A BAYESIAN ANALYSIS OF CLINICAL AND GENETIC RISK FACTORS FOR GLUCARPIDASE REQUIREMENT IN ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Glucarpidase (GCD) is a rescue drug that prevents renal failure in patients who develop delayed clearance or kidney injury from high-dose methotrexate (MTX). A recent analysis demonstrated that 94% of patients who received GCD at TCH were self-reported Hispanic. The purpose of this study is to explore the association between ethnicity and GCD use through a retrospective case-control study of clinical and genetic risk factors.

Materials/Methods: A chart review for all patients who received MTX doses between 1-5g/m2 between Oct. 2010 – Dec. 2018 was performed. A list of genetic variants linked to MTX metabolism in the literature were genotyped on a subset of patients. Multivariable Bayesian logistic regression was performed to associate probability of glucarpidase use with self-reported ethnicity, dose, BMI, leukemia type, age, and genotype. Weakly informative priors were assigned, model diagnostics were assessed, and prior, and posterior predictive simulations were performed.

Results: A total of 426 patients were identified who received 1601 doses of methotrexate. 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). Hispanic ethnicity demonstrated an odds ratio (OR) of 3.58 (95% compatibility interval [CI]: 1.35 – 8.06), and a standard deviation increase in age had an OR of 1.81 (95% CI: 1.16-2.89). Given the model and the priors, there is an 80.6% chance that B-cell ALL is positively associated with GCD use compared to T-cell ALL and an 85.0% chance that BMI > 95th percentile is associated compared to BMI between 10-85%. There were 177 patients in the genomic cohort and 11 patients received GCD. Analysis of 49 candidate variants revealed that patients heterozygous for rs7317112 (GA; ABCC4) had a 93.2% probability of a positive association with GCD use and homozygous patients (GG) had an 89.6% probability of association compared to homozygous AA patients. Patients who were heterozygous at 3 other loci (rs1051266, rs4948496, and rs9345389) also demonstrated probabilities of association between 86-88%.

Conclusions: There is a very high probability that self-reported Hispanic ethnicity and age are positively associated with increased risk for GCD use. Moreover, given the model and the priors, there is a high chance that BMI > 95% and a diagnosis of B-cell ALL are also positively associated. There is also a plausible association with patients both heterozygous and homozygous for rs7317112.