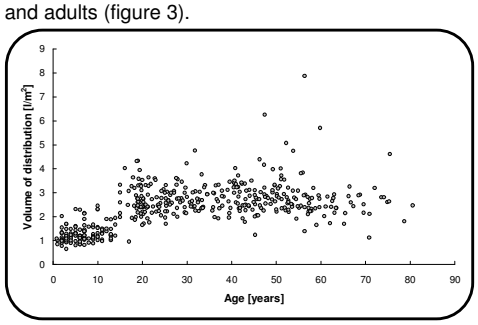

Figure 3 Age of the patients versus the volume of distribution per m²

Model parameter		Population estimate	RSE [%]	IIV [%]
V	l per 1.73 m²	3.48	5.3	18.9
Cl	ml/h per 1.73 m²	6.95	7.2	60.5
Influence TAD on Cl		4.54	4.7	
Residual error				
add. adults	[U/l]	16.8	38.1	
prop. adults	[%]	0.338	6.7	
add. children	[U/l]	2.06	19.2	
prop. children	[%]	0.384	6.2	

Table 2 Final model parameter estimates

Age-dependency of V was best described with a categorical covariate for patients < 18 years. Inclusion of age was associated with a remarkable reduction in OFV (-Δ 326) and also decreased interindividual variability (IIV) as well as unexplained residual variability. Goodness of Fit (GOF) plots are shown in figure 4, final model parameter estimates are given in table 2.

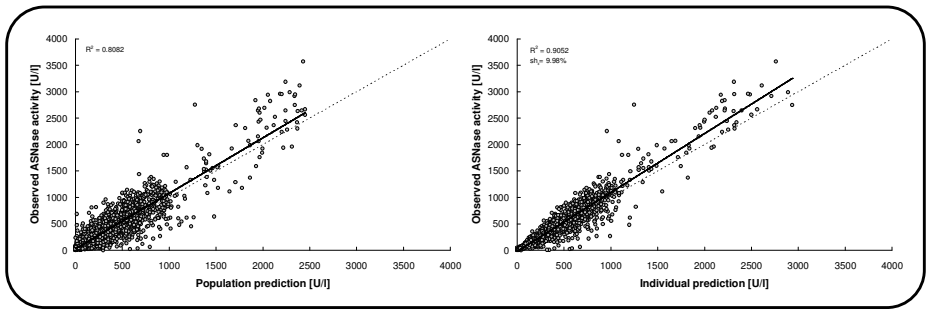

Figure 4 GOF Plots for the final model

Based on the final model 1000 datasets of a typical adult and paediatric patient dosed according to the current adult (GMALL 07/2003) and paediatric ALL treatment protocols (AIEOP BFM 2009) were simulated. Age-dependent V translated into higher peak activities for the paediatric population (figure 5).

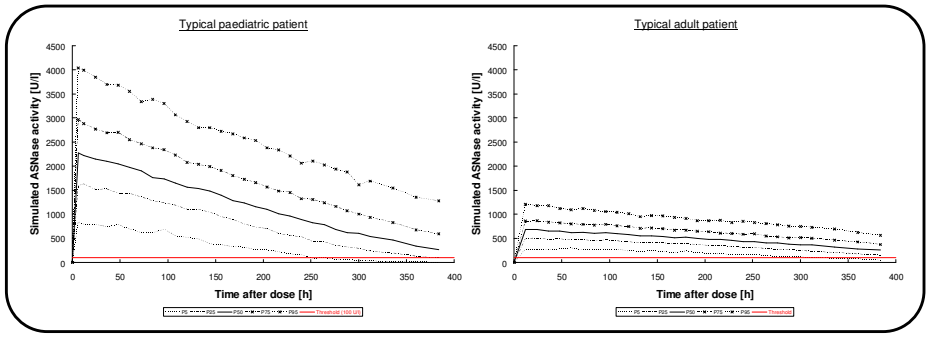

Figure 5 Simulated ASNase activity for a typical paediatric (BSA: 0.88 m²; AMT: 2.500 U/m²) and a typical adult patient (BSA: 1.9 m²; AMT: 2.000 U/m²)

Conclusion

Analysing data of children and adults presented an age-dependency in V for PEG-ASNase. Children and adolescents younger than 18 years of age exhibit a lower volume of distribution normalized to BSA when compared to adults (1.05 vs 2.94 l/m²). The influence of age on dosing and schedule of PEG-ASNase will be analysed in future studies.

References

[1] Avramis VI, Spence SA. Clinical pharmacology of asparaginases in the United States: asparaginase population pharmacokinetic and pharmacodynamic (PK-PD) models (NONMEM) in adult and pediatric ALL patients. J Pediatr Hematol Oncol 2007 Apr; 29(4): 239-47.

[2] Hempel G, Müller HJ, Lanvers C, Würthwein G, Hoppe A, Boos J. A population pharmacokinetic model for pegylated asparaginase in children. *British Journal of Haematology* 2010 Jan;148(1):119-25.

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