Gabrielle Sheets
University of New Orleans

Fern Tsien, PhD
Department of Genetics, Louisiana State University Health Sciences Center, New Orleans, LA

"The Effect of Methotrexate Treatment on Neuroinflammation Gene Expression"

Purpose of Study:
Methotrexate is one of the most effective and widely used chemotherapy agents for treating leukemia and osteosarcoma. In pediatric patients, methotrexate has been associated with the development of long-lasting, neurological, and psychosocial sequelae following cancer survival (i. e., late effects). Symptoms include hyperactivity, inattention, and deficits in executive functioning as well as processing speed. We hypothesize that methotrexate treatment causes changes in neurological and psychosocial development in children and abnormal gene expression.

Methods:
The first portion of our study is a retrospective chart review of cancer survivors. We have obtained medical records of cancer survivors, ages 2-22 years old, enrolled at the Treatment After Cancer Late Effects (TACLE) clinic at CHNOLA for review. Specifically, we are examining neurological, and psychosocial testing (e. g., Behavioral Assessment System for Children, Third Edition, BASC-3 and Wechsler Intelligence Scale for Children, WISC and Wechsler Adult Intelligence Scale, WAIS) results before and after treatment. The second part of our study is a genetic analysis of formalin-fixed, paraffin embedded (FFPE) white matter obtained from deceased methotrexate-treated patients and age-matched controls. RNA was isolated from the samples followed by Nanostring analysis to detect abnormal up or downregulation of neuroinflammation-associated genes. Lastly, we applied Bioinformatics using Ingenuity Pathway Analysis (IPA) to determine affected biological pathways and networks involved with our candidate genes.

Summary of Results:
Preliminary results from the first portion of the project demonstrated that patients who received methotrexate through high-dose IV or intrathecally have a statistically significant risk of experiencing neurocognitive deficits. Patients who were at the highest risk were those who received intrathecal methotrexate, those of the female sex, patients who were of a younger age at diagnosis, and those who received methotrexate in combination with cranial irradiation. Genetic testing of white matter autopsy samples revealed genes that were three to eightfold over or under expressed, including GJA1 (non-syndromic hearing loss), OLFML3 (microglia suppression), and CD24 (myelin sheath).

Conclusion:
The present study will provide information regarding gene-environment interactions and thus reveal candidate risk genes and pathways contributing to neurocognitive and psychiatric late effects. Identifying risk factors and monitoring pediatric cancer patients with regular psychiatric and neurological evaluations are necessary so that they may receive the appropriate intervention and support services to improve their quality of life. As cancer survivorship increases, so does the need for research, routine surveillance, and the prevention of toxic late effects caused by pediatric cancer treatment, particularly methotrexate.