Resection of Malignant Glioma Results in Significant Decrease in Circulating Tumor-Specific Hypermethylated DNA. A Potential Biomarker?

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Introduction

Malignant glioma surveillance and disease burden determination rests largely with contrast enhanced MRI. There are no blood-based biomarkers for malignant glioma in clinical use today. We demonstrate that tumor-specific plasma DNA can be accurately quantitated and reaction variability controlled, and that plasma levels are related to tumor burden which can be significantly altered by surgery.

Methods

32 patients undergoing operation for HGG donated plasma samples immediately before craniotomy and postoperative day 1. Tumor was obtained and assayed. DNA was isolated and bisulfate treated. Reaction variability was normalized using a S. cerevisiae actin spike-in method. Quantitative PCR was used to determine the absolute copy number of methylated 0-6 methylguanine methyltransferase (MGMT) promoter. Pre- and post op plasma was also obtained from 11 patients undergoing craniotomy for microvascular decompression or unruptured aneurysm (controls)

Results

Frequency histograms of concentrations (normalized methylated promoter#/ml plasma or /mg tumor) were constructed and positive/negative cutoffs were determined. Treatment patients demonstrated 6.28x105 copies/ml preoperatively and 2.44x104 copies postoperatively, (p=0.0035, t-test), a 26-fold decrease. There was no significant difference between post-op concentrations in the treatment versus the pre-op control groups (p=0.8104) or between pre- and post-op control groups (p-0.7304). No tumor patients demonstrated the presence of both tumor methylated MGMT and plasma concentrations above the negative cutoff values.

Conclusions

This study demonstrates that absolute copy number of methylated MGMT promoter can be accurately determined and assay variability addressed. There is a significant decrease in plasma concentration by post-op day 1 to near pre-op control levels suggesting a relation to tumor burden/excision and an attractive technique and target for a blood biomarker. Work continues on volumetric analysis, other gene targets, and correlation with longitudinal clinical variables including survival.

Learning Objectives

By the conclusion of this session, the participants should be able to: 1) discuss circulating nucleic acids in plasma of patients with malignant glioma, 2) discuss hypermethylation silencing of tumor suppressor genes, 3) understand the role of plasma biomarkers in the treatment of glioma

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