outcome among the histo-molecular subgroups in Chinese children. METHODS: A total of 93 patients of MB who underwent surgical treatment at Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from January 2006 to December 2015. The clinical profile, treatment, and survival patterns are discussed. The relevant statistical analysis was done using SPSS software, version 21.0. RESULTS: At the most recent follow-up date, 15 (16.1%) had been lost to follow-up , 78 cases were tested for RNA-seq, of which 54 cases were successful, and 24 cases failed the quality control due to sample quality problems.The male-to-female ratio was 2.4:1, and the patients' mean age at diagnosis was 5 years (ranged from 4 months to 11 years).The estimated 5-year overall survival and progression-free survival, based on Kaplan-Meier analysis, were 55.1% ± 5.6% and 40.9% ± 5.7%.Multivariate survival analysis showed that progression -free survival were significantly affected by extent of surgery (P=0.026) and postoperative radiotherapy(P < 0.001).Preoperative metastasis (P=0.032) and postoperative radiotherapy (P=0.001) had a significant influence on overall survival. While , the molecular subtypes showed no statistically significant differences in 5-year PFS and 5-year OS. **CONCLUSION**: Extent of resection of MB and postoperative radiotherapy were the important clinical prognostic factors for survival. In the future, we will continue to expand cases and study the clinical characteristics and prognostic risk factors of different molecular types of medulloblastoma in Chinese children,and to improve the survival rate of children with medulloblastoma.

MEDB-06. SPATIAL TRANSCRIPTOMIC ANALYSIS OF SONIC HEDGEHOG MEDULLOBLASTOMA IDENTIFIES THAT LOSS OF HETEROGENEITY AND INDUCED DIFFERENTIATION UNDERLIES THE RESPONSE TO CDK4/6 INHIBITION

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Medulloblastoma (MB) is a malignant tumour of the cerebellum which can be classified into four major subgroups on the basis of gene expression and genomic features. Single cell transcriptome studies have defined the cellular states underlying each MB subgroup, however the spatial organisation of these diverse cell states and how this impacts response to therapy remains to be determined. Here, we used spatially resolved transcriptomics to define the cellular diversity within a sonic hedgehog (SHH) patient-derived model of MB and identify how cells specific to a transcriptional state or spatial location are pivotal in responses to treatment with the CDK4/6 inhibitor, Palbociclib. We distinguish neoplastic and non-neoplastic cells within tumours and from the surrounding cerebellar tissue, further refining pathological annotation. We identify a regional response to Palbociclib, with reduced proliferation and induced neuronal differentiation in the majority of the tumours. Additionally, we resolve in cellular resolution a distinct tumour "interface" where the tumour contacts neighbouring mouse brain consisting of abundant astrocytes and microglia and continues to proliferate despite Palbociclib treatment. Our data highlight the power of this approach to characterise the response of a tumour to targeted therapy and provide further insights into the molecular and cellular basis underlying the response and resistance to CDK4/6 inhibitors in SHH MB

MEDB-07. LONG-TERM MEDICAL AND FUNCTIONAL OUTCOMES OF MEDULLOBLASTOMA SURVIVORS: A POPULATION-BASED, MATCHED COHORT STUDY

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BACKGROUND: Most medulloblastoma survivors suffer from late treatment-related sequelae. There are no population-based studies examining such late effects in a dedicated cohort of medulloblastoma survivors. METHODS: Using a provincial pediatric cancer registry, all 5+ year medulloblastoma survivors diagnosed between 1987-2015 in Ontario, Canada were identified and matched to cancer-free population controls based on age, sex, and geographical location. Cases were followed from the index date (five years from latest of diagnosis, or relapse or subsequent malignancy prior to age 18 years) until December 31, 2020 or censorship (death, or relapse or new cancer after age 18 years). Clinical data were linked to administrative health databases to estimate cumulative incidences and cause-specific hazard ratios (HR) of mortality, hospitalizations, strokes, hearing loss requiring a hearing aid, and receipt of homecare services between cohorts, accounting for matching and competing risks. RESULTS: We identified 230 cases [65.7% female; median diagnostic age: 7y, interquartile range (IQR) 4-10; median attained age: 24y, IQR 18-31] and 1150 controls. One hundred eighty-seven (81.3%) received craniospinal irradiation. Ten-year survival probability after index was 92.4% in cases and 99.4% in controls (HR 21.5, 95% CI 9.8-54.0). Cases were at higher risk for hospitalizations (HR 3.4, 95% CI 2.7-4.3), stroke (HR 45.6, 95% CI 12.8-289.8), hearing loss (HR 96.3, 95% CI 39.7-317.3), and requiring homecare services (HR 7.9, 95% CI 5.8-10.9). By 10 years after index, 4.8% (95% CI 2.2-9.0) of survivors had experienced a stroke compared to 0.1% (95% CI 0.01-0.7) of controls. CONCLUSIONS: Survivors of childhood medulloblastoma experienced an increased risk of mortality and serious morbidity compared to population controls. Consideration for mitigation strategies or early interventions in preventing neurovascular sequelae and hearing loss is warranted, as are dedicated supports for survivors.

MEDB-08. INHIBITION OF DIFFERENT MITOTIC TARGETS DEMONSTRATED DISTINCT DNA DAMAGE AND CELL DEATH RESPONSE IN P53-MUTANT MEDULLOBLASTOMA

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BACKGROUND: In normal cells, cell cycle is tightly regulated by mitotic proteins to ensure smooth transition through each phase of cell division. Here, we examine two proteins – KIF11, a mitotic kinesin, responsible for assembly and maintenance of mitotic spindle during mitosis; and MELK, a serine/threonine kinase, essential for mitotic progression. Cancer cells can upregulate MELK and KIF11 to promote uncontrolled cell division and protect the cells from apoptotic cell death, leading to tumorigenesis. AIMS: We investigated the response of p53-mutant medulloblastoma (MB) by inhibiting KIF11 and MELK separately to study the effects on cell cycle progression and cell death mechanisms. RESULTS: Cell proliferation was suppressed by inhibition of either KIF11 or MELK in MB, independent of p53-mutant status. Regardless of p53-mutant status, inhibiting KIF11 induced cell cycle arrest at G2/M. In contrast, inhibiting MELK (IC_{50} dose) induced more prominent G2/M arrest in p53-mutant cells compared to p53-wildtype cells. In p53-mutant MB, arrested cells during MELK inhibition subsequently underwent apoptotic cell death at 24h and 48h. With KIF11 inhibition, p53-mutant cells at 24h were already in necrotic stage. p53-mutant cells reached necrotic stage in a shorter time with KIF11 inhibition than MELK inhibition. On immunoblotting, independent of p53-mutant status, KIF11 inhibition produces more significant increase in DNA damage marker and c-PARP indicative of apoptosis, compared to MELK inhibition. Treatment with KIF11 or MELK inhibitor increased p53 protein expression in p53-wildtype (normal stress response). However, in p53-mutant cells, p53 protein expression decreased post-KIF11-inhibition, but remained unchanged post-MELK inhibition. In-vivo, inhibiting KIF11 was less tolerable in a patient-derived orthotopic xenograft model with p53-mutation. CONCLUSION: Inhibition of either mitotic target KIF11 or MELK, can induce anti-proliferative effects in MB. In p53-mutant MB, DNA damage and cell death response with KIF11-inhibition are more marked.

MEDB-09. UNRAVELING THE ROLE OF UNFOLDED PROTEIN RESPONSE IN MEDULLOBLASTOMA CANCER STEM CELLS

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Medulloblastoma (MB) is the most common malignant childhood brain tumor. The current clinical approach consists of multimodal strategies with