MEDB-51. IMPACT OF RESIDUAL TUMOR ON OUTCOMES IN CHILDREN AND ADOLESCENTS WITH MEDULLOBLASTOMA IN THE GERMAN HIT-COHORT

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INTRODUCTION: To date, a historical threshold of 1.5cm^2 extent of resection (EOR) of the primary tumor is used for risk stratification in pediatric medulloblastoma (MB). METHODS: Data of n=348 patients with MB included into the German HIT-MED studies and registries from 2000-2017 were retrospectively analyzed. Kaplan-Meier statistics and Cox regressions were calculated to determine the influence of EOR, histological and molecular subtype, MYC/N-amplification and presence of metastases at first diagnosis on overall and progression-free survival (OS/PFS). ROC curves were calculated aiming at identifying a new EOR cut-off. RESULTS: Median age at diagnosis was 6.8 [0.1-20.5] years. After initial surgery, residual tumor (R) ≥1.5cm^2 was present in 129/348 patients (37%). 57% presented with additional metastases. In most cases, classic histology was found (71%, DMB/MBEN: 20%, LC/AMB: 9%). Molecular subtype was nonWNT/nonSHH in 68% (Group 4: 37%, Group 3: 31%), WNT in 6% and SHH-activated types in 26% of evaluated cases (n=208). MYC/MYCN-amplification was present in 5 and 4%, respectively. 41/348 patients received additional surgery, resulting in 73% GTR (not reported: n=22). EOR had no significant impact on OS/PFS (GTR: 5y-OS/PFS 69.9±3.4/57.6±3.7%, STR: 5y-OS/PFS 71.4±4.1/56.2±4.5%, p=0.6/0.8; Cox: p=0.2/0.4; median follow-up 8.4 [0.1-18.0] years). ROC curves did not identify a significantly improved limit for outcome-relevant EOR cut-off. Analyses confirmed less favorable OS/PFS for patients with metastatic disease (p=0.04/p<0.05), LC/AMB (p<0.05/p<0.05), Group 3 (p<0.05/p<0.05), and MYC-amplification (p<0.05/p<0.05). Cox regression confirmed an increased risk for Group 3 (OS: HR=4.74, p<0.05, PFS: HR=2.90, p<0.05) and M+ (PFS: HR=2.69, p<0.05). DISCUSSION: No distinct influence of EOR </≥1.5cm^2 on OS/PFS in pediatric MB was detected. The relevance of EOR and the historical limit of 1.5cm^2 should be further investigated in distinct MB subtypes and in context of other risk factors.

MEDB-52. ORGANOIDS AS PRECLINICAL MODELS TO IMPROVE AND PERSONALIZE DISEASE OUTCOME FOR SONIC HEDGEHOG MEDULLOBLASTOMA

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Four main medulloblastoma (MB) molecular subgroups are known, including the sonic hedgehog (SHH) subgroup, which represents ~25% of MB cases. The 5-year overall survival of SHH-MB is ~80%. However, survival between patients is highly diverse and dependent on the driver mutation(s) of the tumor. Patients with *TP53* mutated tumors (often accompanied with *MYCN* and/or *GLI2* amplifications) don't respond well to current therapies and have a 10-year overall survival below 20%. Therefore, there is a need for new and more tailored therapies for these patients. In this study we aim to screen patient-derived organoid models of *TP53*-mutated SHH MB with a library of ~200 different compounds. We have optimized the cultures of two PDX-derived and one patient-derived organoid line *in vitro*. The lines will be screened in a high-throughput manner and the best hits and combinations will be validated in corresponding *in vivo* PDX models. To further assess the role of specific mutations in therapy outcome of *TP53*-mutated SHH MB, cerebellar organoids generated from human iPSCs were genetically modified with overexpression of dominant-negative P53 (DNP53) alone or in combination with *MYCN* and/or *GLI2*. Introduction of DNP53 and *MYCN* overexpression in cerebellar organoids at day 28/35 leads to the outgrowth of a Ki67-positive proliferating mass after three weeks, indicating tumor growth. Further analyses are ongoing to see how they match SHH-MB patient tumors. These genetically engineered organoid models may elucidate the role of specific mutations in therapy response and/or resistance. In addition, as tumors in these genetically engineered cerebellar organoids arise in a microenvironment of normal cerebellar cell types, initial safety of drugs on cerebellar cells can be assessed. In conclusion, different organoid models of TP53-mutated SHH MB will enable us to find more effective treatments and to better understand how to treat patients with different mutation combinations.

MEDB-53. INCIDENCE OF HEARING IMPAIRMENT IN CHILDHOOD MEDULLOBLASTOMA SURVIVORS TREATED IN KING FAHAD MEDICAL CITY KFMC SAUDI ARABIA

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Medulloblastoma MB is the most common childhood CNS tumor treated with intensive multimodalities therapy Surgery, Radiation and Cisplatin chemotherapy which causing significant Hearing impairment (HI) with profound impact on child's quality of life. **METHOD:** Retrospective study evaluating risk factors & (HI) incidence in childhood MB survivors treated in KFMC between 2010 and 2020. (HI) was graded using the National Cancer Institute (NCI) Grades (1-4) ALL patients received 6 weeks of Risk adapted CSI radiotherapy concurrent with daily oral Etoposide. patients were treated with 2 different Maintenance chemotherapy German HIT-MED MB protocol 8 Maintenance cycles (Cisplatin 70 mg/m² x 1d /lomustine/VCR) Cumulative dose of Cisplatin 560 mg/m2 KFMC MB SAPHOS protocol 6 Maintenance cycle alternating A&B. cycle A: Cisplatin 90 mg/m² x 1d & 3 weeks of daily oral Etoposide. cycle B: Cyclophosphamide x 2 d & Vincristine Cumulative dose of Cisplatin 270 mg/m2. RESULTS: At Median follow-up of 5 years total of 78 MB survivors, male predominance 66.7% Median age at diagnosis 82 months post end of therapy 28.2% maintain normal hearing while 71.8% had hearing decline compared with baseline audiology Median time of onset of hearing decline was 7 months after start of radiation therapy Significant (HI) (NCI grade 3/4) in 26.9% of patients, and 23.1% required hearing aid use NO statistically difference in incidence of significant (HI) in patients treated with HIT-MED protocol (26.7%) & patients treated with KFMC MB-SAPHOS protocol (27.1%) OR those treated as Average-Risk CSI radiotherapy 22.9% Vs High-Risk CSI radiotherapy (30.2%), patients age at diagnosis (< or > 5 years) does not affects HI incidence. CONCLUSIONS: significant hearing impairment incidence was not affected by Radiation doses OR cumulative Cisplatin dose. Our study will form base line for future studies to modify therapy related Toxicity and improve outcome of childhood MB in Saudi Arabia.

MEDB-54. STANDARD RISK MEDULLOBLASTOMA TREATED SOLELY WITH SURGERY AND CHEMO-RADIATION

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INTRODUCTION: Medulloblastoma is the most common malignant brain tumor in children, with 5-year overall survival (OS) ranging from 60%-95% depending on subgroup and risk status. The POG 8631/CCG 923 trial (accrual 1986-1990) found a 63% 5 year OS for patients with local disease after gross total resection treated with radiation at a dose of 23.4 Gy craniospinal radiation and posterior fossa boost to 54 Gy, vs. 80.5% 5-year OS for patients treated as per full ACNS0331 therapy including maintenance chemotherapy. Herein, we describe a long-term survival with standard-risk medulloblastoma who only received surgical resection and radiation therapy. CASE: A 17-year-old male presented with acute onset of hypertension, bradycardia, headache, and blurry vision and was found to have a heterogeneously enhancing posterior fossa mass with mass effect on the fourth ventricle and hydrocephalus on brain MRI. He underwent gross total resection of the tumor and histopathology revealed medulloblastoma with classic and large cell features. Fluorescence in situ hybridization (FISH) was negative for MYC, MYCN amplification, or HER2 gain. Cerebrospinal fluid cytology was negative for neoplastic cells, and spinal MRI did not