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Pharmacogenetic Determinants of Bone Toxicity Among Children Treated with Chemotherapy for Acute Leukemia

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Background: Bone fractures and osteonecrosis frequently complicate therapy for childhood acute lymphoblastic leukemia (ALL). Bone toxicity has been associated with exposure to corticosteroids and methotrexate and age greater than 10 years.

Study Question: Are common pharmacogenetic polymorphisms associated with bone toxicity in children during treatment for acute leukemia?

Methods: 615 out of 794 children with acute leukemia enrolled on DFCI ALL Consortium protocol 05-001 (NCT00400946) met eligibility criteria for inclusion in this analysis. Nineteen candidate polymorphisms were selected a priori, targeting genes related to glucocorticoid metabolism, oxidative damage, and folate physiology. Polymorphisms were genotyped using either PCR-based allelic discrimination or PCR product length analysis.

Results: Twenty percent of subjects were homozygous for two 28bp repeats (2R/2R) within the 5' untranslated region of the gene for thymidylate synthase (TS). This 2R/2R genotype was associated with increased risk of osteonecrosis among children younger than 10 years at diagnosis (multivariable hazard ratio 2.71; 95% CI 1.23-5.95; p=0.013), and with bone fracture among children ≥10 years (multivariable HR 2.10; 95% CI 1.11-3.96; p=0.022). No significant association was observed between TS genotype and RBC folate, RBC methotrexate, or relapse risk.

Conclusions: A common genetic variant is associated with increased risk of osteonecrosis among children younger than 10 years treated for acute leukemia, and with bone fractures among older children. These findings suggest that children and adolescents with the 2R/2R TS genotype should be closely monitored for the development of bone toxicity during therapy for ALL, and support a clinical trial testing the efficacy of protective interventions specifically in this vulnerable population.