or maintenance of tight junctions in blood vessel endothelial cells in human non-cancer tissues. CLIC2-expressing endothelial cells supposedly prevent hematogenous spread of cancer cells. In this study, we investigated CLIC2 expression in human brain tumor tissues and also addressed its function by employing human meningioma cells, rat glioma cells and rat malignant brain tumor model. Thirty-one meningioma cases, six SFT/HPC cases, twelve pituitary adenoma cases and twenty-three glioblastoma cases who underwent surgery at Ehime University Hospital were included. CLIC2 mRNA expression levels were investigated with immunoblotting and quantitative RT-PCR. Cells from the meningiomas were cultured and their CLIC2 expression was knockdown. Filter-based invasion assays and gelatin zymography were performed using the knocked-down meningioma cells. Rat C6 glioma cells stably expressing rat CLIC2 were established and transplanted into the right striatum of neonatal Wistar rats. Effects of CLIC2 on the survival periods of the animals were investigated. CLIC2 expression levels were high in the low-grade cases but low in the high-grade cases and highly invasive cases. Meningioma cells, of which CLIC2 expression was knocked-down, showed higher invasive activity than control cells. The CLIC2-knock down cells displayed increased activities of MMP-2 and MMP-9. Rat brain tumor models revealed that high expression of CLIC2 was correlated with smaller and less invasive brain tumors compared with those consisted of control cells. The rats transplanted with CLIC2-expressing cells survived longer periods than the rats with control C6 cells. These results suggest that CLIC2 plays a role in suppression of invasive activities of tumor cells.

ADULT CLINICAL TRIALS/THERAPEUTIC STUDIES (ACT)

ACT-01

THE SECOND GENERATION ANAPLASTIC LYMPHOMA KINASE (ALK) INHIBITOR CERITINIB EFFECTIVELY INDUCES CELL DEATH IN HUMAN GLIOBLASTOMA CELLS

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Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase which expresses only in the developmental stage of the brain during embryogenesis of human. On the other hand, a variety of ALK gene alterations, such as oncogenic fusion, activating point mutation, or wild type gene amplification, have been recently discovered as the powerful oncogene in various tumors, and these ALK mutations have also been known as the potential therapeutic targets against tumors harboring these ALK mutations. For example, ALK inhibitors have been already approved and used for the clinical treatment of non-small cell lung cancers harboring oncogenic ALK fusion.

Previously, we reported classical ALK inhibitors triggered cell death in human glioblastoma (GBM) cells, which did not express ALK, via suppression of transcription factor STAT3 activation but not in normal tissue-derived cells.

In this study, we investigated the anti-tumor effect of newly-developed ALK inhibitors in GBM cells. As a result, a second generation ALK inhibitor ceritinib induced cell death in various human GBM cell lines with lower concentration compared to other ALK inhibitors. Besides, ceritinib also suppressed STAT family activity in these GBM cell lines. From these results, we consider ceritinib might be a novel therapeutic agent against GBMs, and further investigation about the specific anti-tumor mechanism of ceritinib in GBM cells is currently on-going.

ACT-02

BORON NEUTRONS CAPTURE THERAPY FOR RECURRENT HIGH-GRADE MENINGIOMAS, FROM REACTOR TO ACCELERATOR

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INTRODUCTION: Recurrent high-grade meningiomas (rHGM) are difficult to control. We have applied tumor-selective particle radiation, reactor-based boron neutron capture therapy (BNCT) with excellent tumor control. METHODS: Forty-six recurrent and treatment-refractory high grade meningiomas were treated with reactor-based BNCT by Osaka Medical College (OMC) and Kyoto University Research Reactor team collaboratively until February 2019. Tumor shrinkage, overall survival (OS), progression free survival (PFS), Lesion/Normal (L/N) ratio in boronophenylalanine positron emission tomography (BPA-PET) and causes of treatment failures are analyzed. RESULTS: Subjects had been almost always treated heavily, high-risk patients for prognosis. They were received surgery 3 times and some radiotherapy 2 times averagely, prior to BNCT. All cases responded well and markedly shrunk by BNCT. The mean L/N ratio in BPA-PET was 4.0 which is higher than glioblastomas. Two-year PFS was 49.0% (95% CI: 28.84–66.49). Unfortunately follow-up was insufficient and 2 year OS was very similar to 2 year PFS. Treatment failures were observed as recurrence out of fields of neutron irradiation, systemic metastasis and in field local recurrence almost equally. SUMMARY AND PROSPECTS: Median PFS and OS of rHGM are 5 months and 2 years respectively in literatures. We achieved relatively favorable results by reactor-based BNCT. On the other hand, we performed accelerator-based BNCT clinical trial for recurrent glioblastomas steadily first in the world. Based on these backgrounds, we applied investigator-lead, clinical trial of accelerator-based BNCT for rHGM as RCT design. Government (PMDA and AMED) has approved our proposal. We start this trial with the primary endpoint as PFS, from August 2019. Treatment arm is BNCT and control one is best-supportive care. If the subjects in control arm show progress disease in follow-up, they can be treated by BNCT as rescue treatments. We will introduce details of this trial in our presentation.

ACT-05

PREDICTIVE FACTORS RELATING TO OUTCOME AFTER RESECTION OF LOW-GRADE GLIOMAS WITHOUT CHEMOTHERAPY OR RADIOTHERAPY

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BACKGROUND: There are several treatment options, including observation, after surgical removal of low-grade gliomas (LGG). If postoperative chemotherapy and/or radiotherapy are not provided, resection-alone approach will probably be alternative to a natural course of LGG under observation. The objective of this study was evaluation of prognostic factors associated with overall survival (OS) of patients with LGG treated with surgery alone. METHODS: A consecutive series of 236 adult patients who underwent surgery for LGG without adjuvant therapy was analyzed retrospectively. In 193 cases (82%) histopathology of the tumor was re-classified based on evaluation of IDH1 mutational status and 1p/19q co-deletion according to criteria of WHO classification 2016. Cox proportional hazards model was used for statistical analysis. RESULTS: Median extent of resection (EOR) was 95% (range, 1–100%) and in 210 cases (89%) EOR was >=90%. During postoperative follow-up tumor progression was noted in 106 patients, and 30 patients died of disease. Overall, 10-year OS rate was 82.0%. There was statistically significant difference (P <0.001) in OS among molecularly re-classified tumors, with 10-year OS rates of 90%, 79%, and 75% in cases of OD, DA IDH1-mutant, and DA IDH1-wild, respectively. In patients with EOR >=90% 10-year OS rate was 75%. Multivariate analysis revealed that only EOR >=90% (RR, 0.23; 95% CI, 0.09–0.66; P<0.007) and presence of 1p/19q co-deletion (RR, 0.41; 95% CI, 0.16–0.97; P = 0.042) are independently associated with OS. In patients with EOR >=90% such factors as type of disease manifestation, time interval between onset of symptoms and surgery, and molecular subtype of the tumor did not show significant associations with OS. CONCLUSION: Survival outcome in patients with LGG who underwent surgical resection alone may be predicted by EOR and presence of 1p/19q co-deletion. In cases with EOR >=90% molecular subtype of the neoplasm does not impact OS.

ACT-09

RETROSPECTIVE INVESTIGATION ABOUT STATUS AND RESULT OF ADMINISTRATION OF BEVACIZUMAB FOR MALIGNANT GLIOMAS IN THE REAL WORLD

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6 years have passed after approval of Bevacizumab for malignant gliomas in Japan, we analyzed the application and the results in our institution. Subjects were 56 patients who were histologically diagnosed as malignant gliomas. Bevacizumab was used in 41 patients among them. In 14 patients, Bevacizumab was introduced after initial therapy. The resection rates were below partial resection in 11 of the 14 patients. In 12 patients, administrations were finished and the average use was 7.6 times. The reason was PD in 6, and side effect in 4. Eight patients died, the average OS of those who died was 9.9 months, the average PFS after Bevacizumab was 5.4 months, and the average time from discontinuation to death was 2.1 months. In 27 patients used at the time of recurrence, the initial excision rate tended to be higher than in the former cases. In 22 patients the administrations were

finished and the average use was 11.1 times. The reason was PD in 17, and side effect in 4. Twenty patients have died, the average OS of those who died was 22.3 months, the average PFS after Bevacizumab was 7.1 months, and the average time from discontinuation to death was 2.6 months. In 12 of 15 unused patients subtotal or total resections were achieved. From results, when it is difficult to control by surgery or TMZ, Bevacizumab is used in most patients, and considering the nature of tumor, it can be said that all patients will be considered for use sometime. However, PFS after introduction is not good and the prognosis after discontinuation is poor. It is necessary to conduct initial treatment that can delay introduction, to provide care that does not lead to discontinuation due to side effects, and to examine what treatment is possible at the time of exacerbation.

ACT-10

TREATMENT FOR GLIOBLASTOMA RECURRED AFTER CONCOMITANT CHEMORADIATION THERAPY WITH TEMOZOLOMIDE AND THEIR PROGNOSIS

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There are few data about treatment for glioblastoma recurred after concomitant chemoradiation therapy with temozolomide (TMZ). We retrospectively examined treatment and prognosis of recurred glioblastoma patients who registered Kansai molecular diagnosis network for central nervous system tumors, and whose clinical information were available. One hundred and fifty-seven patients that were clinically diagnosed as recurrence between November 2007 and April 2019 were included. Their median age at primary diagnosis was 52 years old and median KPS was 80%. Proportion of methylated MGMT promoter was 43.3% (65 patients), and mutated IDH was 5.4% (8 patients). Median overall survival after recurrence (mSAR) was 8.2 months. One hundred and sixteen patients (73.9%) were received any anticancer treatment and their mSAR was 10.5m. Combination of TMZ and bevacizumab (Bev) were most frequently used for 33 patients, followed by Bev monotherapy for 17 patients, surgery + TMZ + Bev for 15 patients, surgery + TMZ for 12 patients, and TMZ monotherapy for ten. Their mSAR were 8.0m, 7.5m, 10.5m, 13.0m, and 8.0m, respectively. Using univariate analysis, MGMT promoter methylation (p=0.0007), TMZ (p=0.00933), surgery (p=0.0126), re-radiation (p=0.0367), and surgery+TMZ+Bev (p=0.0493) significantly affected prognosis. By multivariate analysis, MGMT promoter methylation, TMZ, and re-radiation were statistically significant (p=0.000138, 0.00161, 0.00403, respectively). These data showed that relatively young patients with good performance status would receive anti-cancer treatment beyond progression and MGMT promoter methylation might be one of prognostic factor for longer survival. In this cohort, re-radiation was performed for few patients and nitrosourea such as nimustine was almost not used. Further study would be needed whether these treatments have any positive effect or not.

ACT-13

RESPONSE TO SEIZURE AND TUMOR-PROGRESSION BY TREATMENT WITH PERAMPANEL IN PATIENTS WITH GLIOMAS

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BACKGROUND: Increased extracellular glutamate level activates AMPA type glutamate receptors (AMPA-receptor) and induces seizures. Antagonistic activation of AMPA-receptors inhibits epilepsy and glioma progression in vivo and in vitro studies. PATIENTS AND METHODS: (1) We tested perampanel (PER), an AMPA-receptor antagonist, in fifteen glioma patients with uncontrolled epilepsy. Seizure response, PER concentration, and tumor volume were assessed. (2) We tested PER in thirteen glioma patients (gr 2- 3 cases, gr 3- 4 cases, and gr 4- 4cases) after the initial treatment of surgery and RT (and CT). RESULTS: (1) An objective seizure response was observed in 13 analyzed patients (100%) with 8 cases (62%) of seizure-freedom. Median plasma concentration of PER was 232 ng/ml in patients with 4mg/day PER and 518 ng/ml in patients with 8mg/day PER. High intensity lesions of MRI-FLAIR images were assessed volumetrically to analyze the tumor size. The volume reduction was detected during the 6 months period in correlation with the plasma PER levels. (2) All the 13 cases treated with PER after the initial treatment was seizure free. Two cases of gr 4 were died at 18 and 20 months after the surgical treatment. Other 11 cases are survival-free. CONCLUSION: PER treatment was effective in uncontrolled epilepsy with gliomas. MRI images showed the inhibition of tumor-progression. PER may effective for the inhibition of tumor progression.

ACT-14

A FIRST-IN-HUMAN STUDY OF MUTANT IDH1 INHIBITOR DS-1001B IN PATIENTS WITH RECURRENT GLIOMAS

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BACKGROUND: WHO grade II/III gliomas frequently harbor isocitrate dehydrogenase 1 (IDH1) mutations, resulting in intratumoral accumulation of oncometabolite D-2-hydroxyglutarate (D-2-HG) and subsequent clonal expansion. DS-1001b is an oral selective inhibitor of mutant IDH1 R132X that was designed to penetrate the blood-brain barrier. METHODS: In this first-in-human, multicenter, phase I study (NCT03030066), eligible patients (pts) with recurrent/progressive IDH1 mutant glioma received DS-1001b twice daily (bid), continuous. A modified continual reassessment method was used for dose escalation. RANO and RANO-LGG criteria were used to assess tumor response. Pts who planned to undergo salvage surgery after developing progressive disease (PD) and who provided informed consent received DS-1001b treatment until surgery. Tumor samples were also obtained from those pts to measure the free form of DS-1001b and D-2-HG levels. RESULTS: Between Jan 2017 and May 2019, DS-1001b (125–1400 mg bid) had administered for 47 pts, and 15 pts were continuing treatment. Maximum tolerated dose (MTD) was not reached. Most AEs were Gr 1–2. Gr 3 AEs were observed in 40% of pts. No Gr 4 or 5 AEs or serious drug-related AEs were reported. One dose limiting toxicity was Gr 3 white blood cell count decreased (1000 mg bid). Of 35 evaluable pts with contrast enhancing gliomas, one, five and 11 achieved complete response, partial response and stable disease (SD), respectively. Of evaluable 12 pts with contrast non-enhancing gliomas, four achieved minor response and eight achieved SD. Peak plasma concentration (Cmax) and area under the curve (AUC) increased dose-dependently. CONCLUSIONS: DS-1001b was well tolerated up to 1400 mg bid with favorable brain distribution, and MTD was not reached. Recurrent/progressive IDH1 mutant glioma pts responded to treatment. Investigation is ongoing to determine the recommended Phase II dose. The latest data will be updated. Funding source: This study was funded by Daiichi Sankyo Co., Ltd.

ACT-15

AD-SGE-REIC GENE THERAPY FOR MALIGNANT GLIOMA

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INTRODUCTION: Malignant gliomas are one of the most common and aggressive intracranial neoplasms in humans. Expression of the gene encoding reduced expression in immortalized cells/Dickkopf-3 (REIC/Dkk-3) is reduced in a variety of human cancer cells. We previously showed the antitumor effect of an adenoviral vector carrying REIC/Dkk-3 gene (Ad-CAG-REIC). Recently, we have also developed a novel adenoviral vector expressing REIC/Dkk-3 (Ad-SGE-REIC). We assessed the anti-glioma effect of the Ad-SGE-REIC and planned a clinical trial of Ad-SGE-REIC for malignant glioma. MATERIALS AND METHODS: We evaluated a cytotoxicity assay to treatments with Ad-SGE-REIC, Ad-CAG-REIC, or Ad-LacZ (control) using malignant glioma cells. The survival of mice in each group was analyzed by the Kaplan-Meier method. We also performed Good Laboratory Practice (GLP) toxicology tests and prepared a protocol for this clinical trial. RESULTS: The treatment with Ad-SGE-REIC showed the number of malignant glioma cells attached to the bottom of culture wells was significantly reduced in a time-dependent manner. Mice treated with Ad-SGE-REIC significantly prolonged survival time more than those treated with other vectors. A cGMP product of Ad-SGE-REIC was developed and supplied by a startup biotech company, Momotaro-Gene Inc. We conducted GLP toxicology tests using the intracranial injection of higher doses of Ad-SGE-REIC at Shin Nippon Biomedical Laboratories (SNBL Japan). After finishing the consultation with Pharmaceuticals and Medical Devices Agency (PMDA), we prepared a protocol for a phase I/IIa clinical trial of Ad-SGE-REIC for the treatment of recurrent malignant glioma with our academic research organization (ARO), supported by Japan Agency for Medical Research and Development (AMED). This protocol was reviewed by our institution review board in March 2019. We submitted a notification of this trial in April 2019. CONCLUSIONS: We demonstrated the anti-glioma effect of Ad-SGE-REIC. We start a phase I/IIa clinical trial of Ad-SGE-REIC for the treatment of recurrent malignant glioma (https://jrct.niph.go.jp/en-latest-detail/jRCT2063190013).