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INTRODUCTION: One of the major limitations of pathological diagnosis for intracranial germ cell tumors (iGCTs) is tumor heterogeneity, which cannot be evaluated using limited amount of tumor tissues. In this study, we performed comprehensive analysis of microRNA (miRNA) of iGCTs to identify miRNAs profile to help determine tumor diagnosis. METHODS: RNA was extracted from frozen samples of 16 germinoma and 14 NGGCTs. Five non-iGCT pediatric brain tumor tissues were used as control. miRNA expression analysis was performed using a 3D-Gene Human miRNA Oligo Chip ver.22 (Toray Industries, Inc) which was designed to detect 2565 miRNAs. The miRNA expression profile was analyzed using t-SNE dimensionality reduction and weighted average difference method (WAD). RESULTS: Different histological subtypes of the iGCTs and control samples were clustered into distinct classes. Furthermore, we found that the germinoma, NGGCTs and control samples may be readily distinguished by expression patterns of miR-200 and miR-371a-3p: a high expression of miR-200 was observed in the NGGCTs, whereas a high expression of miR-371a-3p was observed in all cases of germinoma and some of NGGCTs. Neither of miR-200 nor miR371-3p was highly expressed in control samples. CONCLUSION: Our data indicated that germ cell tumor and other pediatric brain tumors, and also germinoma and NGGCT can be distinguished by expression patterns of 2 micro RNA, miR-200 and miR-371a-3p. These 2 microRNA may serve as a useful tool for supporting the pathological diagnosis of iGCTs.

GCT-73. EXPRESSION PROFILING OF INTRACRANIAL GERM CELL TUMORS REVEALS UPREGULATION OF RAS THROUGH MRNA-MICRORNA SIGNALING PATHWAY

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Intracranial germ cell tumors (IGCTs) account for 3% of CNS tumors in children in the U.S. and 11% in Japan and East Asian countries. IGCTs are separated into two distinct subtypes based on histology: germinomas and non-germinomatous germ cell tumors (NGGCTs). The deep central location of IGCTs makes surgical resection and therefore molecular subtype classification difficult, and previous gene expression studies are limited. We performed mRNA expression profiling (Human Genome U133 Plus 2.0) and microRNA expression profiling (ABI TaqMan) with 36 and 49 IGCTs, respectively. Sample stratification using non-negative matrix factorization clustering of gene expression revealed two distinct subgroups that delineated germinomas from NGGCTs. Employing stepwise model building in each data set separately, we were able to separate these groups using only mRNA probes for the LIN28B and L1TD1 genes, and two microRNA, microRNA-26a and microRNA-373. MicroRNA26a suppresses the LIN28B gene and is down-regulated in germinoma. LIN28B directly binds and suppresses the let-7 microRNA family, which suppress the KRAS oncogene, previously found to be mutated in ~19% of IGCTs. L1TD1 is required for human stem cell renewal and directly interacts with LIN28B for its RNA binding function. LIN28B and L1TD1 are both known to be upregulated in other systemic germ cell tumors, but this has not yet been documented in IGCTs. In conclusion, these results show that intracranial germinomas have similar gene expression compared to systemic seminoma, and suggest a mechanism by which activation of LIN28B and L1TD1 downregulates the let-7 microRNA and subsequently upregulates KRAS.

GCT-74. RETROSPECTIVE LITERATURE REVIEW OF CENTRAL NERVOUS SYSTEM (CNS) GERM CELL TUMORS (GCTS) IN PATIENTS WITH DOWN SYNDROME (DS)

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BACKGROUND: A standard-of-care has not been established for the management of DS patients who develop primary CNS GCTs – the most common CNS neoplasm in DS – despite being more susceptible to treatment-related adverse events. METHODS: A review of the English-language medical literature between 1960 and 2020 was conducted. RESULTS: Thirty-one cases of CNS GCTs in DS patients (median nine-years-old; 21 males) were reported; the majority (23/31) originated from East Asia. Twelve had germinomas (39%), 12 had non-germinomatous germ cell tumors (NGGCTs) (39%), and seven had teratomas (22%). Four patients (13%) died from tumor progression (one germinoma *versus* three teratoma). Seven patients (23%) died from treatment-related complications (four germinoma *versus* three NGGCT). Of the germinoma patients, two died from chemotherapy-related sepsis, one from post-surgery cardiopulmonary failure, and one from Moyamoya following radiation-therapy (RT) only. Of the NGGCT patients, one died from chemotherapy-related sepsis, one from post-surgical infection, and one from pneumonia following surgery/chemotherapy/RT. Three-year overall survival (OS) was 58.1% for all patients, 52.5% for germinoma, 64.8% for NGGCT, and 60% for teratoma. Three-year OS for patients who received RT or chemotherapy was 63.6% and 59.6% respectively. Twenty patients (65%) remain alive (seven germinoma *versus* nine NGCCT *versus* four teratoma). Ten patients (32%) experienced serious treatment-related complications (five germinoma *versus* five NGGCT). CONCLUSIONS: Patients with DS and CNS GCTs are at an increased risk of treatment-related complications. Therefore, a different therapeutic approach may need to be considered for this patient population in order to mitigate the treatment-related complications and long-term neurocognitive sequelae.

GCT-75. ISOLATED PITUITARY STALK THICKENING

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OBJECTIVES: Only few studies have examined the predictive factors and outcome of isolated pituitary stalk thickening (PST) in children. We aim to describe our institutional cohort to determine predictors of future malignancy. METHODS: A search of the radiology, endocrinology and neuro-oncology databases was performed to identify patients with isolated PST diagnosed between January 2000 and June 2019. Clinical data was collected. A detailed radiology review of baseline and follow up magnetic resonance imaging (MRI) was undertaken in a blinded fashion by two examiners. RESULTS: Forty-four patients were identified, with 37 meeting criteria for isolated PST and adequate imaging. Median age of baseline MRI was 9.9 years (range 0.9–17.5). Twenty-three were female (62%). Median follow up time was 5 (0.31–18.6) years. Indication for MRI was symptoms of diabetes insipidus (DI) in 28 patients with the remainder having other concerns for endocrine disturbance (7), headache (1) or visual impairment (1). Thirty-five subjects had pituitary dysfunction (95%), including 30 with diabetes insipidus (81%). Nine patients developed a malignancy (24%), with germinoma (5), Langerhans cell histiocytosis (3) and lymphoma (1) at a median of 0.36 years, 0.63 years and 1.1 years respectively. Elevated white blood cell count (>5 x 10^6/L) in initial cerebrospinal fluid analysis was predictive of future diagnosis of germinoma or lymphoma (p=0.027). CONCLUSION: In this cohort 24% of children with PST were eventually diagnosed with a neoplasia after a median of 0.63 years. Pleocytosis in initial CSF samples was predictive for future development of germinoma or lymphoma.

GCT-76. 24GY WHOLE VENTRICULAR RADIOTHERAPY ALONE IS SUFFICIENT FOR DISEASE CONTROL IN LOCALISED GERMINOMA IN CR AFTER INITIAL CHEMOTHERAPY – EARLY RESULTS OF THE SIOP CNS GCT II STUDY

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SIOP CNS GCT II aimed to establish if 24Gy Whole Ventricular Radiotherapy (WVRT) in localised germinoma is sufficient for tumour control. After central review of radiological response after 'CarboPEI' chemotherapy, patients in complete remission (CR) were consolidated with 24Gy WVRT. Between 2/2012 and 7/2018, 182 patients from 8 European countries with histologically-confirmed fully-staged localised germinoma were registered. 70 patients were in CR after chemotherapy, 98 in partial remission (PR), seven had stable disease, two progressive disease, and in five no response data were documented. Of the 70 patients in CR, 58 received 24Gy WVRT alone; two of these relapsed, one local and one disseminated, two and six years after diagnosis. Of the 98 patients in PR after chemotherapy, 86 received 24Gy WVRT and 16Gy boost, of which five relapsed (three local, two distant) 12–24 months from diagnosis. Twelve patients in each of the CR/PR groups received non-protocol or undocumented radiotherapy fields/doses. Median follow-up was 3.7 years. Event-free survival (EFS) for patients in CR and with WVRT only (n=58) was 98% at 4 years. 4-years EFS of patients with PR and WVRT 24Gy and 16Gy tumor boost (n=86) was 95%. Localised germinoma in CR after chemotherapy had an excellent outcome with 24Gy WVRT alone; 24GY WVRT can therefore be considered standard consolidation treatment in this group. International consensus on radiological response criteria is of utmost importance to avoid over- and undertreatment of such patients and to pave the way for further treatment reduction in this group of patients.

HIGH GRADE GLIOMA

HGG-01. ENTRECTINIB IN RECURRENT OR REFRACTORY SOLID TUMORS INCLUDING PRIMARY CNS TUMORS: UPDATED DATA IN CHILDREN AND ADOLESCENTS

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STARTRK-NG (phase 1/2) is evaluating entrectinib, a CNS-penetrant oral, TRK/ROS1/ALK tyrosine kinase inhibitor, in patients <21 years with recurrent/refractory solid tumors, including primary CNS tumors. After determining the recommended dose, 550mg/m^2/day, in all-comers, expansion cohorts with gene-fusion-positive CNS/solid tumors (*NTRK1/2/3*, *ROS1*) are being enrolled. As of 5Nov2019 (data cut-off), 39 patients (4.9m–20y; median 7y) have been evaluated for response, classified as complete (CR) or partial response (PR), stable (SD) or progressive disease (PD) using RANO (CNS), RECIST (solid tumors), or Curie score (neuroblastoma). Responses in patients with fusion-positive tumors were Investigator-assessed (BICR assessments are ongoing) and occurred at doses ≥400mg/m^2. Best responses in fusion-positive CNS tumors (n=14) were: 4 CR (*GKAP1-NTRK2, ETV6-NTRK3* [n=2], *EML1-NTRK2*); 5 PR (*KANK1-NTRK2, GOPC-ROS1, ETV6-NTRK3, TPR-NTRK1, EEF1G-ROS1*); 3 SD (*BCR-NTRK2, ARHGEF2-NTRK1, KIF21B-NTRK1*); 2 PD (*PARP6-NTRK3, EML4-ALK*); and in fusion-positive solid tumors (n=8) were: 3 CR (*ETV6-NTRK3* [n=2], *DCTN1-ALK*); 5 PR (*EML4-NTRK3, TFG-ROS1* [n=3], *KIF5B-ALK*). Responses (Investigator-assessed) in non-fusion tumors (n=17) were: 1 CR (*ALK F1174L* mutation), 3 SD, 10 PD, 3 no data/unevaluable. The objective response rate (CR+PR/total) in patients with fusion-positive tumors was 77% (17/22) versus 6% (1/17) in those with non-fusion tumors. All 39 patients experienced ≥1 adverse event (AE); the most frequent AEs included weight gain and anemia (both 48.7%); increased ALT, increased AST, cough and pyrexia (all 46.2%); increased creatinine and vomiting (both 43.6%); and bone fractures (n=10, in 9 patients). Entrectinib has produced striking, rapid, and durable responses in solid tumors with target gene fusions, especially high-grade CNS neoplasms.

HGG-02. ADOLESCENT AND YOUNG ADULT (AYA) GLIOMA WITH BRAF V600E-MUTANTATION

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BACKGROUND: Biological features of pediatric glioma differ significantly from those of adult glioma, and limited data are available on those of AYA patients. Here, we focused on AYA patients with glioma, especially those harboring BRAF V600E mutation, and investigated their clinical and genetic features. METHOD: We retrospectively analyzed AYA patients with brain tumors harboring BRAF V600E, who were treated in two hospitals in Japan. RESULTS: Clinical information was available for 14 patients. The median age at diagnosis was 25 years (range: 15–38). Five patients were diagnosed with glioblastoma (GBM), including one epithelioid type. These patients were over 25. Although one patient with GBM died of the disease 6.9 years after initial diagnosis, the remaining patients were alive. Two patients were alive without recurrence at 38 and 51 months after the treatment. The patient with epithelioid glioblastoma experienced early recurrence. The remaining nine patients (64%) were diagnosed with low-grade glioma, including ganglioglioma, pilocytic astrocytoma, diffuse astrocytoma, oligodendroglioma, pleomorphic xanthoastrocytoma, and polymorphous low-grade neuroepithelial tumor of the young. No patients died of the disease, and four patients are alive without recurrence after initial operation without adjuvant treatment. Two patients are (epithelioid glioblastoma and ganglioglioma) currently undergoing treatment with a BRAF inhibitor for recurrent tumors. DISCUSSION: Although the number of this study is limited, our study suggested that the prognosis of AYA patients with BRAF-V600E positive GBM may not be as dismal as that of children or adults.

HGG-04. ZINC ENHANCES TEMOZOLOMIDE CYTOTOXICITY IN PEDIATRIC GLIOBLASTOMA MULTIFORME MODEL SYSTEM

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BACKGROUND: Temozolomide (TMZ) is an alkylating agent that has become the mainstay treatment of the most malignant brain cancer, glioblastoma multiforme (GBM). Unfortunately only a limited number of patients respond to it positively. We have shown that zinc metal reestablishes chemosensitivity in adult GBM in vitro and also in vivo but this effect has not been tested with pediatric GBM. METHODS: Using Human pediatric glioblastoma cell lines- KNS42 (mutant p53/ MGMT [+]) and SF188 (mutant p53/ MGMT [-]), we investigated whether addition of zinc to TMZ enhances its cytotoxicity against GBM. RESULTS: *In vitro* cell viability analysis showed that the cytotoxic activity of TMZ was substantially increased with addition of zinc and this response was accompanied by an elevation of p21, PUMA, BAX and a decrease in growth fraction as manifested by low ki67. Beta gal analysis showed that most of the remaining cells after the combination therapy are in senescence state. In order to eliminate the senescent population created as a result of the combined treatment of TMZ and Zinc, we decided to use a senolytic agent Navitoclax (ABT-263) that was demonstrated to be effective in reducing senescent cells by specific in-