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Prospective Analysis of Prognostically Important Genomic Alterations in Glioma Patients

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Introduction

Gliomas are derived from neuroepithelium and comprise ~28% of all CNS tumors. High~grade gliomas (HGG) represent 80% of malignant brain tumors, glioblastomas (GBMs) being the most malignant, with average survival of 15 months. Extensive studies have defined the complex genomic landscape of HGGs, including primary de novo HGGs carrying EGFR amplifications with loss of CDKN2A/B and PTEN, and secondary HGGs harboring recurrent IDH1.R132 mutation, which was correlated with better survival. However, there are no prospective series correlating genomic variants with clinical outcomes

Methods

We created a prospective database comprised of 238 patents with gliomas (80% HGGs), including demographic, clinical, histologic and genomic data. All patients with resectable HGGs underwent gross total resection; >90% received radiation with concomitant temozolomide, unless previously radiated or unable to tolerate; ~70% were treated with salvage chemotherapy, or participated in clinical trials. Whole exome sequencing was performed in all cases and correlated with clinical data, including progression free (PFS) and overall survival (OS)

Results

Prognostically, patients fell into 3 groups based on OS, those with OS<6 months (group1, 10% recurrent), OS 6~20 months (group2), and OS>20 months (group3, 30% recurrent). None of group3 HGGs harbored the IDH1.R132 mutation. Analysis of copy number variations (CNVs) of group1 patients indicated frequent EGFR amplifications, PDGFRA amplifications (absent in other groups), and PTEN/CDKN2A loss. Analysis of mutations in group1 patients identified NF1 and PIK3CA mutations in a third of patients. Conversely, few group3 patients contained genetic alterations in FGFR not identified in other groups. We additionally compared numbers of somatic mutations and percentage of genome affected by CNVs between groups

Conclusions

Whole exome sequencing is a powerful predictor of clinical prognosis. Prospective correlation of specific genomic alterations, including presence of coding mutations and copy number variations, has significant implications not only for designing targeted treatments, but also for predicting survival and therapy response

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Describe the importance of whole exome sequencing in understanding glioma biology; 2) Discuss common genetic alterations in high grade gliomas; 3) Appreciate the importance of prospective data collection for correlating clinical data with genomic data

References

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