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PATH-06. QUANTITATIVE ANALYSIS OF MGMT PROMOTER METHYLATION AND ITS PROGNOSTIC VALUE IN GLIOBLASTOMA MULTIFORME (GBM) PATIENTS TREATED WITH ALKYLATING CHEMOTHERAPY- PRELIMINARY REPORT

Permalink

Journal

ISSN

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Publication Date

DOI

Peer reviewed

period. METHODS: The UCSF500 Cancer Panel assesses approximately 500 cancer-associated genes for mutations, copy number alterations, and structural rearrangements, including fusions. The test can be run on tumor DNA alone or compared with normal DNA, allowing for discrimination of germline variants. Sequencing results are analyzed by a neuropathologist with genomics expertise (D.A.S.). Results from the 165 adult WHO grade IV diffuse glioma cases sequenced to date were analyzed, including 136 glioblastomas, IDH-wildtype; 19 glioblastomas, IDH-mutant; and 10 diffuse midline gliomas, H3 K27M-mutant. RESULTS: Among the 136 IDH-wildtype glioblastomas, the most common alterations were in TERT, EGFR, CDKN2A, PTEN, NF1, TP53, PIK3R1, PDGFRA, CDK4, MDM2, LZTR1, and STAG2. Among the 19 IDH-mutant glioblastomas, the most common additional alterations were in TP53, ATRX, CDKN2A, and PDGFRA. Paired germline sequencing was performed on 71 patients, ten of which were found to harbor a germline mutation associated with increased cancer risk, including the CHEK2, MSH2, and NF1 genes. Somatic hypermutation was present in nine cases, four at initial resection and five at recurrence with a temozolomide-associated mutational signature. Among the four treatment-naïve glioblastomas with hypermutation, two were Lynch syndrome-associated in patients with damaging germline mutations in MSH2, and two were sporadic tumors that harbored somatic mutations in mismatch repair genes. CONCLUSIONS: Genomic profiling in adult glioblastoma patients results in identification of potentially actionable genetic alterations and also previously unknown germline mutations associated with increased cancer risk. A subset of glioblastomas (approximately 5%) harbor somatic hypermutation, indicating potential utility of immune checkpoint inhibition.

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OBJECTIVE: To correlate the percentage of MGMT methylation with progression-free survival (PFS) and overall survival (OS) in GBM patients receiving alkylating chemotherapy. BACKGROUND: MGMT promoter methylation is a known favorable factor for patients with GBM to have better response to the treatment with alkylating chemotherapy and better survival outcome. However, in daily practice, patients with very high percentage of MGMT methylation sometimes were observed to have a shorter survival period. This study is to investigate if the strength of the positivity is correlated to the PFS and OS in GBM patients receiving alkylating chemotherapy. METHODS and PATIENTS: Quantitative MGMT methylation measurement was performed. 5% was defined as positive methylation. Seventeen patients with a diagnosis of GBM and methylated MGMT were reviewed retrospectively. Patients were placed into 3 categories based on their MGMT methylation percentages: 5–33%, 34–66%, and 67–100%. The average PFS and OS were calculated for each category. RESULTS: The 6 patients in the 5–33% methylation category had an average PFS of 14.8 months (range 9 to 32) and OS of 27.2 months (range 10 to 42). The 8 patients in the 34–66% methylation category had an average PFS of 23.9 months (range 0 to 73) and OS of 28.1 months (range 1 to 82). The 3 patients in the 67–100% methylation category had an average PFS of 9.6 months (range 2 to 21) and censored OS of 14.7 months (range 2 to 35) as 2 of the 3 are alive. CONCLUSION: Our sample size is too small to provide conclusions. Comparing the first two methylation categories, the extent of MGMT methylation appears positively correlates with PFS (14.8 versus 23.9 months) but not OS of patients (27.2 versus 28.1 months). Data from additional 15 MGMT methylated patients after follow-ups will be added for analysis.

PATH-07. PRONEURAL GLIOMAS ARE ASSOCIATED WITH POOR SURVIVAL AND MORE LIKELY LOCATED IN PROXIMITY TO THE SUB-VENTRICULAR ZONE

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INTRODUCTION: The Cancer Genome Atlas (TCGA) revealed five sub-classes of astrocytic gliomas; four sub-classes defined by RNA expression (proneural, neural, mesenchymal, and classical), and one by isocitrate dehydrogenase mutation (IDHm). These studies demonstrated prognostic differences only with IDH mutation. Using additional patient and clinical characteristics, we determine if there is a difference in survival between the non-IDH mutated molecular sybtypes of GBM, while accounting for patient age, KPS, or tumor grade. METHODS: We identified 1,073 patients with astrocytomas of all grades from TCGA, excluding IDHm tumors to examine the potential association between RNA expression-based subtype classifications without IDHm as a confounder. We assessed survival using univariate and multivariate Cox proportional hazards analyses adjusted for age,

KPS, and tumor grade. We also used The Cancer Imaging Archive (TCIA) to examine the relationship between molecular subtype and propensity for neuroanatomic location of glioblastomas (GBM). RESULTS: Univariate analyses indicated improved survival with increasing KPS (HR = 0.961, p < 0.001), and worse survival with increasing age (HR = 1.054, p < 0.001) and increasing grade (HR = 3.319, p = 0.004 for grade 3; HR = 11.432, p < 0.001 for GBM; relative to grade 2). While no survival association was observed with regards to the RNA-based subtype classification in univariate analysis, in a multivariate analysis that included age, KPS, tumor grade, and RNA-based subtype classification, proneural glioblastomas are associated with worse survival (HR = 1.524, p = 0.012) relative to the non-proneural glioblastomas. Additionally, analysis of TCIA demonstrated that proneural glioblastomas were more likely to be located near the sub-ventricular zone (SVZ, p < 0.05). CONCLUSION: Our findings suggest that RNA expression-based subtype classification has prognostic utility, and proneural subtype of astrocytoma is associated with worse survival. This subtype was more likely to be located near the SVZ, suggesting potential mechanistic insights for this survival association.

PATH-08. THE IVY GLIOBLASTOMA PATIENT ATLAS - A NOVEL CLINICAL AND RADIO-GENOMICS RESOURCE FOR EARLY PHASE CLINICAL TRIAL DESIGN AND INTERPRETATION

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Newly diagnosed GBM represents a population of increased focus in early phase clinical trials. However, a key limitation of current genomic databases of GBM, such as TCGA, is that patient populations eligible for inclusion in these databases exhibit inherent biases and exhibit limitations on the quality of clinical and imaging data available for integration with genomics. To address these limitations and to better represent the genomics of patient populations commonly enrolled to early phase clinical trials, we prospectively consented and enrolled GBM patients to the Ivy Foundation Glioblastoma Patient Atlas Project. A total of 1591 patients from 7 participating sites of the Ben and Catherine Ivy Foundation Consortium for Early Phase Clinical Trials were consented to the project and clinical data was entered into a centrally managed clinical trials database. Overall 658 subjects had pre- and post-surgical imaging centrally reviewed and recorded and 387 subjects had sufficient tissue for completion of targeted exome sequencing of approximately 500 cancer causing genes (Oncopanel or Impact). More than 308 subjects had a complete set of genomics, imaging, and clinical data, including TMZ/RT use, KPS, progression, and steroid use. Histopathological features, MGMT, and IDH mutation status were also annotated. Of the subjects with full clinical data, 171 had expired by the time of last analysis of the cohort. Genomic and clinical characteristics unique to the early phase clinical trial population compared to TCGA and other cohorts of GBM were identified and radio-genomic and other advanced population-based analyses were performed. All clinical, genomic and imaging data are being utilized to create an Ivy cBio Portal for sharing of this rich dataset within the neurooncology community.

PATH-09. CLINICAL CHARACTERISTICS OF ADULTS WITH H3 K27M-MUTANT GLIOMAS AT UCSF

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