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-