The influence of age on the disposition of cyclophosphamide and its metabolites in infants and young children with brain tumors: A population pharmacokinetic analysis

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The utility of a risk adapted protocol that includes intravenous cyclophosphamide (CTX) in children less than 5 years of age diagnosed with CNS malignancies is being studied in an institutional clinical trial (SJYC07; NCT00602667). The metabolism of CTX, a prodrug, is complex involving several metabolites whose exposures have been inferred to correlate with therapeutic response (4-hydroxycyclophosphamide (4HY)) and toxicity (carboxyethylphosphoramide mustard (CEPM)).

Objective: To assess single dose pharmacokinetics (PK) of CTX and its metabolites in infants and young children with primary brain tumors.

Methods: CTX was administered (1.5 g/m$^2$ over 1 hr) and serial samples were obtained prior to the infusion, 1, 3, 6, and 24 hours post-infusion. CTX, 4HY, and CEPM were quantitated using validated LC-MS/MS methods. Nonlinear-mixed effects modeling incorporating a model with single compartments for CTX and each metabolite was employed using Monolix (2016R1). Covariates evaluated included demographics and blood chemistries. The Likelihood Ratio Test was used to evaluate the significance of covariates.

Results: The analysis included 171 patients with a median (range) age of 21.5 (0.9 to 58.5) months. Average clearance (CL) (or apparent CL) at 21.5 months was 2.56, 51.3, and 46.8 L/hr/m$^2$ for CTX, 4HY, and CEPM, respectively. Age was denoted as a significant covariate towards CTX clearance and apparent CL of both metabolites ($p < 0.05$). Specifically, CL (or apparent CL) of CTX, 4HY, and CEPM increased by 32%, 74%, and 378% over the age range. The addition of age explained 6%, 21%, and 48% of the inter-individual variability ($\omega^2$) associated with CL (or apparent CL) for CTX, 4HY, and CEPM, respectively.

Conclusion: The analysis described the influence of age on the PK of CTX and its metabolites and will be instrumental in the development of improved dosing strategies in this unique patient population. Further investigation will explore the influence of specific genetic markers and concomitant medications on CTX PK.