GCT-44. A CASE OF INTRACRANIAL GERMINOMA WHICH RECURRED IN THE SPINAL CORD 13 YEARS AFTER THE INITIAL TREATMENT

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BACKGROUND: Central nervous system germinoma occurs most often in early teens, accounting for 15% of childhood brain tumors. Here, we report a case of germinoma which recurred in the spinal cord 13 years after complete remission. CASE DESCRIPTION: A 15-year-old boy presented with diabetes insipidus (DI). MRI showed a pineal gland tumor and ventriculomegaly. Biopsy was performed and the histological examinations revealed PLAP and c-kit positive pure germinoma. Ki67 LI was 64.4%. Gamma knife radiosurgery and 3 courses of ICE chemotherapy brought disappearance of the tumor. However, it recurred in lateral ventricles. Forty-Gray whole brain radiation resulted in complete remission of the tumor. For the sake of DI treatment and MRI examinations, he kept periodical visit to our hospital. Thirteen years later, when he was 28y/o, he complained paresthesia in the right upper extremity. MRI demonstrated gadolinium-enhance mass lesion in the cervical spinal cord. Recurrence of the tumor and multiple sclerosis were the principal differential diagnosis. Pulse steroid therapy did not make any change, and radiation therapy to the cervical spinal cord led to tumor disappearance. Nevertheless, the tumor recurred on the dorsal medulla oblongata one and a half years later. Biopsy of the tumor clarified that the tumor was germinoma. ICE chemotherapy which was limited to three courses due to severe bone marrow suppression was carried out. MRI proved no enhanced mass lesion in the central nervous system. DISCUSSION: Germinoma may recur even after long period of remission, demonstrating that long-term follow-up is indispensable.

GCT-45. YOLK SAC TUMOR IN THE CEREBELLAR VERMIS - A CASE REPORT

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Yolk sac tumor (YST) is a non-germinomatous malignant germ cell tumor in a young child. It usually arises along a midline axis, mostly pineal region or suprasellar compartment, and it is exceedingly rare to locate in a cerebellar vermis. In the present report, we describe a case of a pure YST located in the cerebellar vermis and review the previous literature. A three-year-old boy visited a local clinic for gait disturbance and frequent vomiting. Gadolinium-enhanced magnetic resonance imaging (MRI) showed a homogeneously-enhanced mass with a cystic component in his cerebellar vermis, and it resulted in hydrocephalus. By its location and his age, our preoperative diagnosis was a medulloblastoma, and we performed a total resection of the tumor with ventricular drainage. Unexpectedly, the histological investigation revealed it to be a YST. We confirmed that the serum levels of α-fetoprotein (AFP) had elevated at 3176.4 ng/ml in his preserved sample, obtained before the surgery, and it was consistent with the pathological diagnosis. He is receiving chemotherapy consisting of ifosfamide, cisplatin, and etoposide, followed by radiation therapy. In this case, pre-operative MRI revealed that the tumor did not grow into the IVth ventricle in spite of midline location, which was not typical for medulloblastoma. Of note, serum AFP levels had increased, and they might contribute to a precise pre-operative diagnosis and be able to propose an alternative treatment plan, such as neoadjuvant chemotherapy to reduce surgical risk. As a conclusion, a YST should be considered even if it locates in a cerebellar vermis.

GCT-46. MULTI-KINASE INHIBITORS AS NOVEL THERAPEUTIC AGENTS AGAINST INTRACRANIAL NON-GERMINOMATOUS GERM CELL TUMORS

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Central nervous system germ cell tumors (CNS GCTs) are rare intracranial malignancies developing in adolescents and young adults which relatively frequently occur in East Asia region of the world including Japan. However, among CNS GCTs, non-germinomatous germ cell tumors (NGGCTs) are highly resistant to the current chemoradiotherapies, and the prognosis of CNS NGGCTs is still extremely poor. Therefore, development of novel therapeutic strategy against CNS NGGCTs is urgently needed. In this study, we screened small molecule inhibitors of kinases specifically targeting cell membrane receptors, such as receptor tyrosine kinases, and their related molecular signaling, which could effectively exert antitumor effects against NGGCT cells. As the NGGCT model cells, the Tcam2 cell, a mixed germ cell tumor cell line composed of germinoma and embryonal carcinoma components, and the YST1 cell, a novel yolk sac tumor cell line established in our institute, were used. As a result, effective induction of cell death in both cell lines was confirmed only by treatment with two multi-kinase inhibitors. Immunoblotting revealed these multi-kinase inhibitors suppressed activation of various kinases concurrently. Furthermore, these multi-kinase inhibitors also triggered cell death in the Tcam2 cell stably expressing mutant KIT, the most common oncogenic driver genes of CNS GCTs, suggesting that these inhibitors would be also effective against CNS GCTs harboring activated KIT mutants. In vivo studies of these multi-kinase inhibitors using CNS GCT xenografts are currently on going.

GCT-47. TREATMENT STRATEGIES FOR GIANT IMMATURE TERATOMAS IN INFANTS

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INTRODUCTION: Immature teratomas are the most frequent fetal brain tumors and show a poor prognosis. At onset, the tumor is often already giant with deep origins such as suprasellar or pineal region, and easy bleeding is also considered to be a cause of poor prognosis. On the other hand, it is also known that the prognosis is improved in total removal cases. METHODS: We investigated the best treatment strategy based on two cases of total removal of giant immature teratomas in infants. RESULTS: 1.5 month after birth at onset (median), maximum diameter of 75 mm (median). A giant tumor centered around the third ventricle with hydrocephalus. First, biopsy (+septostomy) was performed using an endoscope. The tumor showed easily bleeding. In addition, external ventricular drainage was taken out of the lower abdomen subcutaneously by long tract. After chemotherapy (carboplatin and etoposide), tumor removal was performed by using drainage tract. Both cases showed not easily bleeding at that time and the tumor was safely removed. Regarding the deep blind spot, using a flexible endoscope was effective. They showed no recurrence after total removal (median 50 months). DISCUSSION: There have been reports of cases in which chemotherapy for immature teratomas suppressed tumor growth and reduced bleeding and safely removed totally. In infants giant immature teratomas, chemotherapy before tumor removal can be expected to reduce bleeding, and further increase body weight during that period. In addition, long-term placement of ventricular drainage by long tract during the chemotherapy can prevent brain development delay due to hydrocephalus.

GCT-48. OUTCOME OF CNS MALIGNANT NON-GERMINOMATOUS GERM CELL TUMORS (GCT) WITH AFP > 1000 NG/ML AT DIAGNOSIS TREATED ACCORDING TO SIOP CNS GCT 96

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Analysis of CNS MMGCT with AFP >1000 ng/ml (serum and/or CSF) at diagnosis, treated on trial in SIOP-CNS-GCT-96, revealed an inferior prognosis (32% 5-year progression-free survival) compared with AFP <1000 ng/ml (76%). As this patient group is small, to evaluate a bigger cohort, we revisited all patients treated according to SIOP-CNS-GCT-96, who were registered in the database until July 2015. Between October 1996 and July 2015, 373 patients with CNS MMGCT were registered. 48 patients (13%)

presented with an AFP >1000 ng/ml at diagnosis. 41 patients were evaluable with a median observation time of 2.4 years; 6/41 received chemotherapy alone. Primary site, histological components (if available), metastatic status and outcome were evaluated. Primary site was pineal in 29/41, suprasellar in 6/41, bifocal 1/41 and other in 5/41 patients. 10/41 patients were metastatic at diagnosis. Four to five courses of standard PEI and radiotherapy (RT) or 2 standard and two intensified PEI (as for SIOP CNS GCT II) were administered in 32 patients. Two received less then 4x PEI and RT, 6 patients <6 years were treated with PEI (either standard or intensified) alone. 16/34 patients with PEI and RT are alive in CR; 2/6 patients without RT survived. Overall, 18/40 (45%) survived. 10–15% of CNS MGGCT are high-risk patients by diagnostic AFP, with the pineal as the main tumour site. Outcome of <50% survival is unsatisfactory. Further research, international cooperation and common data analysis is needed to identify additional risk factors and develop alternative treatment strategies.

GCT-49. EVALUATION OF THE PERIOPERATIVE AND POSTOPERATIVE COURSE OF SURGERY OF PINEAL GERMINOMA ACCORDING TO THE SIOP CNS GCT 96 TRIAL

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INTRODUCTION: CNS germinoma, being marker-negative, are diagnosed by surgical biopsy. Here we evaluate the perioperative status and postoperative complications of patients with pineal germinoma who underwent a primary biopsy or resection, treated according to SIOP CNS GCT 96. METHODS: 235 patients with histologically confirmed germinoma were registered, of which 113 were pineal: 55 were biopsied and 58 underwent primary resection. Initial symptoms, tumour size, complications and neurological status were assessed. 111 patients were evaluable. RESULTS: Pure germinoma was present in 101 patients; 10 had additional teratoma components. The main clinical symptoms at diagnosis were headache (n=98), hydrocephalus (n=93), double vision (n=62), Parinaud syndrome (n=57) and papilloedema (n=44). Tumour size was documented in 81 patients (<2cm, n=14; 2-3cm, n=35; ≥3cm, n=32). 17 patients underwent primary total resection, 14 subtotal resection >50%, 26 subtotal resection <50%, 39 stereotactic biopsy, 11 endoscopic biopsy, 2 open biopsy and 2 not documented. The postoperative neurological status after resection was improved in 23 patients, unchanged in 27, deteriorated in 6 and not documented in one. Clinical status after biopsy improved in 26 patients, was unchanged in 15, deteriorated in 2 and not documented in 11. Postoperatively, 16/57 patients after resection and 5/54 after biopsy developed complications (Parinaud syndrome, double vision and hydrocephalus). CONCLUSION: Although surgical techniques have improved within recent decades, these results support the practice of biopsy over resection for histological confirmation of germinoma arising at the pineal site. Supported in part by German Cancer Aid.

GCT-50. LONG-TERM OUTCOMES OF INTRACRANIAL GERMINOMA IN A SINGLE INSTITUTION

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The treatment for intracranial germinoma has been well-established. Complete removal is not necessary, but radiation therapy is important. As the prognosis of patients with germinoma has become better, side effect of radiotherapy and chemotherapy must be well considered. The aim of this study was to evaluate the outcome of intracranial germinomas at Kyoto University Hospital from 1979 to 2019. 64 patients were diagnosed as intracranial germinoma. Patients with hCG > 100 IU/l and/or AFP > 10 ng/ml were excluded. Patients, who were histologically diagnosed as germinoma without information of hCG and AFP, were included. Follow-up time was from 2 to 486 months (median 136 months). Recently, germinoma patients were diagnosed with biopsy and received low dose whole-ventricle irradiation with intensity modulated radiation therapy (IMRT) (total 24-30Gy) and chemotherapy dominated by platinating agent. 10-year PFS was 80.21% (high dose radiation alone), 86.36% (high dose radiation with chemotherapy) and 100% (low dose radiation with chemotherapy). Many recurrent sites were out of irradiation areas. Late cognitive dysfunction was identified in 6 patients, and 5 of them were treated with high dose radiation. Patients with intracranial germinoma can obtain long-term survival. It is important to prevent recurrence without increasing late iatrogenic complications. Low dose radiotherapy and chemotherapy is highly effective, and it potentially reduces late adverse effects.

GCT-51. IMMUNE CHECKPOINT MOLECULES AND TUMOR INFILTRATING LEUKOCYTES IN THE TUMOR MICROENVIRONMENT ARE ASSOCIATED WITH THE GROWTH OF INTRACRANIAL GERMINOMAS

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The role of immune checkpoint molecules and the tumor immune microenvironment in the development of intracranial germ cell tumors remains unclear. In the present study, we investigated the expression of immune checkpoint molecules, as well as the number of tumor-infiltrating lymphocytes (TILs), in intracranial germinomas to determine whether there were any correlations between the statuses of these immune-related molecules/cells and clinical manifestations in patients with germinoma. The 8 patients were categorized based on the duration between symptom onset and pathological diagnosis into the long-term onset (LTO) group (> 1 year of symptoms, 3 patients) and the short-term onset (STO) group (< 1 year of symptoms, 5 patients). Compared with STO tumors, LTO tumors were significantly associated with a lower ratio of programed cell death ligand-1 (PD-L1)–positive tumor cells ($p = 0.012$), higher number of infiltrating CD3- and CD8-positive lymphocytes ($p = 0.016$, 0.003, respectively), and lower ratio of programed cell death-1 (PD-1)–positive cells per CD8–positive lymphocytes ($p = 0.047$). LTO germinomas were significantly smaller in size than STO tumors and tended to be present in patients with atypical tumor location. Our data suggest that the tumor immune microenvironment, including PD-1/PD-L1 signaling, is associated with the growth of intracranial germinomas. Immune checkpoint inhibitors might be a reasonable treatment option for recurrent germinomas or as replacement for radiotherapy in patients with intracranial germinomas.

GCT-52. TRANSCRIPTOME OF CENTRAL NERVOUS SYSTEM GERM CELL TUMOR REVEALS ITS PATHOGENESIS AND CONTRASTS WITH TESTICULAR COUNTERPARTS IN INTEGRATED OMICS ANALYSIS

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Germ cell tumors (GCTs) are unique neoplasms in that they arise from the migrated cells which were supposed to be directed to gonads. They occur in the central nervous system (CNS), as well as gonadal organs such as testis and ovary. Our genomic analysis revealed that they are characterized by mutations in MAPK and PI3K pathways, chromosomal instability and global