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3367

A Mouse Model of APOE Genotype in Chemotherapy Related Cognitive Impairment

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OBJECTIVES/SPECIFIC AIMS: Chemotherapy-related cognitive impairment (CRCI) affects 15-35% of breast cancer survivors and constitutes a significant challenge for survivor quality of life. Among older breast cancer survivors who received chemotherapy treatment, carriers of at least one ε4 allele of the APOE gene, which encodes apolipoprotein E, are at higher risk for developing CRCI than non-carriers. APOE4 is well characterized as the strongest genetic risk factor for Alzheimer's disease, but how it contributes to CRCI is not yet understood, and no animal models of APOE genotype and CRCI have yet been established. To better understand how APOE4 acts as a risk factor for CRCI, we used APOE targeted replacement (TR) mice to develop a model of its effects on cognition following treatment with doxorubicin, a chemotherapy drug commonly used in breast cancer treatment. METHODS/STUDY POPULATION: Twelve-to-thirteen month old APOE3 and APOE4 targeted replacement mice expressing human APOE3 or human APOE4 under control of the endogenous murine promoter were treated with 10 mg/kg doxorubicin or equivolume saline given via two IP injections spaced one week apart. One week post-treatment, mice were tested using Open Field and Elevated Zero apparatuses to assess baseline locomotive activity and anxiety and exploratory behaviors. Five weeks post-treatment, mice were assessed using the Barnes Maze over four days of training trials and one 72 hour memory probe. RESULTS/ANTICIPATED RESULTS: We found no differences in Open Field and Elevated Zero behavior, indicating limited influence of doxorubicin treatment on locomotive and anxiety behaviors in both genotypes. During Barnes Maze training, APOE4 mice treated with doxorubicin showed increased latency compared to untreated APOE4 mice as well as treated and untreated APOE3 mice, indicating deficiencies in spatial learning. In APOE3 mice, no differences in performance were seen between doxorubicin-treated and untreated mice ($n = 15\text{-}16$/group, $p < .0001$). DISCUSSION/SIGNIFICANCE OF IMPACT: These results indicate that APOE4 targeted replacement mice have specific cognitive vulnerabilities to doxorubicin treatment that can be reliably detected using the Barnes Maze assessment. Future directions include experiments to determine how other chemotherapy drugs or drug combinations impact cognition of APOE4 mice. Ultimately this model may be used to assess preventive measures or therapies for CRCI in the vulnerable APOE4 carrier population with the ability to validate cognitive impacts of these interventions.

3552

Advancing Glioblastoma (GBM) drug regimen development to support combination therapy through integrated PKPD modeling and simulation-based predictions

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OBJECTIVES/SPECIFIC AIMS: Despite advancements in therapies, such as surgery, irradiation (IR) and chemotherapy, outcome for patients suffering from glioblastoma remains fatal; the median survival rate is only about 15 months. Even with novel therapeutic targets, networks and signaling pathways being discovered, monotherapy with such agents targeting such pathways has been disappointing in clinical trials. Poor prognosis for GBM can be attributed to several factors, including failure of drugs to cross the blood-brain-barrier (BBB), tumor heterogeneity, metastasis and angiogenesis. Development of tumor resistance, particularly to temozolomide (TMZ), creates a substantial clinical challenge.The primary focus of our work is to rationally develop novel combination therapies and dose regimens that mitigate resistance development. Specifically, our aim is to combine TMZ with small molecule inhibitors that are either currently in clinical trials or are approved drugs for other cancer types, and which target the disease at various resistance signaling pathways that are induced in response to TMZ monotherapy. METHODS/STUDY POPULATION: To accomplish this objective, an integrated PKPD modeling approach is used. The approach is largely based on the work of Cardilin, et al, 2018. A PK model for each drug is first defined. This is subsequently linked to a PD model description of tumor growth dynamics in the presence of a single drug or combinations of drugs. A key outcome of these combined PKPD models are tumor static concentration (TSC) curves of dual or triple combination drug regimens that identify combination drug exposures predicted to arrest tumor growth. This approach has been applied to TMZ in combination with abemaciclib (a dual CDK4/6 small molecule inhibitor) based on data from a published study evaluating abemaciclib efficacy in combination with TMZ in a glioblastoma xenograft model (Raub, et al, 2015). RESULTS/ANTICIPATED RESULTS: A PKPD model was developed to predict tumor growth kinetics for TMZ and abemaciclib monotherapy, as well as combination therapy. Population PK models in immune deficient NSG mice for temozolomide and abemaciclib were developed based on data obtained from original and published studies. Subsequently, the PK model was linked to tumor volume data obtained from U87-MG GBM subcutaneous xenografts, again using both original data as well as data from the Raub, et al, 2015 study. Model parameters quantifying tumor volume dynamics were precisely estimated (coefficient of variation < 30%). The developed PKPD model was used to calculate plasma concentrations of TMZ and abemaciclib that would arrest tumor growth, as well as combinations of concentrations of the two drugs that would accomplish the same endpoint. This so-called TSC curve for the TMZ and abemaciclib combination pair evidenced