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"Analysis of Neurocognitive Gene Expression in Pediatric Cancer Patients Treated with Methotrexate"

Introduction: In recent years, scientific advances in pediatric cancer treatments have earned record-high survival rates for afflicted patients. Therefore, pediatric cancer research has shifted from investigating cancer survivorship to exploring the well-being of patients following treatment. Several common chemotherapy agents have been discovered to induce long-lasting side effects, termed late effects, in pediatric patients as they mature after treatment. Particularly, the folic acid antagonist methotrexate (MTX) has been suggested to cause poor neurological outcomes for some cancer survivors, such as motor skill dysfunction, attention span depletion, and processing speed reduction. Therefore, this study hypothesizes that MTX deregulates the expression of multiple genes related to healthy neurological function. Furthermore, results may illustrate a neurological genotype-phenotype correlation that explains the late effects experienced by chemotherapy patients.

Methods: To analyze gene expression, formalin-fixed paraffin-embedded samples of brain white matter were previously collected from the Pathology Department at Children's Hospital of New Orleans (n = 60) for patient autopsies performed within 48 hours of death. Specimens were identified for patients between 2 and 22 years of age who were treated with MTX and for aged-matched controls. Next, tissue samples were sectioned, excess paraffin was dissolved in xylene, and the *Covaris truXTRAC® FFPE total NA Kit* was utilized to isolate DNA and RNA. A prior experiment has been conducted with the RNA-targeted *Nanostring Neuroinflammation Panel* to compare gene expression to controls (n = 3). This study intends to confirm these preliminary findings by completing another *Nanostring Neuroinflammation Panel* with additional RNA samples. In addition, bisulfite modification and the *Infinium Human MethylationEPIC version 2.0* microarray will be used to examine DNA methylation, which suppresses expression.

Preliminary Results: Several genes associated with neurological deficiencies are abnormally expressed in patients treated with MTX when compared to age-matched controls. For example, the *GJA1* gene for neuron recovery was overexpressed in MTX patients by 8.17 times the amount measured in control specimens. *CD24*, another gene that is used for axonal growth, was found to be expressed 8.26 times less than in controls. Finally, the gene that codes for angiotensinogen, which plays a role in memory, was increased by a factor of 5.23. Because of the health risks associated with these genes and others identified within the previous experiment, this data encourages the confirmatory work continued in this study.

Discussion: If the confirmatory study supports the preliminary results of abnormal neurocognitive gene expression, it will illuminate the importance of following up clinically with pediatric cancer patients to screen for potential neurological risks into adulthood. Early detection and preemptive treatments will be crucial for improving quality of life. Abnormal genetic results from this study would also motivate future research into MTX late effects.