SUPPLEMENTARY APPENDIX

Population pharmacokinetics of intravenous Erwinia asparaginase in pediatric acute lymphoblastic leukemia patients

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Supplement

Pharmacokinetic analysis

Time profiles of Erwinia asparaginase concentrations were analyzed using the nonlinear mixed effects modeling approach implemented in NONMEM (version 7.2; Icon Development Solutions, Ellicott City, Maryland, USA). Additionally Pirana (version 2.7.1, for the model environment Pirana, Pirana Software & Consulting BV, The Netherlands)[1], Xpose (version 4.4.1, Nicholas Jonsson and Mats Karlsson, Uppsala, Sweden)[2] and Perl speaks NONMEM (PsN) (version 4.2.0, Uppsala, Sweden)[3] were used.

All Erwinia asparaginase concentrations were log transformed prior to analysis. First order conditional estimates with interaction (FOCE+I) was used as method of analysis throughout the model building procedure. The data was initially fitted to a one-compartment linear model without an absorption compartment as the drug was administered intravenously. More complex models were evaluated; improvement of the fit of the model was evaluated by the precision of the estimated PK parameters, the change in the objective function values (OFV), goodness-of-fit plots (GOF) and visual predictive checks (VPC). A 3.84 point decrease in OFV for one degree of freedom was considered a significant improvement with a p-value of <0.05.

The data was obtained in a pediatric population, hence PK parameters were allometrically scaled to adequately describe the parameters across a wide range of body weights. For allometric scaling standard fixed exponent values of 0.75 for the flow dependent physiologic process parameters clearance (CL) and intercompartmental clearance (Q), and 1 for the volume related parameters apparent volume of distribution of the central compartment (V_c) and peripheral compartment (V_p) were used.[4–6]

Inter-patient and inter-occasion variability in clearances and volumes of distribution were characterized with exponential models. An occasion was defined as one month of treatment due to

the limited number of samples per occasion. For example, clearance in the i^{th} individual at the j^{th} occasion was estimated using equation 1:

Eq.1 $$CL_{i,j} = CL_{pop} *(WT/70)^{0.75} * exp\ (\eta_i + \kappa_j)$$

Where CL_{pop} (= Θ_{CL}) is the typical population value for clearance in a patient with a standardized body weight of 70 kg and η_i and K_j represents the random effect accounting for inter-individual deviation from the typical population value (IIV) and typical individual values (IOV) respectively. η_i and k_j are assumed to be symmetrically distributed with a mean of 0 and estimated variance of ω^2 and π^2, respectively. An additive error model was used to describe the residual error in plasma concentrations.

After the finalization of the structural model, covariate models were built by a stepwise forward inclusion procedure. Continuous covariates were centered at the median and included in the model as described in equation 2. Categorical covariates were included in the model as described in equation 3:

Eq.2 $$CL_{i,j} = [CL_{pop} *(COV/median\ COV)^{\Theta cov} * (WT/70)^{0.75}]* exp\ (\eta_i + \kappa_j)$$

Eq.3 $$CL_{i,j} = [CL_{pop} *(\Theta_{cat})^{FLAG} * (WT/70)^{0.75}]* exp\ (\eta_i + \kappa_j)$$

Where COV is the continuous covariate, Θ_{cov} is the estimated exponent parameter of the continuous covariate. Θ_{cat} is the estimated fraction parameter of the categorical covariate. FLAG is either 1 (covariate present) or 0 (not present). Other parameters are described in equation 1.

Covariates were included one at the time. The covariate with the greatest reduction in OFV was added to the base model. This was iterated over all the covariates until no statistically significant decrease in

OFV occurred. The available covariates were: weight, age, height, body surface area (BSA), sex, treatment protocol (ALL-10 and ALL-11) and treatment center. Dose interval was evaluated as covariate for patient on thrice weekly or every other day Erwinia asparaginase versus patients who switched to twice weekly Erwinia asparaginase.

For the internal validation of the model a non-parametric bootstrap procedures (n=1000) was performed and prediction corrected visual predictive checks (VPC) were obtained. The final model including covariates was used to perform Monte Carlo simulations (n=5000) for doses ranging from 100 to 2000 IU/kg (per 100 IU/kg steps) for patients weighing 10 to 100 kg (per 10 kg steps). Conversion of IU/kg dose to IU/m^2:

Eq.4 $Dose\ (IU/m^2) = (dose\ (IU/kg) * body\ weight\ (kg))/BSA\ (m^2)$

BSA is the body surface area used in this formula is the BSA calculated from weight alone as described by Sharkey et al.[7]

Dose interval correction

Doses are adjusted according to asparaginase levels. Patients with high levels can switch to twice weekly administration. These patients have samples in the 84-118 hour timeframe. Figure 1 shows the pcVPC with the covariate interval (patients with twice weekly dosing versus thrice weekly). This improves the median predictions especially concerning the 84-118 hour timeframe. However variability is under predicted.

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Figure 1: Asparaginase concentration vs time after dose (interval adjustment)

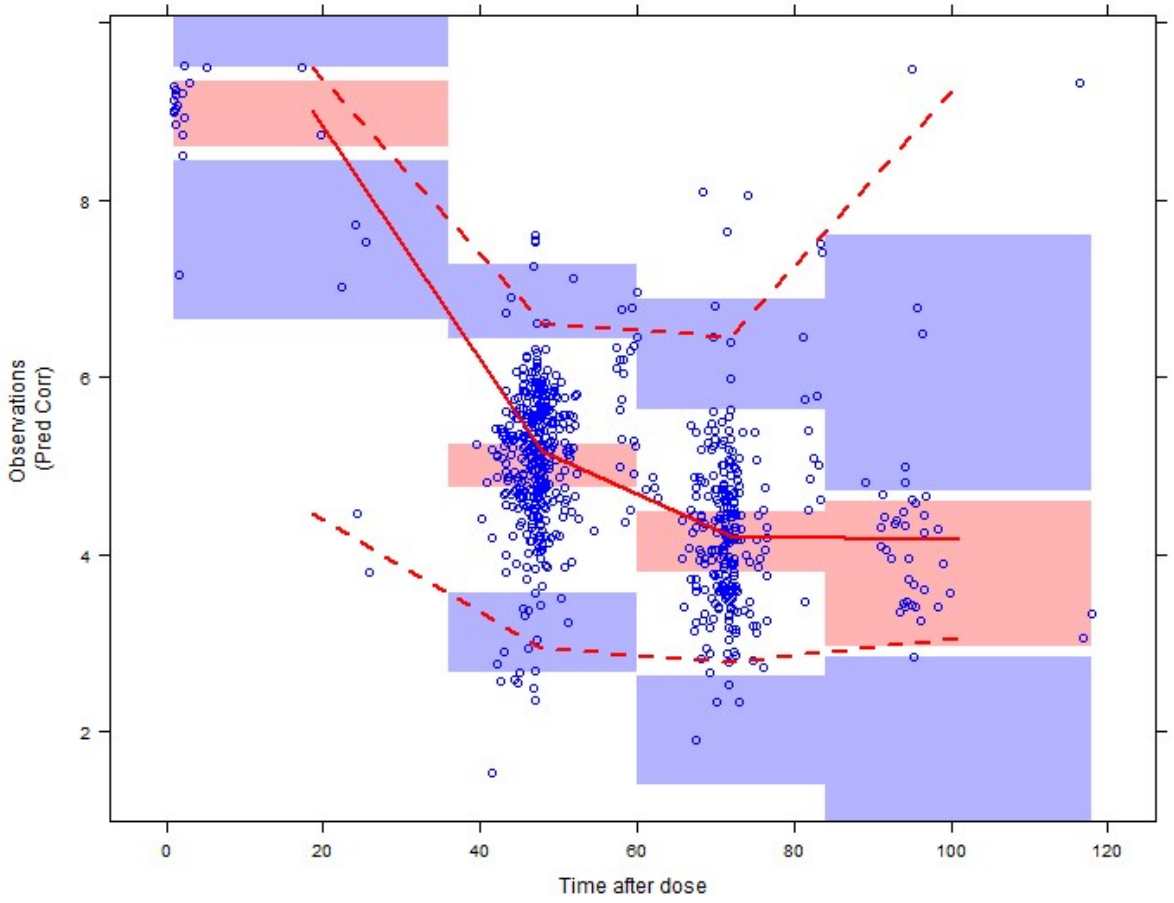

Figure 1 Prediction corrected Visual prediction plot of observed log asparaginase levels versus time after dose (hours) of the final model with covariate dose interval. The red solid line indicates the median observed levels and the surrounding opaque red area the simulation based 95% interval for the median. The red dashed lines indicates the observed 5% and 95% percentiles and the surrounding opaque blue areas show the simulated 95% confidence intervals for the corresponding predicted percentiles.