GLUCARPIDASE USE IN CHILDHOOD ALL: A BAYESIAN ANALYSIS OF CLINICAL AND GENETIC RISK FACTORS

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Background: Glucarpidase (GCD) is a rescue drug for patients who develop delayed clearance or kidney injury from high-dose methotrexate (MTX). While there is evidence that Hispanic ethnicity is associated with GCD use, this has not been confirmed in independent studies, and little is known about other risk factors. Therefore, our objective was to evaluate the role of clinical and genetic factors on GCD use.

Materials/Methods: Cases that received GCD and controls were identified in a chart review of patients with ALL who received MTX doses between 1-5g/m2 at Texas Children's Cancer Center between 10/2010-12/2018. Multivariable Bayesian logistic regression was performed to evaluate the probability of GCD use given a range of variables, including self-reported ethnicity, MTX dose, body mass index (BMI), ALL subtype, and age at diagnosis. The effect of 49 genetic variants previously associated with MTX metabolism were also evaluated on a subset of patients.

Results: A total of 426 patients were identified who received 1601 doses of MTX. Of the 18 patients who received GCD, 17 (94%) were self-identified Hispanic. Mean age of the patients was 8.9 years (SD: 5.0). The variables that demonstrated strong associations with GCD were Hispanic ethnicity (OR: 3.58; 95% compatibility interval [CI]: 1.35 – 8.06) and older age (OR of 1.81 per 1 SD increase in age; 95% CI: 1.16-2.89). Although other variables' 95% CI included the null, evaluation of the posterior predictive distribution revealed that B-ALL had an 80.6% probability of positive association with GCD use compared to T-ALL and BMI >95% had an 85.0% probability compared to normal BMI. In the genomic cohort, 11 patients received GCD. Compared to homozygous patients with the common allele of ABCC4 rs7317112 (AA), heterozygous patients (AG) had a 93.2% probability of positive association, whereas homozygous patients with the minor allele (GG) had an 89.6% probability. Variants in three other genes (SLC19A1 rs1051266, ARID5B rs4948496, and TSG1 rs9345389) also demonstrated probabilities of association between 86-88%.

Conclusions: Our assessment indicates that self-reported Hispanic ethnicity and older age are positively associated with GCD use. Examination of the posterior probability distribution indicates there is a high chance that BMI >95%, B-ALL, and heterozygosity or homozygosity for the risk allele at rs7317112 are positively associated with GCD use. These results identify important risk factors for GCD use and suggest promising areas of further study.