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mRNA & miRNA Expression in Taxane Induced Peripheral Neuropathy During Taxane Treatment: A 12-Month Longitudinal Analysis

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Introduction: Taxanes are an effective class of chemotherapeutics commonly associated with chemotherapy-induced peripheral neuropathy (CIPN), which complicates clinical management and may necessitate treatment alterations or discontinuation. Genetic factors such may contribute to the development of CIPN. This study aims to investigate the relationships between selected biomarkers and the development and resolution of CIPN in patients receiving taxanes. To explore this aim, we conducted a longitudinal analysis of breast cancer patients undergoing taxane therapy during adjuvant or neo-adjuvant treatment. We hypothesized that there would be differences in selected genetic and epigenetic biomarkers in patients that do and do not develop CIPN when treated with taxanes for breast cancer. Differences in biomarkers were used to conduct a preliminary molecular pathway analysis to identify potential pathways associated with CIPN.

Methods: Following internal review board approval, patients diagnosed with breast cancer were invited and consented to participate in this multicenter observational study. Data was collected over 12 months at of seven time points: pre-treatment (visit 1), 3 months of treatment (visits 2-4) and 9 months post-treatment (visits 5-7). CIPN was measured using the CIPN 20item (CIPN20) questionnaire. Patients with CIPN20 scores 8 points above baseline were classified as having CIPN. Panels of 194 mRNAs and 798 miRNAs were analyzed at each of the seven time points, representing changes across six time intervals. Changes in biomarkers were examined using the semi-parametric OmicsLonDA package, focusing on the activation (Zscore > 0) and inhibition (Z-score < 0) of molecular pathways associated with CIPN, mapped using Ingenuity Pathway Analyses.

Results: Data collection was completed in 363 breast cancer patients treated with taxanes at the Cleveland Clinic and University of Utah. CIPN reached its highest severity 3 months after initiation of taxane therapy. Significant differences (FDR P<.05) were found in 99 mRNAs (out of 194) and 147 miRNA features with and without CIPN across time intervals. Notable findings included elevated opioid receptor mu 1 (OPRM1) mRNA in CIPN-negative patients and increased calcium/calmodulin dependent protein kinase ID (CAMK1D) mRNA in those with CIPN.

Differentially expressed mRNAs were linked to 120 canonical pathways. As presented in Figure 4, a heatmap analysis identified four pathways of interest that included the CREB signaling (FDR P=1.39x10-11), opioid signaling (FDR P=1.79x10-9), endocannabinoid neuronal synapse pathway (FDR P=4.89x10-8), and neuropathic pain signaling in dorsal horn neurons (FDR P=6.62x10-5).

Conclusions

Our results suggest that expression of selected mRNAs and miRNAs are different in patients that do and do not develop CIPN in response to taxane therapy. Our preliminary exploration of possible molecular pathways suggests several pathways may be different between patients that do and do not develop CIPN. Future work is warranted to explore the potential of these findings and molecular pathway analysis to serve as biomarkers of patients at high risk for developing CIPN severe enough to alter therapy.