

Ex Vivo Neurite Outgrowth of Sensory Neurons Derived from Patients Suffering from Taxane-Induced Peripheral Neuropathy

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Introduction: Taxane-induced peripheral neuropathy (TIPN) is a devastating side effect commonly seen in African American women being treated with chemotherapy for breast cancer and can cause significant dose reduction or cessation of treatment. EAZ171, a first NCI sponsored clinical trial focusing only on African American women with breast cancer, demonstrated that docetaxel clinically caused significantly less TIPN than paclitaxel. In the current project, we have investigated the impact of two taxanes, paclitaxel and docetaxel, on the morphology of neurons derived from EAZ171 patients.

Methods: Using an ex vivo model of induced pluripotent stem cell-derived sensory neurons (iPSC-dSNs) derived from peripheral blood of EAZ171 TIPN case and control patients, we measured neurite outgrowth of the induced neurons treated with vehicle or taxane. The change in neurite outgrowth was analyzed between vehicle- and taxane-treated groups. Differences in taxane induced neurite outgrowth between patients who experienced TIPN (cases) and those who did not (controls) were assessed for the differential impact of paclitaxel vs docetaxel.

Results: Taxane treatment significantly reduced the neurite outgrowth of iPSC-dSNs in a combined analysis and an analysis stratified by taxane type. Compared to the iPSC-dSNs derived from their control counterparts, iPSC-dSNs derived from paclitaxel therapy cases had a greater reduction in neurite outgrowth than that from docetaxel therapy cases.

Conclusions: The differences between paclitaxel and docetaxel in this model mirror the clinical differences in EAZ171 and provide an opportunity for unraveling mechanistic differences in this ex vivo model system. Further investigation involving fluorescence-based calcium imaging, whole transcriptome sequencing, methylation analysis, and ATAC-Seq can uncover differences between taxane types and factors that predispose patients to TIPN.