BACKGROUND: Pilotocic astrocytoma is one of the common tumors found during childhood. However, the clinical course of disseminated pilocytic astrocytoma is not clearly known. Here, we present two cases with disseminated pilocytic astrocytoma and discuss the treatment strategy. Patients We treated a 7-year-old female (case 1) and a 9-year-old male (case 2) with hypothalamic pilocytic astrocytomas. The results of magnetic resonance imaging showed diffuse spinal dissemination at diagnosis. Chemotherapy and carbotatin may be administered before radiotherapy. The tumors showed some shrinkage, and symptoms improved. During chemotherapy, the patients developed allergies to carbotatin. Therefore, we changed the chemotherapy treatment to vincristine. Other adverse events were not observed. In case 1, we observed an intratumoral hemorrhage and hydrocephalus due to occlusion of the foramen Monro. Endoscopic surgery was performed, and no clinical deficit was observed. Case 2 underwent ventricular peritoneal shunt procedure for communicating hydrocephalus and a reoperation for shunt malfunction because of dense cerebrospinal fluid with elevated protein levels. The patients have not undergone radiotherapy until now. They had no severe clinical symptoms and went to school for 5 and 10 years, respectively, after the diagnoses. CONCLUSION: Chemotherapy for disseminated pilocytic astrocytoma is effective and may help in avoiding radiotherapy. Chemotherapy should be administered before radiotherapy, considering long-term complications.

PEDT-07
RECURRENT MEDULLOBLASTOMA 9 YEARS AFTER THE PRIMARY TUMOR
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Medulloblastoma is one of the most common malignant brain tumors in children. Despite multi-disciplinary treatment for medulloblastoma, including surgery, chemotherapy, and radiation, which have resulted in significant improvement of the prognosis, about 30% of patients still experience recurrence. Most recurrences occur within the first 15 months from diagnosis and led to diagnosis of a primary tumor is quite rare. We report a case of a 15-year-old female patient with recurrent medulloblastoma 9 years after the primary tumor. At the age of 6, this patient developed a posterior fossa tumor without metastasis and underwent near-total resection. The pathological diagnosis was medulloblastoma with focal desmoplasia. After the surgery, she received multi-agent chemotherapy and radiation therapy consisting of 18 Gy craniospinal irradiation and 51.2 Gy local irradiation. She was in complete remission for 9 years after the treatment. However, gait disturbance began to gradually appear, and magnetic resonance imaging (MRI) showed an intradural lesion in her thoracic spine. The lesion was biopsied, and the pathological findings confirmed the recurrence of medulloblastoma. Currently, we plan to administer local radiation therapy concomitantly with temozolomide to the patient. The case reminds us of the importance of long-term careful follow-up of patients with medulloblastoma.

IMMUNOLOGIC THERAPY (IMT)

IMT-01
Therapeutic Effect Against Lower Grade Glioma Induced by Dendritic Cell Based Immunotherapy
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BACKGROUND: This trial was designed to evaluate the safety and clinical responses to an immunotherapy with fusions of dendritic and glioma cells in patients with lower grade glioma (LGG; WHO grade II-III glioma). METHOD: Autologous cultured glioma cells obtained from surgical specimens were fused with autologous dendritic cells (DC) using polyethylene glycol. The fusion cells (FC) were inoculated intradurally in the cervical region of subjects. Toxicity, progression-free survival (PFS), overall survival (OS), and MRI findings were evaluated. DNA for whole exome and RNA for whole transcriptome extracted from HLA-A*24:02 positive glioma cells were analyzed by next generation sequencer. Variant peptides showing strong binding affinity to HLA-A*24:02 but not the corresponding wild type peptides were selected as candidate of neo-antigens. RESULTS: The number of subjects of this trial were 24 (initially diagnosed cases: 20, recurrence cases: 4). WHO grade III cases were 20, and grade II cases were 4. Male were 15, and female were 9. Mean of follow up periods were 53.0 months (the longest follow up period: 1322 months). The number of events on PFS and OS were 8 and 6, respectively. Mean of candidate of neo-antigen peptides in HLA-A*24:02 positive patients (n=8) was 34. Among these candidates, twelve types of common neo-antigen peptide were identified. Neo-antigen peptides specifically expressed in the glioma cells from the effective group were not identified. CONCLUSIONS: These results indicate that the efficacy of neo-antigen immunotherapy may be dependent on the number of gene mutations or the expression of the specific neo-antigens. FC-immunotherapy, as a means of producing specific immunity against neo-antigens may safely induce anti-tumor effects in patients with LGG. Analysis of prognostic factor in glioma immunotherapy may be the next area of major interest.

IMT-02
VEGF Receptors Expression and Report of Clinical Trial of Peptide Vaccine in Skull Base Chordoma
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Chordoma is a rare refractory neoplasm that arises from the embryological remnants of the notochord. Vascular endothelial growth factor (VEGF) is a potent activator of angiogenesis that is associated with the tumor-immune microenvironment. To evaluate the characteristics of vascular and tumor cells in chordoma, we first analyzed the expression of VEGF receptor (VEGFR) 1, VEGFR2, CD34, and Brachyury in a cell line and with primary tumors. Patients with primary tumor less than 3 cm were divided into the two groups as per the tumor growth rate. The expressions of VEG-A, VEGFR1, and VEGFR2 on tumor cells; tumor infiltrative immune cells, including regulatory T-cells (Tregs) and tumor-associated macrophages (TAMs); and immune-checkpoint molecules (PD-1/PD-L1) were analyzed with the clinical courses. Both VEGFR1 and VEGFR2 were strongly expressed not only on vascular endothelial cells, but also on tumor cells. The recurrent cases showed significantly higher VEGFR1 expressions on tumor cells than the primary cases. The expression of VEG-A, and the numbers of CD163+ TAMs and Foxp3+ Tregs were significantly higher in the patients with rapid progressive course than the patients with slow progressive course. Based on the present results, VEGFRs-targeted therapy may show efficacy in regulating growth of chordomas.

IMT-03
Clinical Trial for Newly Diagnosed Malignant Glioma With WT1-W10 Vaccination
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OBJECT: Wilms’ tumor 1 (WT1) peptide vaccination is considered a potentially effective therapy against malignant glioma. We conducted a Phase I/II study to investigate the safety and feasibility of novel WT1 peptide (WT10) vaccination therapy for patients with newly diagnosed malignant glioma. METHODS: WT1 vaccination therapy was performed for patients with malignant glioma who have undergone concurrent radiotherapy and temozolomide therapy. A mixture of WT1 peptide with inactivated peritumoral immune cells was administered before radiotherapy, considering long-term complications. A means of producing specific immunity against neo-antigens may safely induce anti-tumor effects in patients with LGG. Analysis of prognostic factor in glioma immunotherapy may be the next area of major interest.

IMT-05
Phase III Randomized Clinical Trial of AFTV for Newly Diagnosed Glioblastoma
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BACKGROUND: The highly fatal glioblastoma has an extremely poor prognosis and development of a new treatment is desired. Local treatment

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is limited due to its high invasiveness, and immunotherapy utilizing self-immune mechanism is theoretically expected. An autologous formalin-fixed tumor vaccine (AFTV) is a vaccine that is prepared using formalin-fixed tumor tissue and recognizes tumor antigen peptides to induce cytotoxic T cells. We have previously conducted three clinical trials using AFTV for patients with newly diagnosed glioblastoma since 2004. The third trial was a double-blind multicenter phase IIb/III trial with 63 case registries, which did not make a significant difference in OS (study group 25 months, placebo group 31 months), the total removal group showed excellent clinical results (3-year survival rate; 67%, median survival; not reached). Since the study was designed to go to Phase III if the test group was not inferior to the placebo group, so it went on to go to Phase III. METHODS: Target patients were all patients with newly diagnosed glioblastoma undergoing pathologic diagnosis, who have undergone total removal of contrast-enhanced lesions and received standard chemoradiation therapy. STUDY DESIGN: Double-blind, 3-year enrollment period, 18-month observation period. Stratification factor: Photodynamic therapy (PDT), facility, age, KPS. Administration method: After standard chemoradiotherapy, in parallel with maintenance chemotherapy, a total of 9 times intradermal administration of vaccine. Primary endpoint: PFS of FAS patients, Secondary endpoints: 18 months PFS of the FAS patient, OS, PFS of the ITT analysis target case. Based on the results of the Iib trial, we limited the registered patients with total tumor removal, and in view of the fact that the prognosis of patients with combined PDT and AFTV were excellent, PDT was added to the stratification factor. We outline our efforts and problems aimed at clinical approval of AFTV for glioblastoma.

IMT-07

CLINICAL TRIAL OF A COCKTAIL WILMS’ TUMOR 1 (WT1) VACCINATION USING TWO HLA CLASS I PEPTIDES AND ONE CLASS II PEPTIDE FOR RECURRENT MALIGNANT GLIOMAS

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PURPOSE: Our clinical trials shows the safety and clinical efficacy of Wilms’ tumor 1 (WT1) human leukocyte antigen (HLA) class I (Izumoto S et al. J Neurosurg. 2008) and class II (Tsutobi A et al. Cancer Immunol Immunother. 2019) peptide vaccination for recurrent malignant gliomas have been established. We have developed a cocktail vaccine (WT1 trio) containing two class I peptides (HLA-A*24:02 and HLA-A*02:01) and one class II peptide to improve more effective immunological response and improve patient’s prognosis. Clinical trial of a cocktail vaccination using WT1 HLA class I and II peptides for recurrent malignant gliomas is planned to verify its safety, clinical efficacy and usefulness of surrogate markers. PATIENTS AND METHODS: Twenty-three patients with recurrent malignant gliomas, which showed WT1-positive in tumor samples and HLA-A*24:02 or HLA-A*02:01-positive in blood sample, were enrolled. These patients (age: 26–72 years old; average: 49.4) included 15 cases of glioblastomas and 8 of anaplastic astrocytomas. Patients received a WT1 trio vaccine intradermally, 7 times at 2-week intervals during 3 months. WT1-DTH and WT1-IgG antibody were regularly measured. Vaccine-related adverse events, best clinical response and the transfer rate of long-term administration of WT1 trio vaccination were estimated. RESULTS: WT1-DTH positive cases were 12, WT1-IgG antibody positive were in 11. In most patients, WT1-DTH positiveness coincided with that of WT1-IgG antibody. 9 of 11 cases showed stable disease at 3 months and transferred long-term administration of WT1 trio vaccination. Transfer rate in GBM and AA of long-term administration was 33% and 25%, respectively. Grade1 skin eruption was observed at the injection sites in 15 cases, but no significant adverse events related with vaccination were shown. CONCLUSION: the safety and clinical efficacy of WT1 trio vaccination was verified for recurrent malignant gliomas. WT1-DTH and WT1-IgG antibody may be useful surrogate markers.

SURGICAL/INTRAOPERATIVE THERAPY/ MONITORING (STMO)

STMO-01

APPLICATION OF THE AMINOLEVULIC ACID HYDROCHLORIDE FOR INTRAOPERATIVE DETECTION OF MALIGNANT BRAN CH TUMORS

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BACKGROUND: A maximal safe resection has been shown as an independent prognosis factor for high grade glioma (HGG). Intraoperative photo dynamics diagnosis (PDD) facilitates an increased rate of tumor resection, thereby taking an important role in accomplishment of “maximal safe resection” along with neuro-navigation and monitoring of motor nerve function. Since the approval of aminolevulinic acid (5-ALA) for PDD in 2013 in Japan, we have been utilizing the PDD when HGG is suspected by preoperative assessment. Here we retrospectively analyze clinical outcomes of PDD-mediated tumor resection. METHODS: From February 2014 to March 2019, 285 consecutive patients (132 females) with suspected HGG underwent total of 302 PDD-mediated resection. Median age was 61 yo (11–90). A single oral dose of 5-ALA 20 mg/kg was given within three hours before microsurgery. Positivity of excited fluorescence was assessed qualitatively under surgical microscope. RESULTS. Among 195 gliomas, the fluorescence positivity rates were 89.6% (120/134) for glioblastoma, 40.3% (15/37) for grade III, and 13.6% (3/22) for grade II. The positive rates for other histologies were 30.2% (13/43) for malignant lymphoma, 32.1% (9/28) for metastatic brain tumor, 0% (0/7) for meningioma (including atypical), and 4.5% (1/22) for other types. In gliomas the high positivity correlated with histological grades, while all fluorescence-positive grade II gliomas were recurrent tumors. Serious adverse events were not observed. CONCLUSIONS. The qualitative PDD showed a clinical utility to aid accurate resection in glioblastoma, whereas its positivity was inconsistent in lower grade gliomas as well as other malignant brain tumors. This unreliability might attribute, at least in part, to fluorescent intensity heterogeneity in situ, a reduced excitation by an inappropriate radiation angle of the light source, and the qualitative fluorescence detection. Impacts of introducing quantitative detection system as well as molecular and histopathological features on better discrimination will be discussed.

STMO-02

PREOPERATIVE FENCE-POST METHOD PLANNING WITH 3D-FUSION IMAGING

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The fence-post method has been used for removal of intra-axial tumors. Preoperative detailed planning with only navigation work system is sometimes difficult to identify actual brain surface, small feeding artery and passing artery. Recently, 3-dementional imaging is well developed to integrate various anatomical findings. The purpose of this study is pursuit of perfect preoperative planning for removal intra-axial tumors with 3D-fusion imaging. From May 2017 to June 2019, 21 patients with intra-axial tumor were included. The software “AZE” was used to create 3D-fusion imaging. The brain tumor, brain surface and tractography were built from MRI, artery from digital angiography and vein from subtraction enhanced computed tomography. Then detailed preoperative planning was planned including how many fence-posts, procedure of cutting feeder, making sulcotomy or corticotomy, and finally cutting drainer. The average bleeding volume was 10±129ml, and there were no patients who had transfusion. All patients did not show additional neurological impairment after surgery. Detailed and perfect preoperative planning with 3D-sulcion imaging should be effective for secure neurorsurgery.

STMO-03

ROLE OF INTRAOPERATIVE COMPUTED TOMOGRAPHY IN GLIOBLASTOMA RESECTION GUIDED BY 5-ALA

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OBJECTIVE: To improve resection rate, multiple operative modalities have been essential for glioblastoma (GBM) surgery. Aim of this study is to clarify the impact of intraoperative computed tomography (i-CT) for GBM surgery with 5-aminolevulinic acid photodynamic diagnosis (5-ALA PDD). METHODS: Consecutive 24 patients newly diagnosed GBM were analyzed, retrospectively. To exclude 6 patients decided timing for i-CT based on neural monitoring, 18 patients performed i-CT after total resection of GBM. RESULTS: The median age was 58 years old, and average preoperative tumor volume was 47.78 cm3. Tumor locations were frontal lobe 9 (50%), and corpus callosum 1 (6%). Seventeen tumors (78%) harbored in eloquent area. After i-CT performed, 7 (39%) were confirmed residual tumor, and additional patients newly were needed. Subtotal resection (STR) was 5 and partial resection (PR) was 2 on volumetry in i-CT before additional resection. After additional resection, those cases were judged as 2 gross total resection (GTR), 4 STR and 3 PR in postoperative MRL. In 18 patients confirmed...