1. Project description: Leveraging treatment resistance for immunotherapeutic strategies for glioblastoma

Immunotherapy has promising results in phase III trials for treatment of solid refractory tumors, and is a novel strategy for glioblastoma multiforme (GBM). GBM is associated with dismal outcomes despite aggressive treatment. Our group has extensive experience with cellular immunotherapy to target GBM. An important component of this research is the interaction between immunotherapeutic strategies and standard treatment with temozolomide (TMZ) and radiation. The most well known mechanism of TMZ resistance in GBM is due to an unmethylated promoter of O(6)-methylguanine-DNA methyltransferase (MGMT). MGMT promoter unmethylated GBM is associated with different expression of certain tumor associated antigens compared to methylated tumors. Moreover, TMZ exposure also results in genetic mutations and TMZ resistance. Therefore, TMZ-resistant tumors (both inherent and acquired) are genetically and phenotypically different from TMZ-sensitive tumors. Although the synergy between TMZ and immunotherapy is well established, the mechanisms involved and the role of TMZ resistance have not been explored.

The long-term goal of our research is to evaluate the role of immunotherapy in the treatment of patients with a resistant or recurrent malignant glioma. Our proposal will demonstrate TMZ resistance (via MGMT expression or TMZ exposure) is associated with tumor antigen and immunobiologic differences which improve response to PD1 blockade therapy. The central hypothesis is that TMZ resistant (both inherent and acquired) GBM has a different immunobiologic phenotype compared to TMZ sensitive tumors and results in an improved response to immune checkpoint blockade. The results of this study will determine the role of immunotherapy in resistant phenotypes of GBM, determine the role of stratifying by MGMT status prior to immunotherapy, and evaluate mechanisms by which to optimize immunotherapy for resistant GBM.

The medical student’s role would be to perform cell culture, in vitro and in vivo experiments to test response to immunotherapy, PCR and flow cytometry. Funding is provided by the UFBTIP.

References

2. Project description: Impact of surgical morbidity on overall survival in glioblastoma

Glioblastoma is the most common primary malignant brain tumor and is associated with dismal outcomes despite surgery, chemotherapy and radiation. There is compelling non randomized data demonstrating improved outcomes with gross total resection of the enhancing tumor on imaging. However, retrospective data shows that increasing the extent of resection is associated with increasing morbidity. We hypothesize that of...
patients who have a gross total resection of malignant glioma, those with a new neurologic deficit after surgery will have worsened overall survival. To test this hypothesis, we will perform a retrospective analysis of patients at UF and other centers that participate in the Florida Center for Brain Tumor Research (FCBTR) to analyze clinical data and measure tumor volumes on MRI scans prior to and after surgical resection. We will evaluate patients in whom a gross total resection was achieved on imaging. These patients will be analyzed for correlation between neurologic morbidity and overall survival. The role of the medical student will include IRB submission, collaboration with outside institutions, chart review, tumor volume measurement, and data analysis.

References


