

A Case Controlled Study Utilizing an In-Silico GBM Mathematical Model to Predict Temozolomide Response and Progression Free Survival

Chirag Gadkary Patil MD; Shireen Vali; J. Manuel Sarmiento MD; Jethro Hu; Jeremy D. Rudnick BS, MD; Rakhi P Suseela; Upasana Mitra; Neeraj K Singh; Keith L. Black MD; Christopher J. Wheeler PhD

Introduction

Although Methylation status of glioblastoma (GBM) has been reported extensively as a predictor of response to temozolomide (TMZ), there are many false response predictions. We present here a case controlled study that uses mathematical modeling of genomic information in addition to MGMT methylation status to predict PFS.

Methods

Twelve newly diagnosed GBM patients treated with SOC TMZ and RT were included. Six responders (PFS >15 months) and 6 non-responders (PFS < 6 months) matched on age, KPS and initial treatment were included. Exome wide mutational and CNV analysis was performed. Cellworks genome based mathematical modeling was performed which predicted each tumor to be resistant or sensitive to TMZ based on MGMT methylation status along with impact on its transcriptional regulators (STAT3, NFkB1 and HIF1A) and homologous recombination and DNA mismatch repair pathways. The clinical data was then unblinded and sensitivity, specificity and PPV analysis were performed between the known clinical response (responder versus non-responder) and the mathematical model prediction.

Results

The study included 12 GBM patients with mean age of 53 years and median KPS of 80. The mathematical model correctly predicted the non-responder group (all 6 clinical non-responders) and 5 out of 6 clinical responders. There was 1 mismatch. The sensitivity of the model was 83%; specificity 100%; PPV 100%; NPV 86%. We had 3 patients with mismatch between MGMT methylation alone and clinical response and this could be explained by our model through transcriptional upregulation of MGMT via STAT3, NFkB1 and HIF1A. Use of MGMT methylation status as the sole predictor of PFS/TMZ response (PPV 0.625; NPV 0.75; Sensitivity 0.83; Specificity 0.5) was worse than our mathematical model predictions.

Conclusions

A novel mathematical model using MGMT as well as other DNA repair pathway mutations is more accurate in predicting clinical response to TMZ than solely the GBM Methylation status.

Learning Objectives

By the conclusion of this session, participants should be able to:

1. Understand the limitations of MGMT methylation on predicting GBM response to temozolomide.
2. Describe other DNA repair pathways that can influence clinical outcome
3. Understand how using genomic information from other DNA repair pathways in a mathematical model help improve response prediction
4. Why response prediction in GBM is clinically important

References

1. DNA Repair Capacity in Multiple Pathways Predicts Chemoresistance in Glioblastoma Multiforme PMID: 27793847
2. Complex DNA repair pathways as possible therapeutic targets to overcome temozolomide resistance in glioblastoma PMID: 23227453
3. Augmented HR Repair Mediates Acquired Temozolomide Resistance in Glioblastoma PMID: 27358111
4. STAT3 inhibition overcomes temozolomide resistance in glioblastoma by downregulating MGMT expression PMID: 22532597
5. HIF-1 α inhibition sensitizes pituitary adenoma cells to temozolomide by regulating MGMT expression. PMID: 23970362
6. Temozolomide: mechanisms of action, repair and resistance PMID: 22122467