ACT-26

ABT-414 (DEPATUX-M) IN NEWLY DIAGNOSED AND RECURRENT GLIOBLASTOMA: WHERE DO WE STAND?

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Epithelial growth factor receptor (EGFR) amplifications are found in approximately half of glioblastoma cases and targeting of the EGFR axis is an attractive treatment paradigm in this tumor type. However, several anti-EGFR drugs have failed to achieve significant and meaningful improvements in clincial trials. ABT-414 (Depatux-M) is an antibody-drug conjugate (ADC) that combines a cytotoxic agent with an antibody targeting EGFR, thus aiming at specific tummor cell killing through intracellular toxin delivery. The activity of ABT-414 has been evaluated in two large clinical trials enrolling glioblastoma patients. Intellance-2 enrolled 260 patients with first recurrence of EGFR-amplified glioblasoma into a chemotherapy control arm (temozolomide or lomustine) or one of two experimental arms (ABT-414 monotherapy or ABT-414 combined with temozolomide). Depatux-M in combination with temozolomide showed a trend towards improved survival times compared to temozolomide/lomustine alone, with patients relapsing more than 4 months after the last adjuvant temozolomide cycle deriving the greatest benefit. Intellance-1 was a randomized, placebo-controlled Phase 3 study and was designed to evaluate the efficacy and safety of Depatux-M versus placebo when administered with concurrent radiation and temozolomide and with adjuvant temozolomide in subjects with newly diagnosed EGFR-amplified glioblastoma. The primary endpoint was overall survival. Recently, it was announced that a preplaned interim analysis based on data from 639 patients showed the lack of a survival benefit for patients exposed to Depatux-M. In summary, the currently available data do not support routine use of Depatux-M in glioblastoma patients and further studies are needed to understand resistance mechanisms limiting therapeutic efficacy of EGFR-targeting in glioblastoma.

Key words: epithelial growth factor receptor, glioblastoma, antibody-drug-conjugate

PEDIATRIC CLINICAL TRIALS/THERAPEUTIC STUDIES (PEDT)

PEDT-02

DIAGNOSIS, TREATMENT AND CLINICAL OUTCOME OF ATYPICAL BRAINSTEM TUMOUR IN CHILDHOOD

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BACKGROUND: Brainstem tumours account for 10–15% of brain tumors in childhood. Diffuse intrinsic pontine glioma (DIPG) accounts for 60–80% of them and are diagnosed based on clinical findings and radiologic features. All the rest of tumours excluding DIPG are very rare, heterogeneous group of tumours including low-grade glioma and malignant embryonal tumors. It is often difficult to diagnose and decide treatment strategy for their rarity. METHODS: To present our experience with atypical brainstem tumours, a retrospective chart review was conducted to identify eligible cases treated over a ten-year period. All tumors involving brainstem, felt not to be DIPGs for absence of clinical/neuroimaging features were included. Demographic information, pathological findings, neuroimaging characteristics, surgical and nonsurgical management plans, and survival data were collected for analysis. RESULTS: Between April 2007 and March 2017, 16 patients (14 initial and 2 recurrent) aged from 3 to 20 years were identified. 14 of them were symptomatic and 4 of them were asymptomatic at reference. Of 10 symptomatic cases, 10 were biopsied and pathological diagnosis was low-grade glioma in 8, glioblastoma in 2 cases. They had treatment depending on the pathological diagnosis. Of 4 asymptomatic cases, one with small focal tumour, with no findings suggesting malignant tumour with 11C-methioninePET or MRS, progressed to show typical clinical and image findings of DIPG in a year. For other three, they remain asymptomatic without progression with no treatment for 25months, 60months, and 65 months respectively. Malignant transformation was observed in one with biopsy-conformed oligoastrocytoma with no K27M-H3 mutations treated with chemotherapy and another with pilocytic astrocytoma treated with chemotherapy and radiotherapy. CONCLUSIONS: Though molecular findings such as K27M-H3 mutations can predict clinical outcome in some cases, it still remains difficult to diagnose and find treatment strategy of atypical brainstem tumours. The need and usefulness of nationwide registry study is warranted.

PEDT-04

SIX CASES OF RETINOBLASTOMA WITH CNS INVOLVEMENT

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Although the survival rate of intraocular retinoblastoma (RB) is nearly 100%, the outcome of central nervous system (CNS) involvement or Trilateral retinoblastoma (TRb: very rare RB which associated with brain tumor) is dismal. We retrospectively reviewed our six cases of these rare tumors. Their ages at diagnosis are 0y3m-1y10m (median 1y3m) (Male 4, Female 2). Only one had RB family history. Their affected eyes were bilateral 2, unilateral 3 and no 1. Their CNS diseases were suprasellar tumor 3, pineal tumor 1 and cerebrospinal fluid (CSF) cytology positive 2. Two of the suprasellar tumor patients had spinal metastasis. Three of the six patients were TRb. One TRb patient was treated with chemotherapy and high-dose chemotherapy without radiotherapy. Although he suffered with secondary osteosarcoma seven years later, he got complete remission and alive 5 years more without any tumor recurrence. The second TRb patient was treated with chemotherapy and local radiotherapy but relapsed 20 months later. The third TRb patient was chemotherapy resistant. Two CSF positive patients had optic nerve invasion. One patient with chiasm invasion died 11 months later because of treatment resistance. The other patient with optic nerve invasion before optic canal had no CNS tumor nor CSF involvement at diagnosis. Chemotherapy before enucleation was given to avoid dissemination. However, CSF cytology became positive after enucleation and remained even with intensified chemotherapy. Finally, he got remission with radiotherapy and high-dose chemotherapy, and alive without disease for 3.8 years. The last patient had suprasellar genetically classified retinoblastoma tumor and cerebrospinal metastasis. This patient showed good chemotherapy response and is still under treatment. Even with &quotso called° fatal RB cases, some case could survive with intensified therapy. Data accumulation is necessary for better survival of these tumors.

PEDT-05

USEFULNESS OF BEVACIZUMAB IN MAINTAINING QOL AT DIPG RELAPSE

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INTRODUCTION: Even in the age of molecular diagnosis, diffuse intrinsic pontine glioma (DIPG) is still a dismal disease, and there is no effective treatment. The usefulness of bevacizumab for DIPG relapse is reported. SUBJECTS AND METHODS: The treatment and outcomes of 10 patients with DIPG who were treated at our institute since 2001 were retrospectively reviewed. All patients were diagnosed with DIPG by MRI imaging and underwent radiation therapy first. Chemotherapy was performed in combination with radiation therapy in 4 cases, and 3 of them did not receive chemotherapy at the time of relapse (Untreated Group). In 7 cases, chemotherapy was performed at the time of relapse with ACNU/vincristine or interferon beta (Other Treatment Group), and 2 cases with bevacizumab (Bv Group). The change in the Karnofsky Performance Status Scale (KPS) from the time of relapse was compared.

RESULTS: The average overall survival (OS) for all 10 cases was 10.0 months, 8.1 months in the Untreated Group, 9.5 months in the Bv Group, and 11.4 months in the Other Treatment Group. No prolongation of OS by bevacizumab was observed. However, it was only in the Bv Group that the KPS increased from the time of relapse. Comparison of the KPS at the time of relapse and the KPS after 4 months showed that the Bv Group remained unchanged or increased from 80 to 90, while the Untreated Group decreased by 60–100, and the Other Treatment Group also decreased by 20–50. In the Other Treatment Group, hospitalization was required for treatment, and side effects of bone marrow suppression were observed. However, in the Bv Group, outpatient treatment was possible, there were no side effects, and all could be observed at home. CONCLUSION: From the above results, bevacizumab appears useful for palliative treatment for maintaining quality of life after DIPG relapse.

PEDT-06

THERAPEUTIC STRATEGY FOR DISSEMINATED PILOCYTIC ASTROCYTOMAS

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BACKGROUND: Pilocytic 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 9-year-old male (case 2) with hypothalamic pilocytic astrocytomas. The results of magnetic resonance imaging showed diffuse spinal dissemination at diagnosis. Chemotherapy with vincristine and carboplatin was administered as the firstline therapy. The tumors showed some shrinkage, and symptoms improved. During chemotherapy, the patients developed allergies to carboplatin. 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 late relapse of the 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. Further studies are warranted for the treatment of relapsed medulloblastomas due to the limited information available at present.

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 intradermally 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 FC-immunotherapy may not always depend 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 54 tumor tissues. Patients with primary skull base chordomas were divided into the two groups as per the tumor growth rate. The expressions of VEGF-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 VEGF-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 (W10) 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 pertussis whole cell vaccine was injected intradermally once a week for at least 12 weeks. RESULTS: Twenty-seven patients (12 men, 15 women; median 65 years) with the following tumors were enrolled: WHO grade IV (15), WHO grade III (12). PFS and OS of glioblastoma cases were 12.7 months 21.9 months, respectively. PFS of the MGMT unmethylated group was shorter than the methylated group. Interestingly enough, overall survival in the MGMT unmethylated group was not significantly different from the methylated group. Analysis of recurrent cases after immunotherapy showed decreased expression of WT1 antigen and increased Treg. They were suggested as a cause of treatment resistance. No serious adverse events were observed except for Grade 1 erythema at the injection sites. CONCLUSIONS: This study of a novel WT1 vaccination therapy demonstrated safety and feasibility in the management of newly diagnosed malignant gliomas.

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