fined based on the new consensus (Sharma 2019) in group I (n = 1); group II (n = 5); group III (n = 2); group IV (n = 4); group V (n = 3); group VI (n = 2); group VII (n = 6); group VIII (n = 7). CONCLUSIONS: This study carried out the first classification of Medulloblastomas diagnosed in Italy through DMP, demonstrating its high reproducibility, precision and accuracy. The molecular classification improves diagnostic accuracy and provides further information that can guide personalized treatment.

## MBCL-19. CHEMOTHERAPY STRATEGIES FOR YOUNG CHILDREN NEWLY DIAGNOSED WITH DESMOPLASTIC/ EXTENSIVE NODULAR MEDULLOBLASTOMA UP TO THE ERA OF MOLECULAR PROFILING – A COMPARATIVE OUTCOMES ANALYSIS OF PROSPECTIVE MULTI-CENTER EUROPEAN AND NORTH AMERICAN TRIALS

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BACKGROUND/OBJECTIVE: Survival has been poor in several multi-center/national trials since the 1980s, either delaying, avoiding or minimizing brain irradiation in young children with medulloblastoma. The introduction of German regimens incorporating both intravenous high-dose (HD-MTX) and intraventricular (IVENT-MTX) methotrexate, and North American regimens utilizing marrow-ablative chemotherapy with autologous hematopoietic cell rescue (HDCx+AuHCR), have reported encouraging outcomes. We performed a comparative outcomes analysis of these strategies for young children with desmoplastic/extensive nodular medulloblastoma (D/ENMB). DESIGN/METHODS: Data from 12 trials reported between 2005 and 2019 for children <six-years-old with D/ENMB were reviewed; event-free (EFS) with standard errors were compared. RESULTS: The German HIT-SKK'92 and HIT-SKK'00 trials incorporating HD-MTX and IVENT-MTX reported 85+/-8% and 95+/-5% 5-10-year EFS respectively; a third trial (ACNS1221) incorporating HIT-SKK therapy but *without* IVENT-MTX reported 49+/-10% EFS. Three trials (Head Start I/II combined and CCG-99703) employing induction chemotherapy *without* HD-MTX, followed by 1/3 HDCx+AuHCR cycles, reported 3-5-year EFS of 67+/-16% and 79+/-11%. Two trials employing HD-MTX-containing induction chemotherapy (Head Start III and ACNS0334), followed by 1/3 HDCx+AuHCR cycles, reported 3-5-year EFS of 89+/-6% and 100%, respectively. Finally, four trials utilizing neither IVENT-MTX nor HDCx+AuHCR (UK-CNS-9204, CCG-9921, COG-P9934 and SJYC07) reported 2-5-year EFS of 35+/-11%, 77+/-9%, 58+/-8% and 53+/-9%. CONCLUSIONS: A trend towards better EFS for young children with D/ENMB is observed in trials including *either* HD-MTX as well as IVENT-MTX *or* including HD-MTX-containing induction chemotherapy and HDCx+AuHCR. Trials excluding HD-MTX, IVENT-MTX and HDCx+AuHCR have poorer outcomes.

## MBCL-20. DETECTION OF SOMATIC MUTATIONS BY USING RNA-SEQ DATA IN CHILDHOOD MEDULLOBLASTOMA AND ITS POTENTIAL CLINICAL APPLICATION: A COHORT SERIES OF 52 CASES STUDY IN TAIWAN

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BACKGROUND: In 2016, a project was initiated in Taiwan to adopt molecular diagnosis of childhood medulloblastoma (MB). Part of our aim was to explore the clinical application for drug target identification and finding clues to genetic predisposition. METHODS: In total, 52 frozen tumor tissues of childhood MBs were collected. RNA-Seq and DNA methylation array data were generated. Molecular subgrouping was performed. We selected 51 clinically relevant genes for somatic variant calling using RNA-Seq data. Correlated clinical findings to genetic predisposition were defined. Potential drug targets and genetic predispositions were explored. RESULTS: Four core molecular subgroups (WNT, SHH, Group 3, and Group 4) were identified. Potential drug targets were detected in the pathways of DNA damage response. Five patients with relevant clinical findings to genetic predisposition clustered in SHH MBs. The corresponding somatic driver mutations involved TP53, MSH6, PTEN, PTCH1, and TERT promoter (suspicious). For validation, whole exome sequencing (WES) of blood and tumor tissue was used in 10 patients with SHH MBs in the cohort series. This study included the five patients with potential genetic predispositions. Four patients exhibited relevant germline mutations named as TP53, MSH6, PTEN, and SUFU. CONCLUSION: The findings of this study provide valuable information for personalized care of childhood MB in our cohort series and in Taiwan.

## MBCL-21. GERMLINE ELONGATOR MUTATIONS IN SONIC HEDGEHOG MEDULLOBLASTOMA

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BACKGROUND: Our previous analysis of established cancer predisposition genes in medulloblastoma (MB) identified pathogenic germline variants in ~5% of all patients. Here, we extended our analysis to include all protein-coding genes. METHODS: Case-control analysis performed on 795 MB patients against >118,000 cancer-free children and adults was performed to identify an association between rare germline variants and MB. RESULTS: Germline loss-of-function variants of *Elongator Complex Protein 1* (*ELP1*; 9q31.3) were strongly associated with SHH subgroup ($MB_{SHH}$). *ELP1*-associated-MBs accounted for ~15% (29/202) of pediatric $MB_{SHH}$ cases and were restricted to the SHHα subtype. *ELP1*-associated-MBs demonstrated biallelic inactivation of *ELP1* due to somatic chromosome 9q loss and most tumors exhibited co-occurring somatic *PTCH1* (9q22.32) alterations. Inheritance was verified by parent-offspring sequencing (n=3) and pedigree analysis identified two families with a history of pediatric MB. *ELP1*-associated-$MB_{SHH}$ were characterized by desmoplastic/nodular histology (76%; 13/17) and demonstrated a favorable clinical outcome when compared to *TP53*-associated-$MB_{SHH}$ (5-yr OS 92% vs 20%; p-value=1.3e-6) despite both belonging to the SHHα subtype. *ELP1* is a subunit of the Elongator complex, that promotes efficient translational elongation through tRNA modifications at the wobble ($U_{34}$) position. Biochemical, transcriptional, and proteomic analyses revealed *ELP1*-associated-MBs exhibit destabilization of the core Elongator complex, loss of tRNA wobble modifications, codon-dependent translational reprogramming, and induction of the unfolded protein response. CONCLUSIONS: We identified *ELP1* as the most common MB predisposition gene, increasing the total gen-

etic predisposition for pediatric $MB_{SHH}$ to 40%. These results mark $MB_{SHH}$ as an overwhelmingly genetically-predisposed disease and implicate disruption of protein homeostasis in $MB_{SHH}$ development.

**MBCL-22. EFFICACY OF DOUBLE-CONDITIONING REGIMEN COMPRISING THIOTEPA AND MELPHALAN FOR RELAPSED MEDULLOBLASTOMA – A SINGLE INSTITUTION EXPERIENCE**

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BACKGROUND: The prognosis of relapsed medulloblastoma was dismal. Recently, we published the promising outcome of metastatic medulloblastomas treated with a double-conditioning regimen comprising high-dose thiotepa and melphalan (HD-TM). Here, we report a single-center study of HD-TM for relapsed medulloblastomas. MATERIALS AND METHODS: From April 2006 to January 2019, 17 consecutive medulloblastoma patients with the first relapse were identified, and of which 10 received HD-TM were retrospectively reviewed. RESULTS: The median age at first relapse was 11.9 years (range 1.8–31.7). The median follow-up period was 23.5 months after 1st relapse. Four localized relapses at the posterior fossa and 6 metastatic relapses including 3 with multiple sites were observed. Surgical resection and re-irradiation were administered in 5 and 9 patients, respectively. Two-year PFS and OS after relapse were 21±18.1% and 60±21.9%, respectively, and significantly better than in patients who did not receive HD-TM. Among 7 evaluable patients, tumor shrinkage was observed in 6 after HD-TM administration including 3 patients who were resistant to prior chemotherapy. At the present time, 5 patients are alive with no evidence of disease (NED). The last 5 patients received re-irradiation including 12 Gy craniospinal irradiation (CSI), and 4 are alive with NED. In multivariate analysis for all patients, both HD-TM and re-irradiation were associated with improved OS and PFS, but disseminated relapse had no prognostic value (p=0.56). CONCLUSION: HD-TM contributes to prolonged survival when combined with re-irradiation. HD-TM might become a curative approach for relapsed medulloblastoma, especially when combined with CSI.

**MBCL-23. PRELIMINARY ANALYSIS OF TREATMENT-RELATED TOXICITIES DURING INDUCTION CHEMOTHERAPY FOR PATIENTS ON THE HEAD START 4 TRIAL**

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The currently active, prospective multi-center Head Start 4 (HS4) trial for CNS embryonal tumors differs from prior HS I-III trials by utilizing absolute phagocyte count (APC) as a measure of myeloid recovery instead of absolute neutrophil count. The aim of this study was to determine if utilization of APC resulted in unanticipated treatment-related toxicities during induction chemotherapy for patients enrolled on HS4. Review of the RedCap database was conducted for treatment-related CTCAE grade 3 and 4 toxicities. Data were summarized descriptively. Nonparametric statistical methods were used for comparisons. At the time of this most recent analysis, a total of 180 induction cycles were completed for the 57 patients enrolled. Of the 57 patients, nine voluntarily discontinued therapy after completing a median of three cycles each. These patients had a higher number of documented infections (59% *versus* 24%, $p$=0.0004). Veno-occlusive disease (VOD) occurred in five patients, three of whom voluntarily discontinued therapy. Since the protocol amendment utilizing milligram per kilogram dosing for patients less than six years of age, there have been no documented episodes of VOD. The overall toxicities for this cohort were comparable to those reported for induction chemotherapy in HS I-II trials. The toxic death rate is lower for HS4 compared to HS I-II (0.018% *versus* 4.7–6%) (Chi et al 2004). Other than the high rate of infection, possibly associated with shorter duration of the immediately prior cycles, the use of APC as part of a dose-compression strategy in HS4 does not appear associated with more significant toxicities.

**MBCL-24. CAN YOUNG CHILDREN WITH RELAPSED MEDULLOBLASTOMA BE SALVAGED AFTER INITIAL IRRADIATION-SPARING APPROACHES?**

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INTRODUCTION: Irradiation-sparing approaches are used in young children with medulloblastoma (MB) given the vulnerability of the developing brain to neurocognitive impairment. Limited data are available following relapse for these patients. We aimed to describe the management and outcomes of young children with MB who relapsed after initial treatment without craniospinal irradiation (CSI). METHODS: International retrospective study including patients with MB diagnosed between 1995–2017, ≤ 72 months old, initially treated without CSI, who subsequently relapsed. RESULTS: Data are available for 52 patients (32 male). Median age at initial diagnosis was 27 months (range, 6–72) with 24 being metastatic. Initial therapy included conventional chemotherapy alone or high-dose chemotherapy (HDC) in 21 and 31 subjects, respectively. Three received upfront focal irradiation. Molecular subgrouping, available for 24 tumors, included 9 SHH and 15 non-WNT/non-SHH. Median time to relapse was 13 months (range, 3–63). Relapse was local, disseminated or combined in 20, 15, and 16, respectively. Salvage therapy with curative intent was given in 42/52 patients, including CSI in 28 subjects (median dose 36Gy, 18–41.4) or focal irradiation in 5 others. Three received HDC only. At a median follow-up time of 46 months (range, 4–255), 25 (48%) were alive, including 7/9 SHH and 7/15 non-WNT/non-SHH. The 2- and 5-year OS was 67% and 56% (SE, 7%), respectively. Two of 3 patients with SHH who did not receive salvage radiotherapy are survivors. CONCLUSION: A substantial proportion of young children who relapse following irradiation-sparing strategies can be salvaged. Neurocognitive and ototoxicity outcomes are being evaluated.

**MBCL-25. PILOT STUDY OF A SURGERY AND CHEMOTHERAPY-ONLY APPROACH IN THE UPFRONT THERAPY OF CHILDREN WITH WNT-POSITIVE STANDARD RISK MEDULLOBLASTOMA: UPDATED OUTCOMES**

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BACKGROUND: Wnt+ medulloblastoma (WPM) is a favorable subtype with EFS > 90% when treating postoperatively with craniospinal irradiation and posterior fossa boost (CSI/XRT) followed by adjuvant chemotherapy. This pilot study explored the safety of omitting radiation in standard-risk WPM. METHODS: Subjects had to meet standard-risk criteria (< 1.5 cm2 residual tumor, no metastatic spread, no anaplasia) and have a WPM. Subjects received chemotherapy following the COGACNS0331 AAB-AAB-AAB (A=cisplatin/CCNU/VCR; B=cyclophosphamide/vincristine) backbone. RESULTS: Six children were enrolled on study treatment prior to early study closure. Subject #1 completed planned protocol therapy but relapsed 3 months following the completion of therapy. Subject #2 completed