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HGG-18. CLINICAL EFFICACY OF ONC201 IN THALAMIC H3 K27M-MUTANT GLIOMA

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BACKGROUND: Data about high-grade glioma (HGG) in very young children (≤3 years old at diagnosis) is scarce. METHODS: 180 pediatric HGG patients were treated at the Children Cancer Hospital - Egypt (CCHE-57357) between July 2007 and June 2018, with 17 patients aged ≤3 years at diagnosis. Medical records were retrospectively reviewed for clinical, radiological and histopathological data, treatment received and survival outcome. RESULTS: Median age was 29.2 months (range: 2.4 – 35.8 months; males = 9). Most frequent pathological diagnosis was Glioblastoma, WHO grade-IV (n = 11, 64.7%) and one patient had H3-mutant diffuse midline glioma. All patients underwent surgery (gross-total resection, n = 6, 35.3%; subtotal-resection, n = 5, 29.4%; biopsy, n = 6, 35.3%). One patient (age = 7 months) progressed and died before starting adjuvant therapy. All patients ≤1 year of age (n = 5) received adjuvant chemotherapy (CT) only, older children (n = 11) received adjuvant radiotherapy (RT) (total dose range: 54 – 60 Gy) and CT (CCG-945 protocol). The 1-year overall survival (OS) rate was 47.1%; and event-free survival (EFS) rate was 35.3%. EFS differed between those who received RT and those who did not (1-year EFS 54.5% and 0% respectively, p = 0.001). Compared to older children, anatomical distribution of tumors was significantly different with non-midline locations being the commonest in patients ≤3 years old (88.2% vs 46.4%, p=0.01). CONCLUSIONS: HGG in very young children arise predominantly in non-midline locations and usually lack the H3-mutation. RT seems crucial in the management of pHGG regardless of age subgroup.

HGG-18. CLINICAL EFFICACY OF ONC201 IN THALAMIC H3 K27M-MUTANT GLIOMA

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ONC201, a bitopic DRD2 antagonist and allosteric ClpP agonist, has shown encouraging efficacy in H3 K27M-mutant glioma. Given that the thalamus has the highest extra-striatal expression of DRD2, we performed an integrated preclinical and clinical analysis of ONC201 in thalamic H3 K27M-mutant glioma. ONC201 was effective in mouse intra-uterine electroporation (IUE)-generated H3 K27M-mutant gliomas, with an *in vitro* IC_{50} of 500 nM and 50% prolongation of median survival *in vivo* (p=0.02, n=14). We analyzed thalamic H3 K27M-mutant glioma patients treated with ONC201 on active clinical trials as of 5/22/19 enrollment (n=19 recurrent and 10 post-radiation, non-recurrent; 5–70 years old). As of 12/18/2019, PFS6 and OS12 are 26.3% and 36.8%, respectively, in the recurrent group. For non-recurrent patients, with median follow up of 21.9 months (8.6–26.6) from diagnosis, median PFS or OS have not been reached. This surpasses historical OS of 13.5 months. Best response by RANO includes 1 CR, 3 PR, 4 SD, 8 PD for recurrent patients and 2 PR, 4 SD, 1 PD for non-recurrent patients (4 on-trial patients experienced regressions that are yet unconfirmed responses). Median duration of response for recurrent patients is 14.0 months (2.0–33.1). Furthermore, H3 K27M cell-free tumor DNA in plasma and CSF correlated with MRI response. In summary, single agent ONC201 administered at recurrence, or adjuvantly following radiation, demonstrates promising clinical efficacy in thalamic H3 K27M-mutant glioma patients who currently have no effective treatments following radiation. Investigations are ongoing to assess whether micro-environmental DRD2 expression explains the early exceptional responses in thalamic H3 K27M-mutant glioma.

HGG-19. IDENTIFICATION OF NOVEL SUBGROUP-SPECIFIC MIRNA EXOSOMAL BIOMARKERS IN PEDIATRIC HIGH-GRADE GLIOMAS

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Pediatric high-grade gliomas (pHGG) are heterogeneous brain tumors for which new specific diagnostic/prognostic biomarkers are needed. In this study, we aimed to identify new pHGG subgroup specific biomarkers by exploiting exosomes, known vehicles of oncogenic signals. We used plasma from 23 patients (including 6 controls) and conditioned medium from 12 patient-derived cell-lines, representing all locational and molecular subgroups. Upon exosome isolation, total RNA was extracted and miRNAs were assessed using a PCR Panel. Analysis of plasma miRNome showed that tumor exosomal samples were largely clustered together, independently from their locational and/or molecular subgroup. We identified 20 significantly upregulated and 25 downregulated miRNAs compared to controls. Interestingly, 27 miRNAs were expressed only in tumors. Furthermore, the unsupervised clustering showed a clear separation based on locational (hemispheric *vs* pontine) and mutational (WT *vs* H3.3G34R or H3.3G34R *vs* H3K27M) subgroup comparisons, with the identification of distinct miRNomes underlying the key role of location and mutations in defining the pHGG exosomal miRNA profile. This was further confirmed analyzing the miRNOme from cell-line derived exosomes. Moreover, we identified a pool of significantly differentially regulated miRNAs in diagnose *vs* relapse and biopsy *vs* autopsy cell-lines. Most importantly, when comparing hemispheric *vs* pontine and H3.3G34R *vs* H3.3K27M, we identified respectively four and three miRNas equally dysregulated and in common between plasma and cell-lines. Those were strongly associated mainly to transcriptional regulation and targeting *TTC9*, linked to cancer invasion and metastasis. Based on this, we suggest exosomal miRNAs as a powerful new pHGG diagnostic/prognostic tool.

HGG-20. DIAGNOSTIC AND BIOLOGICAL ROLE OF METHYLATION PATTERNS IN REPLICATION REPAIR DEFICIENT HIGH GRADE GLIOMAS

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