PATH-10. EFFECTS OF 19Q-LOSS IN IDH-MUTATED ASTROCYTOMAS ON BETTER PROGNOSIS AND OLIGODENDROGLIOMA-LIKE MORPHOLOGY

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We previously reported that there was a subgroup of *IDH*-mutated astrocytomas harboring only 19q-loss showing oligodendroglioma-like morphology and significantly longer overall survival (OS) compared with 19q-intact astrocytomas. To further explore the biological characteristics of this possible subgroup and obtain insight into the mechanism of their clinical behavior, we compared gene expression pattern between five 19q-loss and five 19q-intact *IDH*-mutated astrocytomas by microarray analysis. Comparing expression level of each genes between 19q-loss and 19q-intact astrocytomas,136 up-regulated genes and 203 down-regulated genes were extracted. Gene expression patterns of 19q-loss astrocytomas were partially different from that of 19q-intact astrocytomas. More down-regulated genes distributed on 19q and 4p, and more up-regulated genes distributed on 4q. Multiple genes associated with stem cell maintenance were down-regulated in 19q-loss astrocytomas, and genes associated with glioma progression were differentially expressed. Comparing expression patterns among 19q-loss astrocytomas and other IDH-mutant glioma subgroups using TCGA datasets by t-SNE analysis revealed that expression pattern of 19q-loss astrocytomas did not shift to that of oligodendrogliomas with 1p/19q codeletion but were a subgroup in astrocytomas. These results indicated that 19q-loss in astrocytomas was an acquired event different from 1p/19q codeletion in oligodendrogliomas, and better prognosis morphological features in 19q-loss astrocytomas were derived from differentially expressed genes associated with stem cell maintenance and glioma progression.

PATH-11. PROGNOSTIC SIGNIFICANCE OF EPIGENETIC SUBTYPES AND CPGS ASSOCIATED WITH PROGRESSION TO G-CIMP LOW IN THE EORTC RANDOMIZED PHASE III INTERGROUP CATNON

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BACKGROUND: Uncontrolled studies have suggested that methylation-based epigenetic subtypes can be used for prognostication of glioma. We used the prospective randomized CATNON trial to validate the clinical relevance of these epigenetic subtypes. METHODS: The phase III CATNON trial randomized 751 adult patients with newly diagnosed 1p/19q non-codeleted anaplastic glioma to 59.4 Gy radiotherapy +/- concurrent and/or adjuvant TMZ. CNV data and methylation data were derived from Infinium MethylationEPIC arrays. Epigenetic subtyping and risk of progression to G-CIMP low were determined from random forest models and 7 specific CpGs (PMID: 29642018). *IDH1/2* status was determined with a glioma-tailored NGS panel. Overall survival (OS) was measured from date of randomization. RESULTS: Methylation analysis was performed on 654 tumors: 440 were *IDH1/2mt*, 204 *IDH1/2wt* and of 10 *IDH1/2* status was unknown; 8 *IDH1/2mt* were 1p/19q codeleted. Based on methylation, tumors were classified as G-CIMP high (n=409), G-CIMP low (n=19), codel-like (n=18), mesenchymal-like (n=107), classic-like (n=48), and PA-like tumors (n=53). Median OS between these epigenetic subtypes varied considerably: codel-like 9.1 yrs, G-CIMP high 9.5 yrs, G-CIMP low 2.8 yrs, mesenchymal-like 1.3 yrs, classic-like 1.6 yrs, and PA-like 2.8 yrs. The difference in OS of the *IDH1/2mt* astrocytoma subgroup patients was prominent [G-CIMP low vs G-CIMP high: HR 4.12, 95% CI 2.37-7.19, p < 0.001]. Within the *IDH1/2mt* G-CIMP high astrocytoma patients, 115 tumors were predicted to have risk of progression to G-CIMP low and patients with such tumors indeed had poorer survival [risk vs no-risk: HR 1.59, 95% CI 1.10-2.31, p = 0.02]. Median OS in G-CIMP high tumors with (n=37) and without (n=366) *CDKN2A/B* HD was 3.3 yrs versus not reached [p< 0.001], in G-CIMP low tumors it was 1.2 yrs (n=6) versus 4.4 yrs (n=12) [p=0.008]. CONCLUSIONS: In *IDH1/2mt* anaplastic astrocytoma, G-CIMP status and *CDKN2A/B* HD are of independent prognostic value.

PATH-12. TEMOZOLOMIDE-INDUCED HYPERMUTATION IS ASSOCIATED WITH HIGH-GRADE TRANSFORMATION, DISTANT RECURRENCE AND REDUCED SURVIVAL IN INITIALLY LOW GRADE IDH-MUTANT GLIOMAS

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Temozolomide, a commonly used alkylating agent, can induce somatic hypermutation in gliomas. The prevalence and implications of this phenomenon are not well characterized. Using targeted and whole exome sequencing from a cohort of 82 patients with recurrent *IDH*-mut LGG, we evaluated the clinical implications of hypermutation. Hypermutation was identified at transformation in 57% of recurrent gliomas exposed to TMZ and occurred for both *IDH*-mutant astrocytomas (52%) and oligodendrogliomas (64%). Among astrocytomas, receipt of radiotherapy prior to transformation was associated with decreased risk of hypermutation (11% vs 70%, p=0.0052), but this trend was not observed for oligodendrogliomas (78% vs 54%, p=NS). Among hypermutated tumors, 94% were transformed to higher WHO grades. Hypermutation was associated with transformation to higher WHO grade (OR 12.0 95% CI 2.5-115.5, p=0.002) and shorter survival after transformation (HR 2.1, 95% CI 1.1-4.0, p=0.018) compared with non-hypermutated transformed tumors. It remained prognostic (controlling for grade, molecular subtype, age, and prior radiotherapy. Patients with transformation to glioblastoma had poor survival regardless of hypermutation (p=0.78). Multivariate models were validated using an external, independent dataset (Harrel's C=0.72). Strikingly, hypermutated tumors were also associated with development of discontiguous disease after transformation (3-year CI 41% vs 8% p=0.005), including ependymal and leptomeningeal distributions and four cases of spinal dissemination that were not observed in non-hypermutated tumors. These data have significant implications for management of *IDH*-mut LGG at recurrence.

PATH-13. CHARACTERIZING TEMPORAL GENOMIC HETEROGENEITY IN PEDIATRIC LOW-GRADE GLIOMAS

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BACKGROUND: Recent discoveries have provided valuable insight into the genomic landscape of pediatric low-grade gliomas (LGGs) at diagnosis, facilitating molecularly targeted treatment. However, little is known about their temporal and therapy-related genomic heterogeneity. An adequate understanding of the evolution of pediatric LGGs' genomic profiles over time is critically important in guiding decisions about targeted therapeutics and diagnostic biopsy at recurrence. METHODS: Fluorescence *in situ* hybridization, mutation-specific immunohistochemistry, exome analyses, and/or targeted sequencing were performed on paired tumor samples from diagnostic and subsequent surgeries. RESULTS: Ninety-four tumor samples from 45 patients (41 with two specimens, four with three specimens) from three institutions underwent testing. Conservation of *BRAF* fusion,