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).