Title

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

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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.

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

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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

Robin Buerki[1], Sarah Lapointe[1], David Solomon[1], Joanna J Phillips[2], Arie Perry,[3] Javier Villanueva-Meyer[1], Annette Molinaro[4], Nancy Ann

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BACKGROUND: Histone H3.3 or H3.1 mutant protein is commonly expressed in pediatric and adult diffuse midline gliomas, including diffuse intrinsic pontine gliomas (DIPGs), and portends a poor prognosis, regardless of histologic features. As such, "Diffuse midline glioma, H3-K27M-mutant" (DMG-H3K27M) was added to the 2016 WHO Classification as a grade IV entity. Knowledge of the clinical experience and natural history of this recently defined tumor in adults is limited. METHODS: We retrospectively reviewed the pathology of adult (age ≥ 18) DMG-H3K27Ms diagnosed at our institution either via H3-K27M mutant-specific immunohistochemistry or via the UCSF500 targeted next-generation sequencing panel that includes the *H3F3A*, *HIST1H3B*, and *HIST1H3C* genes. Treatment, outcome, and imaging characteristics were reviewed. RESULTS: We identified 26 adults with DMG-H3K27M and 2 with non-midline-H3K27M. Tumor locations included thalamus/basal ganglia (15), hypothalamus (2), pineal region (1), cerebellum (3), brainstem (2), spinal cord (2), mesial temporal (1), and non-midline sites (2). MRI imaging for 21/25 evaluable cases demonstrated enhancement. Of the 26 DMG-H3K27M cases, median age was 35 years (22–68 years). Of these, 17 patients had biopsy only. Median OS was 41 months (95%-CI 31-NA). In the 22 DMG-H3K27M patients with available clinical treatment data, 21 received radiation (19 with temozolomide) at initial diagnosis. At progression/recurrence, 11 patients received bevacizumab, 5 were re-treated with temozolomide, 8 received other chemotherapy, and 8 received > 1 course of re-irradiation. CONCLUSION: While still poor overall, clinical outcome in adults with DMG-H3K27M is often better than that of pediatric DIPGs and other IDH-wildtype high-grade gliomas, such as glioblastoma. This may reflect a different cell of origin or other distinct biologic differences. Further investigation of both DMG-H3K27M and non-midline H3K27M mutant tumors in adults is warranted to study the genetic and epigenetic features of these rare tumors, as well as optimal treatment strategies.

PATH-10. COPY NUMBER (CN)/SINGLE NUCLEOTIDE POLYMORPHISM (SNP) MICROARRAY ANALYSIS OF THE EGFR LOCUS IN GLIOSARCOMA

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Epidermal growth factor receptor (EGFR) is overexpressed or mutated in a variety of malignancies, most notably non-small cell lung cancer, colorectal cancer and glioblastoma (GBM). Glioblastoma is an aggressive primary brain tumor and 35–50% of glioblastomas show amplification of the *EGFR* locus (7p11.2). Interestingly, gliosarcoma, a histologic variant of GBM, has a lower frequency of *EGFR* alterations (4–8%). We characterized *EGFR* alterations in gliosarcoma using a DNA copy number/single nucleotide polymorphism cytogenomic microarray using formalin fixed paraffin embedded tissue. A retrospective search for "gliosarcoma" from our database yielded 19 cases on which microarray analysis was performed. Of these cases, 2 showed an amplification at the *EGFR* locus (13%), 5 cases showed a gain of the entire chromosome 7 (26.3%), 3 cases showed gains at loci other than *EGFR* (15.8%) and the remaining 9 cases were negative for chromosome 7 alterations (47.4%). Our preliminary data show that amplification of the *EGFR* locus are infrequent (13%) in gliosarcomas. These preliminary findings demonstrate antithetical results regarding *EGFR* amplifications in conventional glioblastoma compared to gliosarcoma and suggests there may be an alternate driver in gliosarcoma genesis.

PATH-11. TRANSLATING GENOMIC DATA OF GLIOBLASTOMA INTO CLINICAL PRACTICE: A CASE STUDY

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Glioblastoma (GBM), a malignant brain tumour that occur in adults and children, represents a major challenge for treatment. Tumor heterogeneity has been shown to contribute to this problem. The aim of this study was to overcome this issue by exploring an individualized treatment approach by selecting treatment options using whole genome sequencing, drug-screening panel and a network analysis. We present a case of a 51-year old female long-term GBM survivor with an unmethylated MGMT promoter gene who survived more than three years. Whole genome sequencing (WGS) revealed an ultra-mutated genotype in both primary and recurrent tumour samples with 421 substitutions per megabase. In depth analysis of the WGS revealed an average of 30 cancer driver genes were mutated with a 91% similarity in both primary and recurrent tumors. A drug screening panel and network analysis helped identify actionable targets. The drug screening panel included 165 compounds, of these we identified YM155, an experimental survivin inhibitor as a potential treatment. On the other hand, the network analysis revealed over 130 interconnected pathways affected by mutations in the driver genes. Pathways of interest were selected based on an FDR (false discovery rate) of 0.05 or less. These pathways included PTEN/PI3K/AKT pathway, DNA repair pathway, cell cycle pathway and various signaling pathways. EGFR was found to be predominant in 37% of the affected pathways. Hence, an EGFR inhibitor was recommended for treatment. Genome-guided treatment selection to individualize treatment for GBM patients was demonstrated to be possible in clinic. It remains a promising avenue for further translational research, with larger databases and integrated platforms to increase the efficiency of analyzing and interpreting the individual genomic data of GBM.

PATH-12. CHARACTERISTICS OF GIANT CELL MORPHOLOGY IN LONG-TERM SURVIVORS OF GLIOBLASTOMA: CONSIDERATION OF SEX DIFFERENCES

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The hallmark of glioblastoma (GBM) is poor survivorship. However, a small subset (5%) of patients live greater than 5 years (extreme survivors (ES)). The pathological and tumor determinants of ES are unknown. Giant cell (GC) morphology occurs in < 1% of all GBM, is typically IDH1 wildtype, shows a high frequency of p53 mutations, and is reportedly associated with a somewhat better survival than other IDH1-wildtype GBM. However, the clear association between ES and GC GBM has not be established. We aimed to describe the characteristics of ES tumors that presented with GC GBM features and examine sex differences. In our retrospective multi-institutional database, we identified 90 ES patients with GBM. We reviewed neuropathological reports for the diagnosis of GC GBM or pathology description that included the descriptor(s) of GC: monstrocellular or giant cell or bizarre multinucleated and evaluated phenotypical features in order to describe ES with GC GBM. Values are presented as means. Sixteen (17.8%) ES patients were characterized as GC GBM (males (n=9, 56.25%), females (n=7, 43.75%)). Males were significantly younger than females (39.67 vs 56.29, p=0.018). Females presented with significantly smaller tumors than males (F: 9.49 mm, M: 21.14 mm, p=0.0008). Males less often presented with seizures (33.33%) compared to females (42.86%, p=0.7686). Calculations of invasion/proliferation ratios from our mathematical model revealed no statistically significant differences between females and males. Overall survival between males and females was not statistically significant. Across the board, GC GBM occurred most often in frontal lobes (All: 56% (n=9), 66.67% of males (n=6), and 42.86% of females (n=3)). Extreme survivors of GBM exhibit giant cell features at greater than five-fold incidence than the general GBM population. Sex differences warrant significant attention in future explorations of pathological and tumor characteristics in GC GBM.

PATH-13. THE ORIGIN OF HUMAN GLIOBLASTOMA (IDH WILDTYPE) IS NOT THE LOCATION OF THE TUMOR BUT THE SUBVENTRICULAR ZONE

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Two hypotheses about the origin of human glioblastoma (GBM) genesis are known to be dedifferentiation of cancer cells and orthodox differenti-