or maintenance of tight junctions in blood vessel endothelial cells in human non-cancer tissues. CLI2C-expressing endothelial cells supposedly prevent hemagenous spread of cancer cells. In this study, we investigated CLI2C 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. CLI2C mRNA expression levels were investigated with immunoblotting and quantitative RT-PCR. Cells from the meningiomas were cultured and their CLI2C 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 CLI2C were established and transplanted into the right striatum of neonatal Wistar rats. Effects of CLI2C on the survival periods of the animals were investigated. CLI2C expression levels were high in the low-grade cases but low in the high-grade cases and highly invasive cases. Meningioma cells, of which CLI2C expression was knocked-down, showed higher invasive activity than control cells. The CLI2C-knock down cells displayed increased activities of MMP-2 and MMP-9. Rat brain tumor models revealed that high expression of CLI2C was correlated with smaller and less invasive brain tumors compared with those consisted of control cells. The rats transplanted with CLI2C-expressing cells survived longer periods than the rats with control C6 cells. These results suggest that CLI2C 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 CERTINIB EFFECTIVELY INDUCES CELL DEATH IN HUMAN GLOBLASTOMA CELLS

Daiske Watanuki,1 Masami Bachisaka, Shun Yamamuro,1 Tatsuya Kobayashi,2 Eita Uchida,1 Yasuo Iwashita, Koichi kimihara,1 Arata Tomiyama1;1Division of Brain Tumor Translational Research, National Cancer Center Research Institute

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 certinib induced cell death in various human GBM cell lines with lower concentration compared to other ALK inhibitors. Besides, certinib also suppressed STAT family activity in these GBM cell lines. From these results, we consider certinib might be a novel therapeutic agent against GBMs, and further investigation about the specific anti-tumor mechanism of certinib in GBM cells is currently on-going.

ACT-02
BORON NEUTRONS CAPTURE THERAPY FOR RECURRENT HIGH-GRADE MENINGIOMAS, FROM REACTOR TO ACCELERATOR

Soko Ikura1, Takashi Maruyama1, Tatsuya Sato1, Masayuki Nitta, Syunsuke Tsuzuki, Atsushi Fuku, Takakazu Kawamata, Yoshihiro Muragaki1;1Institute of Advanced Biomedical Engineering & Science,Graduate School of Medicine, Tokyo Women’s Medical University, Tokyo, Japan

BACKGROUND: Several treatment options, including observation, proton beam therapy and gamma knife, are available for recurrent meningiomas. However, the outcomes of these treatments are often not adequate, and most patients receive surgery. However, only 50% of patients with recurrent meningiomas achieve complete response and overall survival is 66% at 2 years. The prognosis of recurrent meningiomas is significantly poorer than that of newly-diagnosed meningiomas. Recurrent high-grade meningiomas (rHGM) have been treated with BNCT by accelerator-based BNCT with excellent results. In this study, we explored the possibility of reactor-based BNCT for rHGM.

METHODS: Thirty-one meningioma cases were treated with reactor-based BNCT by KL-2BNCT. Tumor shrinkage, overall survival (OS), local control rate (LCR) and progression-free survival (PFS) were evaluated. A two-year PFS of 49.0% (95% CI: 28.84−66.49) was achieved in 27 patients. Follow-up was insufficient. Two partial recurrences were observed in one patient. The patient died of metastasis to the brain and the head 1 year after BNCT. The overall survival was 96.8% at 2 years. A median PFS was 5 months, and the median OS was 2 years. After BNCT, patients with CNS metastasis and field local recurrence were treated with BNCT as rescue treatments.

RESULTS: Median LCR and OS of rHGM were 96.8% and 96.8% at 2 years, respectively. The median PFS was 5 months, and the median OS was 2 years. After BNCT, patients with CNS metastasis and field local recurrence were treated with BNCT as rescue treatments.

PROSPECTS: Median PFS and OS of rHGM are 5 and 2 years respectively. Treatment failures were noted in patients with CNS metastasis and field local recurrence. The patients 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

Soko Ikura1, Takashi Maruyama1, Tatsuya Sato1, Masayuki Nitta, Syunsuke Tsuzuki, Atsushi Fuku, Takakazu Kawamata, Yoshihiro Muragaki1;1Institute of Advanced Biomedical Engineering & Science,Graduate School of Medicine, Tokyo Women’s Medical University, Tokyo, Japan

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PROSPECTS: Median PFS and OS of rHGM are 5 and 2 years respectively. Treatment failures were noted in patients with CNS metastasis and field local recurrence. The patients can be treated by BNCT as rescue treatments. We will introduce details of this trial in our presentation.

ACT-05
RETROSPECTIVE INVESTIGATION ABOUT STATUS AND RESULT OF ADMINISTRATION OF BEVACIZUMAB FOR MALIGNANT GLIOMAS IN THE REAL WORLD

Tetsuo Hashiba1, Katsuyu Ueno1, Nobuki Naito1, Mayuko Miyata1, Natsumi Yamamura1, Ichiru Lee2, Ryoihi Iwata1, Jinnichi Takeda1, Kunikazu Yoshimura1, Masahiro Nonaka1, Aki Azai1;1Department of Neurosurgery, Kansai Medical University, Osaka, Japan

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, the initial extent was higher than in the former cases. In 22 patients the administrations were never stopped, 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 neuron irradiation, systemic progression, and in field local failure almost equally. SINCE ITY AND PROSPECTS: Median PFS and OS of HGM are 5 months and 2 years respectively. 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 HGM 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.
finished and the average age 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 to discontinuation to death was 2.6 months. In 12 or 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 consensual for use somehow. 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 RECURRENT AFTER CONCOMITANT CHEMORADIATION THERAPY WITH TMZ: THE 2ND REPORT Genki Moritomi, Tomoko Shofuda, Masayuki Mano, Yoshinori Kodama, Manabu Kinoshida, Hideyuki Arita, Shusuke Moruchi, Takehiro Uda, Takuyu Taki, Junya Fukas, Masahiro Nonaka, Kenichi Ishibashi, Daichi Yamaizumi, Shusuke Tsuyuguchi, Naohiro Nakajima, Koji Takano, Naoya Hashimoto, Naohiro Tsuyuguchi, Takashi Koda, Takahiro Achiwa, Nobuhide Hayashi, Makoto Dehara, Yonehiro Kanemura; 1Department of Neurosurgery, Kansai Rosai Hospital

There are few data about treatment for glioblastoma recurrent after concomitant chemoradiation therapy with temozolomide (TMZ). We retrospectively assessed treatment and prognosis of recurrent 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 receiving anticancer treatment beyond progression, and 28 patients (21.6%) were receiving anti-epileptic drugs. Median overall survival after recurrence (mSAR) was 13.0 months, 10.5 months, and 8.0 months, respectively. Using univariate analysis, MGMT promoter methylation (p=0.0007), TMZ (p=0.0093), surgery + TMZ + Bev (p=0.0367), and surgery+TMZ+Bev (p=0.0493) significantly affected prognosis. By multivariate analysis, MGMT promoter methylation (p=0.00138, 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-irradiation was performed for few patients and nitrosourea such as mustine 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 PERAMYLANGINE IN PATIENTS WITH GLIOMA Shuichi Izumoto1, Masaru Miyauchi, Akira Watanabe1, Saori Murakami1, Naohiro Tsuyuguchi, Amami Kato; 1Department of Neurosurgery, Kindai University Nara Hospital

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 animal 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 control 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 surgery and PER treatment. Other 11 case 10.5 months. CONCLUSION: PER treatment was effective in uncontrolled epilepsy with glioma. 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 IDH INHIBITOR DS-1001B IN PATIENTS WITH RECURRENT GLIOMAS Yoshiki Arakawa1, Yohi Mineharu1, Yoshitoku Wakabayashi, Kazuki Nishida1, Yasuo Miyakawa, Yoshihisa Nakazawa, Fusumiyuki Yamazaki, Kazuhiko Sugiyama, Nobuoji Hata, Yoshihiro Muragaki, Ryu Nishikawa, Naoki Shinomizu, Yoshitomo Kumabe, Ruya Saito, Kazumi Ito, Masaya Tachibana, Yasuyuki Kakurai, Tomoyuki Yamaguchi, Soichiro Nishijima, Hiroshi Tsuabuchi; 1Kyoto University Graduate School of Medicine, Kyoto, Japan

BACKGROUND: WHO grade II/III gliomas frequently harbor isocitrate dehydrogenase 1 (IDH1) mutations, resulting in intratumoral accumulation of oncometabolite D-2-hydroxoglutarate (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 (NCT03030866), eligible patients (pts) with recurrent/progressive IDH1 mutant glioma received DS-1001b twice daily (bid), continuously. 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 despair of progressive glioma were treated with DS-1001b until surgery. RESULTS: Between Jan 2017 and May 2019, DS-1001b (125–1400 mg bid) had administers 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). 15 evaluable pts were contrast enhancing gliomas, one, five and 11 achieved complete response, partial response and stable disease, 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. Further 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-SGEGE-REIC GENE THERAPY FOR MALIGNANT GLIOMA Kazuhiko Kurozumi1, Kentarou Fuji1, Youke Shimmazu1, Yasuaki Tomita1, Yuji Matsunoto1, and Hiroshi Umeda1, Nobushige Tsuibo2, Keisuke Kaneda2, Keigo Makino1, Hiromi Kuman, Isao Date1; 1Department of Neurosurgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

INTRODUCTION: Malignant gliomas are one of the most common and aggressive intracranial neoplasms in humans. Expression of the gene encoding reduced expression in glioma cells (IDH) (IDH1-R132H) 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-SGEGE-REIC). We assessed the anti-glioma effect of the Ad-SGEGE-REIC and planned a clinical trial of Ad-SGEGE-REIC for malignant glioma. MATERIALS AND METHODS: We evaluated a cytotoxicity assay to treatments with Ad-SGEGE-REIC, Ad-CAG-REIC, or Ad-LacZ (control) using patients’ malignant glioma cells. The survival of mice in each group was analyzed by the Kaplan-Meier method. We also performed Good Laboratory Practice (GLP) toxicity tests and prepared a protocol for this clinical trial. RESULTS: The treatment with Ad-SGEGE-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-SGEGE-REIC significantly prolonged survival time more than those treated with other vectors. A cGMP product of Ad-SGEGE-REIC was developed and supplied by a startup biotech company, Momentaro-Gene Inc. We conducted Ad-SGEGE-REIC toxicity tests using the intracranial injection of higher doses of Ad-SGEGE-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 IIa clinical trial of Ad-SGEGE-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 institutional review board in March 2019. We submitted a notification of this trial to AMED. CONCLUSION: With demonstrated antitumor activity of Ad-SGEGE-REIC, we start a phase IIa clinical trial of Ad-SGEGE-REIC for the treatment of recurrent malignant glioma (https://jct.niph.go.jp/en-latestdetail/RCT2061390013).