

The Glioblastoma Multiforme Brain Tumor Research Grant

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Towards personalized medicine in neurooncology: multigene predictor of response in glioblastoma

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Abstract

A recent phase III clinical trial demonstrated the efficacy of chemotherapy by improving overall survival in GBM(1). The 2-year survival rate was more than double (26%) in the temozolomide-chemoradiation (TMZ-CR) arm compared to the radiation-only arm (10%). This has changed standard of care for GBM. Correlative studies indicated that methylation at the MGMT promoter was associated with improved outcome (2). Among the patients in the TMZ-CR arm, those with MGMT promoter-methylated tumors experienced a 2-year survival rate of 46% compared to 14% among patients with unmethylated tumors. While exciting, MGMT methylation status is not sufficiently sensitive to determine therapy for newly diagnosed GBM, since approximately half (54%) of the patients in the MGMT-methylated group did not survive 2 years. Since a wide range of treatment responsiveness is observed in patients with newly diagnosed GBM following TMZ-CR the ability to prospectively identify and distinguish patients likely to respond from patients likely to progress through TMZ-CR would be of great clinical utility in determining up-front therapy. Patients whose tumors are predicted to be responsive to TMZ-CR might receive this as initial therapy, while those who are likely to progress might be selected for TMZ-CR plus an additional agent tailored towards molecular alterations present in his/her tumor profile. Towards this goal of personalized medicine in neuro-oncology we have conducted a meta-analysis of microarray data to identify reproducible gene expression markers of patient outcome in newly diagnosed GBM. Our multigene set was composed of 38 genes, all of which were consistently associated with 2-year survival in 4 independent Affymetrix data sets. This multigene set was also associated with radiation response on patients for whom pre- and post imaging data were available. To validate this multigene set we created qRT-PCR assays for these 38 genes. In anticipation of a future clinical test amenable to all samples available in pathology laboratories, we designed/optimized our qRT-PCR assays for formalin-fixed, paraffin embedded (FFPE)-derived RNA. Using a set of 69 GBM samples (none of which were in the original affymetrix set) we validated this signature as a predictor of overall survival as well as response to radiation. Although the gene set as a whole was validated, it was clear that is the move from a frozen/Affymetrix platform to an FFPE/qRT-PCR platform some of the genes in the 38-gene set remained highly predictive of outcome, while others were less so. Therefore, further optimization of this multigene set may increase its reliability as a predictor of outcome. In addition, since our multigene set was created from patient samples prior to the advent of TMZ-CR as standard

therapy, the gene set needs to be shown to be predictive in TMZ-CR-treated patients, with inclusion of MGMT methylation status as an additional marker in the multigene set.

Accordingly, the **Specific Aim of this proposal is to refine and optimize a multigene predictor of outcome in GBM patients treated with TMZ-CR.** We will use as the primary outcome measure 6-month progression-free survival in order to optimize this marker panel as a gene set which predicts response to initial therapy in GBM. Our studies will capitalize our involvement in the RTOG 05-25 clinical trial. Dr Aldape is the reference pathologist for RTOG 05-25, a large (n=1100) clinical trial comparing regular dose +RT vs. high dose TMZ +RT in GBM. A key element of this trial is *the requirement of a paraffin block with tumor of sufficient size (1 square cm on H&E) for study entry*. This requirement ensures availability of tumor tissue for potentially every patient on the study. We will perform our multigene predictor on a subset of patient samples (n=300) from 05-25 to optimize the predictor. Data will be sent to the RTOG statisticians, who will analyze 6-month progression free survival. They will perform this in a manner that does not compromise the conduct of the study. A predictive model will be created, with optimal weighting for each marker. The sample size of 300 is sufficient to allow statistical cross-validation studies to develop a robust model. Once a predictor is optimized, we will use the remainder of the samples for validation. In addition predictive power within each treatment arm will be determined. Successful completion of this aim will position us well for 1) future development as a diagnostic test to individualize therapy in GBM.