recurrent beta-catenin nucleopositive Wnt-MBs treated with an irradiation-sparing strategy, incorporating HDCx/AuHPCR. PATIENT 1: A nine-year-old female experienced local recurrence of a non-metastatic Wnt-MB nine months after gross total resection (GTR) followed by 18Gy craniospinal irradiation (CSI) with primary site boost to 54Gy, accompanied by weekly vincristine, followed by a maintenance regimen of nine cycles of cisplatin/lomustine/vincristine alternating with cyclophosphamide/vincristine every third cycle. GTR of the relapsed tumor was followed by three cycles of HDCx/AuHPCR. She is disease-free for over three years following relapse treatment. PATIENT 2: A 17-year-old male initially underwent GTR, followed by 23.4Gy CSI with 54Gy posterior fossa boost with concomitant weekly vincristine, followed by a maintenance regimen that included nine alternating cycles of vincristine/lomustine/cisplatin and cyclophosphamide/vincristine. Isolated right frontal horn metastatic recurrence developed 19 months post-treatment; three cycles of irinotecan/temozolomide/bevacizumab and gamma-knife radiosurgery produced complete response. A second isolated metastatic recurrence within the left frontal horn occurred 13 months post-treatment, which was treated with two cycles of cyclophosphamide/etoposide followed by two cycles of HDCx/AuHPCR. MRI of the brain showed no residual tumor one month post-treatment. He currently awaits follow-up stereotactic radiosurgery. CONCLUSION: Patients with recurrent Wnt-MB may be treated with curative intent using a multidisciplinary approach that includes HDCx/AuHPCR, and minimization or avoidance of re-irradiation.

MBCL-48. OUTCOMES OF TREATMENT BASED ON THE ST. JUDE MEDULLOBLASTOMA-96 REGIMEN FOR JAPANESE CHILDREN WITH MEDULLOBLASTOMA

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Medulloblastoma is a type of malignant embryonal tumor in childhood that is considered to require multiagent chemotherapy followed by radical resection and craniospinal irradiation (CSI). However, the outcomes of chemotherapy for this tumor in Japan are unclear. Here, we performed a multicenter retrospective study to determine the prognosis of pediatric medulloblastoma patients in Japan treated with the St. Jude medulloblastoma-96 (SJMB96) regimen. Thirty patients with newly diagnosed medulloblastoma received treatment with the SJMB96 regimen at Juntendo University Hospital in Tokyo (n=10), Saitama Medical University International Medical Center in Saitama (n=10), and Tohoku University Hospital in Miyagi (n=10) from 2011 to 2018. All patients underwent tumor resection and CSI, with radiation doses of 23.4Gy for standard-risk patients (n=11) and 39.6Gy for high-risk patients (n=19). Six weeks after radiation therapy, patients received four cycles of high-dose chemotherapy with autologous peripheral blood stem cell transplantation according to the SJMB96 regimen. We found that 5-year overall survival was 80.8% among standard-risk patients and 74.2% among high-risk patients. No treatment-related deaths occurred. Eight patients who experienced recurrence died within 80 months of diagnosis. As these treatment outcomes are comparable to those previously reported outside of Japan, our findings indicate that this regimen is a therapeutic option for medulloblastoma patients in Japan.

MBCL-50. DISMAL OUTCOME OF HIGH RISK MEDULLOBLASTOMA TREATED WITH CHEMOTHERAPY FIRST APPROACH IN MALAYSIA

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INTRODUCTION: Patients with high risk medulloblastoma are treated either with high dose chemotherapy or hyperfractionated radiotherapy. Both approaches are not feasible in resource-limited countries. POG9031 trial has reported favourable outcome for high risk medulloblastoma using standard chemotherapy and radiotherapy only. Hence, we have adopted the protocol using chemotherapy first approach due to logistical reasons. OBJECTIVE: To review the outcome of children diagnosed with high risk medulloblastoma in Hospital Kuala Lumpur. METHODS: Patients diagnosed with high risk medulloblastoma between January 2015 and June 2018 treated using the chemotherapy first approach as per POG9031 protocol were identified. Data was then extracted and analysed. RESULTS: Nine patients were identified, 3 boys and 9 girls. Median age was 9.3 years (range 2.6 – 15.9 years). Median follow up for survivors are 3.6 years. Five patients (55.6%) had macroscopic metastatic disease at diagnosis. All patients had significant residual disease post-op. Only 3 patients are disease free till last follow up, giving a 3 years event free survival of 16%. Of the 6 patients who had relapsed, 4 have died, giving a 3 years overall survival of 46%. Patients with no metastasis at diagnosis (M0) fared better with 3 years event free survival of 38%, but 3 years event free survival for patients with macroscopic metastatic disease (M+) was 0%. CONCLUSION: Outcome of children with high risk medulloblastoma treated with chemotherapy first approach was dismal.

MBCL-51. POST-AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION (AUHCT) PRACTICES FOR YOUNG CHILDREN WITH MALIGNANT BRAIN TUMORS

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BACKGROUND: "Head Start" protocols have used autologous hematopoietic stem cell transplant (AuHSCT) for infants and young children with malignant brain tumors in order to avoid cranial irradiation. The post-AuHSCT practice for children with a brain tumor diagnosis varies greatly. The goal of this research study is to explore practices and attitudes about post-AuHSCT care for children with brain tumors. DESIGN: An anonymous REDCap survey link was provided to all site primary investigators and additional support personnel at "Head Start" institutions. The survey questions defined the role of the medical provider completing the form and explored the various practices relating to transition, management, communication and overall satisfaction. RESULTS: Twenty-one individual replies have been received so far. The majority report that prophylactic medicines were discontinued upon WBC recovery; however, management of discontinuation was split evenly between the neuro-oncology and stem-cell transplant teams. Nearly half of responders follow T-cell recovery following transplant without immunology guidance. Post-AuHCT vaccination practices are highly variable, with no clear consensus. Lastly, most responders reported adequate ease of transition and communication between the neuro-oncology and transplant teams. CONCLUSIONS: This work underscores the need for both multidisciplinary communication for children with brain tumors in the post-AuHCT period and for the development of standardized vaccination and other prophylaxis practices.

MBCL-52. ENDOCRINE PROFILE AFTER MEDULLOBLASTOMA TREATMENT

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BACKGROUND: Treatment of medulloblastoma has evolved substantially with more chemotherapy, risk-adapted dosing of radiotherapy (RT) and new RT techniques. We present the endocrine profile for our patients treated over a 20-year period. METHODS: The charts of patients treated for medulloblastoma between 1/1/00 and 31/12/19 were reviewed. 105 were available. Group 1 received chemotherapy alone, Group 2 received 23.4 Gy whole CNS RT with a posterior fossa (PF) boost to 54 Gy, Group 3 received > 35 Gy whole CNS RT with PF boost to 54–59 Gy, Group 4 received PF RT to 54 Gy. All received chemotherapy according to national guidelines or clinical trials relevant at the time. RESULTS: Group 1 (M:F 11:6, 7 survivors mean age 2 years range 1–7) had no endocrinopathies. At 5 years from diagnosis Group 2 (M:F 15:13) and Group 3 (M:F 35:14) had the following % RESULTS: Survival 77:61; Growth Hormone deficiency 92:100; Thyroid deficiency 75:81; ACTH deficiency 42:33. Girls were more likely to need sex hormone replacement than boys. Group 4 (M:F 7:5 mean age 2) were all treated in the first decade. 3 survivors, one GH deficiency, one thyroxine deficiency, one both. CONCLUSIONS: There is a trend to earlier endocrinopathies in the group 3 vs group 2 patients, but it does not reach statistical significance. Girls are more likely to need sex hormone replacement than boys. This investigation provides a contemporary profile of

endocrinopathy after treatment for medulloblastoma that can be used for future comparisons.

MEDULLOBLASTOMA (RESEARCH)

MBRS-01. DISSECTING REGULATORS OF THE ABERRANT POST-TRANSCRIPTIONAL LANDSCAPE IN MYC-AMPLIFIED GROUP 3 MEDULLOBLASTOMA

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Medulloblastoma (MB) is the most common solid malignant pediatric brain neoplasm, with Group 3 (G3) MB representing the most aggressive subgroup. *MYC* amplification is an independent poor prognostic factor in G3 MB, however, therapeutic targeting of the MYC pathway remains limited and alternative therapies for G3 MB are urgently needed. Here we show that an RNA-binding protein, Musashi-1 (MSI1) is an essential mediator of G3 MB in both *MYC*-overexpressing mouse models and patient-derived xenografts. Unbiased integrative multi-omics analysis of MSI1 function in human G3 MB suggests a paradigm shift beyond traditional gene-based profiling of oncogenes. Here we identify MSI1 as an oncogene in G3 MB driving stem cell self-renewal through stabilization of HIPK1 mRNA, a downstream context-specific therapeutic target for drug discovery.

MBRS-02. BET BROMODOMAIN PROTEIN-KINASE INHIBITOR COMBINATIONS FOR THE TREATMENT OF MEDULLOBLASTOMA

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Recent sequencing studies have implicated many epigenetic regulators in medulloblastoma. The epigenetic reader protein Brd4 has been implicated in various cancers including medulloblastoma. Brd4 controls expression of the medulloblastoma essential genes *MYC* in G3 medulloblastomas, which have poor prognosis as well as *GLI1* and *GLI2* levels in Sonic hedgehog (SHH) driven medulloblastomas, which have intermediate prognosis. Highly selective Brd4 inhibitors have been developed that reduce *MYC*, *GLI1* and *GLI2* levels. These inhibitors have gone into clinical trials for multiple cancer indications including medulloblastoma. However, resistance is common for Brd4 inhibitors warranting combination therapies for improved clinical outcome. We have developed a computational pipeline termed SynergySeq that predicts patient specific combinations of Brd4 inhibitors along with kinase inhibitors. We demonstrate that Brd4-kinase inhibitors robustly reduce proliferation of Shh and MYC driven medulloblastoma cells. Improved efficacy is related to dampening the adaptive kinome reprogramming response that occurs after Brd4 inhibition. Our findings suggest that SynergySeq can be utilized to inform patient selection for clinical trials utilizing Brd4 inhibitors in medulloblastoma and other brain tumors.

MBRS-03. SINGLE NUCLEUS TRANSCRIPTOME PROFILES FROM HUMAN DEVELOPING CEREBELLUM REVEAL POTENTIAL CELLULAR ORIGINS OF MEDULLOBLASTOMA BRAIN TUMORS

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Medulloblastoma (MB) is a highly malignant pediatric brain tumor originating from the cerebellum and brainstem. Identification of molecular subgroups forming this heterogeneous tumor entity was initially achieved from transcriptome characterization and further strengthened using DNA methylation profiling. While subgroup classification improved clinical diagnosis and treatment options, the lack of knowledge of the cell-of-origin for some of the subgroups hinders further treatment improvements. In addition identification of the precise cells of origin for each subgroup could help to understand tumor cell biology. Single cell sequencing is the optimal way to solve this task; recently, there were attempts to uncover putative MB cell-of-origin by using such information obtained from mouse embryonic cerebellum. However, such a comparative strategy can miss important results due to the differences between mouse and human. To solve this issue, we performed global single nucleus sequencing on human cerebellum pre- and postnatal materials across several developmental time points and generated transcriptome profiles from ~200k single cells. We identified known cell types forming the human cerebellum and performed detailed comparison of normal cells to RNA-seq bulk data from MB brain tumors across all subgroups. By selecting an optimal analysis strategy, we verified granule neuron precursors as cells of origin for the SHH MB subgroup. Additionally, we also found other cell types in conjunction with the remaining MB subgroups, suggesting new potential targets for investigation. Notably, this strategy can be further applied to the examination of other brain tumors and has perspectives in medical application.

MBRS-04. MEDULLOBLASTOMA DETECTION BY BLOOD TEST

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INTRODUCTION: Long non coding RNAs (lincRNAs) are functionally defined as transcripts longer than 200 nucleotides in length with no protein coding potential. lincRNA involvement in human cancers etiology is being increasingly proved. Cancer-secreted long non-coding RNAs (lncRNAs) in exosomes are emerging mediators of cancer-host cross talk communication in tumor microenvironments. The ability to monitor and detect tumor markers in real time enables access to tumor biology and may allow highly personalized treatment for each patient. METHODS AND RESULTS: We analyzed RNA sequencing of 64 Medulloblastoma samples and quantified the genome wide long non coding RNAs (lincRNA) expression levels. We identified a lincRNA that is distinctively highly expressed in group 4 (MB4). MB4 expression was further examined in microarray analysis on a larger cohort of medulloblastoma patient samples and a large cohort (n=1405) of patient samples that include normal brain and different brain tumor samples. MB4 proved to be specific and highly expressed in group 4 Medulloblastoma. MB4 was detected in the plasma of medulloblastoma patients with active disease, or subtotal resection. MB4 was not detected in patients that their tumors were resected. MB4 expression is not detected in the serum of medulloblastoma type SHH, penioblastoma, ewing sarcoma and neuroblastoma patients. CONCLUSIONS: We have found that MB4 lncRNA is a highly specific medulloblastoma tumor biomarker and is sensitive and noninvasive biomarker that can be quantified from a blood test. MB4 can be a good diagnostic marker, and in future both may also be a good target for therapy.

MBRS-06. GLI3 INDUCES NEURONAL DIFFERENTIATION IN WNT- AND SHH- ACTIVATED MEDULLOBLASTOMA

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BACKGROUND: We have previously investigated the expression of Gli3, a downstream target of the Sonic Hedgehog pathway, which main function is to suppress Gli1/2 in medulloblastomas. We found that Gli3 is associated with neuronal and glial differentiation in desmoplastic / nodular (D/N) type medulloblastomas (Miyahara *et al.*, Neuropathology, 2013). In the present study, we investigated the expression of Gli3 in molecular subgroups. METHOD: Thirty-one medulloblastomas treated at Niigata University between 1982 and 2013 were studied. Molecular classification into 4 subgroups (WNT-activated, SHH-activated, Group 3 and Group 4) using Nanostring and immunohistochemistry was performed. Furthermore, Gli3 and Gli1 expression in molecular subgroups was assessed using public data bases. RESULTS: Nanostring was considered reliable (confidence > 0.9) in 28 cases. Four cases were classified as WNT-, 5 cases as SHH-activated, 4 cases as Group 3 and 16 cases as Group 4. Gli3 was positive in 7 out of 9 (78%) WNT-/SHH- cases, but positive in only 8 out of 19 (42.1%) non-WNT-/SHH- subgroup cases ($p = 0.1145$, Fisher's exact test). R2 database analysis confirmed that Gli3 was significantly elevated in WNT- and SHH-activated medulloblastoma. Gli1 was elevated in SHH-activated cases but suppressed in WNT-activated cases. IHC analysis revealed that Gli3 was elevated inside nodules showing neuronal differentiation in D/N type