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Background: Germ cell tumors (GCTs) preferentially occurs in pediatric and young adult age groups. Chemo- and radiation therapies cause long-term sequelae in their later lives. We searched for clinical and histopathological features to predict the prognosis and affect treatment response, with a future goal of treatment stratification.Methods: A total of 154 GCT cases were included in the analysis. Total of 114 germinoma cases underwent measurement of tumor cell content on H-E specimen, and 82 GCT cases underwent 450K methylation analysis. 12p gain was determined on methylation-based copy number computation and FISH. Association with progression-free and overall survival (PFS/OS) was investigated. Results: The tumor cell content was widely distributed from <5% to 90% in the specimens, with a median value of 50%. Patients with a higher tumor cell content (>=50%) showed shorter PFS than those with a lower tumor cell content (<50 %) (p=0.03). In the multivariate analysis with tumor location, tumor cell content was the sole statistically significant prognostic factor (p=0.04). 12p gain was found in 25-out-of-82 cases (30%) and was more frequent in NGGCTs, particularly in cases with malignant components. The presence of 12p gain correlated with shorter PFS and OS, even with histology and tumor markers incorporated in the multivariate analysis. Among NGGCTs, 12p gain still had prognostic significance for PFS and OS. The 12p copy number status was shared among histological components in mixed GCTs. Whole-genome amplification was suggested by FISH.Conclusions: We found that tumor cell content significantly affected the prognosis of germinomas. 12p gain predicts the presence of malignant components of NGGCTs, and poor prognosis of the patients. Furthermore, 12p is likely to be an early event in the tumorigenesis of CNS GCT. These potentially open the possibility of leveraging these pathological and molecular factors in the future clinical trials when stratifying the treatment intensity.

Key words: Germ cell tumor | Tumor cell content | 12p gain

BOT-5

CHRYSANTHEMUM MORIFOLIUM EXTRACT IMPROVES DOXORUBICIN-INDUCED CARDIOMYOPATHY BY SUPPRESSING APOPTOSIS IN MOUSE HEART

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Background: Doxorubicin is widely used for the treatment of various malignant tumors. However, doxorubicin causes cumulative and dose-dependent cardiotoxicity, ranging from occult changes in myocardial structure and function to severe cardiomyopathy and congestive heart failure. Since this problem affects the QOL and survival of cancer patients, solutions for this problem are urgently needed. Recently, it has been reported that Chrysanthemum morifolium extracts (CME) have antioxidant and anti-inflammatory activities. The purpose of this study is to clarify whether CME decreases doxorubicin-induced cardiotoxicity and prevents the development of heart failure. Methods and Results: H9C2 cardiomyoblast cells were treated with CME (0.3, 1 mg/mL) for 2 hours and then stimulated with doxorubicin. After 24 hours incubation, surviving cells were evaluated by MTT assay. CME dose-dependently decreased doxorubicin-induced cardiotoxicity in H9C2 cells. Western blotting showed that CME significantly suppressed doxorubicin-induced increases in four markers of apoptosis: p53, phosphorylated p53, and cleaved caspase-9 and -3. Next, to investigate the effects of CME on doxorubicin-induced cardiomyopathy in vivo, C57BL6 mice were orally administered with CME (400 mg/kg/day) or vehicle daily from 2 days before doxorubicin treatment and then treated once intraperitoneally with doxorubicin (20 mg/kg). The survival ratio of the CME-treated group was significantly higher than that of the vehicle-treated group. Echocardiographic analysis at 7 days after doxorubicin stimulation revealed that CME had significantly improved doxorubicin-induced left ventricular systolic dysfunction. Apoptotic cells in mouse heart tissue were detected by TUNEL assay, which showed that CME significantly suppressed doxorubicin-induced apoptosis. Discussion: These results indicate that CME decreases doxorubicin-induced cardiotoxicity both in vitro and in vivo, suggesting that CME might possess the therapeutic potency to reduce doxorubicin-induced cardiotoxicity in cancer patients. Further studies are required to assess the effectiveness of CME for preventing doxorubicin-induced heart failure in clinical settings.

Key words: apoptosis | cardiomyopathy | doxorubicin

ADULT CLINICAL TRIALS/THERAPEUTIC STUDIES (ACT)

ACT-1

MULTICENTER INVESTIGATOR-INITIATED REGISTRATION-DIRECTED PHASE 2 STUDY OF E7090 IN SUBJECTS WITH ADVANCED OR RECURRENT SOLID TUMORS WITH FIBROBLAST GROWTH FACTOR RECEPTOR (FGFR) GENE ALTERATION: FORTUNE TRIAL

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Background: Genetic alterations of FGFRs are known to play an important role in the proliferation, survival, and migration of cancer cells as well as tumor angiogenesis and drug resistance. E7090 is an orally available selective tyrosine kinase inhibitor for FGFR1-3. A global Phase 2 study of E7090 in subjects with unresectable advanced or metastatic cholangiocarcinoma harboring FGFR2 gene fusion is ongoing (NCT04238715). We recently reported FGFR alterations that are highly sensitive to E7090 using a high-throughput functional evaluation method called MANO method (Nakamura et al. npj Precision Oncology, 2021), narrowing down the most promising FGFR alteration targets. Here, we designed a single-arm, open-label, investigator-initiated multicenter Phase 2 basket study to evaluate the efficacy and safety of E7090 in subjects with advanced or recurrent solid tumors harboring FGFR gene alterations, focusing on alterations identified by MANO method, as a sub-study under the nationwide large registry for rare cancers in Japan (MASTER KEY Project). Methods: The key eligibility criteria are: 1) Histologically confirmed metastatic or locally advanced solid tumor; 2) Ineffective to or intolerant to first line treatment, or for which standard treatment is no longer available; and 3) Confirmed FGFR gene alterations via next-generation sequencing assays that are reimbursed by insurance. Subjects will receive E7090 140 mg orally once daily until disease progression or development of unacceptable toxicity. The primary endpoint is objective response rate (ORR) by independent central review (RECIST v1.1), and the secondary endpoints include ORR by investigator assessment, progression-free survival, overall survival, disease control rate, safety, duration of response, and time to response. For primary brain tumors, RANO criteria is also applied in assessment of response. The study enrolls approximately 45 subjects. (Clinical Trial Registry: jRCT2031210043, ClinicalTrials.gov: NCT04962867)

Key words: FGFR | clinical trial | E7090

ACT-3

REACTOR-BASED BORON NEUTRON CAPTURE THERAPY WITH ADD-ON BEVACIZUMAB FOR RECURRENT MALIGNANT GLIOMA: THE FINAL REPORT

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Background: Re-irradiation had a higher rate of radiation injury because recurrent MG had already irradiated in the first-line treatment. Recently, combination therapy of re-irradiation and bevacizumab showed a lower incidence of radiation injury than re-irradiation alone. Boron neutron capture therapy (BNCT), a tumor-selective particle radiation therapy, also increased radiation injury for recurrent MG, despite the greater focus on tumor cells. In this study, we evaluated the efficacy of BNCT plus bevacizumab with early induction after BNCT. Methods: Patients with recurrent MG were prospectively enrolled in this study. BNCT was performed using Kyoto University Research Reactor as a neutron source. Bevacizumab of 10 mg/kg was initiated 1–4 weeks after BNCT and was

continued every 2–3 weeks until disease progression. Newly-diagnosed (de novo) glioblastoma was categorized as primary GBM (pGBM). Other MG were categorized as non-pGBM. Results: Kyoto University Research Reactor stopped irradiation for clinical use in February 2019. Twenty-five patients (14 pGBM and 11 non-pGBM) were treated with this combination therapy between June 2013 and February 2019. The median Overall survival (OS) after BNCT was 21.4 months for pGBM and 73.6 months for non-pGBM, respectively (p = 0.0428). The median progression-free survival (PFS) after BNCT was 8.3 months for pGBM and 15.6 months for non-pGBM, respectively (p = 0.0207). The objective response rate was 72 %. Alopecia occurred in all patients. Adverse events ≥ grade 3 were grade 3 proteinuria in four patients, grade 5 myocardial infarction in one patient, and grade 5 meningitis in one patient. Conclusion: BNCT plus bevacizumab showed a long OS and a long PFS, compared to our previous studies of BNCT alone for recurrent MG. Bevacizumab could provide beneficial effects not only for tumor itself, but also radiation injury. Further research with a larger sample using accelerator-based BNCT and bevacizumab is required to elucidate the efficacy and safety of this combination therapy.

Key words: bevacizumab | BNCT | glioma

ACT-5

PROGNOSIS OF IDH-MUT LOWER-GRADE GLIOMAS IN HOKKAIDO UNIVERSITY HOSPITAL

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Background: WHO grade 2 and 3 adult gliomas are nowadays getting together as lower-grade gliomas (LrGGs), but we had been recognized grade 3 (G3) tumors as high-grade and grade 2 (G2) tumors as low-grade. In this report, we investigate the treatment and prognosis of the patients with LrGG harboring IDH mutations in our institutions. Methods:We retrospectively review primary treatments and their prognosis for LrGG patients with IDH mutation since 2003. They categorized as astrocytomas and oligodendrogliomas according to 1p/19q loss-of-heterozygosity status. Prognosis were evaluated by overall survival. Postoperative primary treatments applied chemo-radiotherapy (CRT), radiotherapy only (RT), chemotherapy only (CT), and observation (Ob). Results: 36 astrocytomas and 60 oligodendrogliomas were identified. In astrocytomas, the patients with G3 (N=16) were treated by CRT (N=14) or CT (N=2), and the patients with G2 (N=20) were treated by CRT (N=2), RT (N=3), CT (N=3), or Ob (N=12). In oligodendrogliomas, the patients with G3 (N=34) were treated by CRT (N=32) or CT (N=2), and the patients with G2 (N=26) were treated by CRT (N=3), RT (N=1), CT (N=5), or Ob (N=17). 10-year survival rate (10yOS) of astrocytomas and oligodendrogliomas are 54% and 90%, respectively (p=0.002). According to histological malignancy, 10yOS of G3 and G2 astrocytomas were 54% and 54%, respectively (p=0.97) and that of G3 and G2 oligodendrogliomas were 86% and 100%, respectively (p=0.64). In both group, there are no different of prognosis according to histological malignancy. Discussion: There was no prognostic different between G2 and G3 astrocytomas in our institution. Since the treatment intensity for G2 and G3 astrocytomas were clearly different, the primary treatment for G2 astrocytomas might be insufficient. On the other hand, there were no prognostic different between G2 and G3 oligodendrogliomas in our institution, as with recent reports, so the primary treatment intensity for oligodendrogliomas should be appropriate.

Key words: lower-grade glioma | overall survival | IDH

ACT-6

CLINICAL MANIFESTATIONS OF THE PATIENTS WITH RELAPSED GLIOBLASTOMA AFTER BEVACIZUMAB TREATMENT

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Introduction:The outcome of glioblastoma (GBM) is improving recently, but still only temozolomide and bevacizumab (BEV) are recognized as the effective agents that are reimbursed in Japan. On large clinical trials, BEV prolonged progression free survival (PFS) but the remaining survival period from the relapse after BEV is only 3–5 month. On this study, we retrospectively analyzed the data of GBM patients who were treated with BEV to explore the best usage of BEV.Methods:230 patients were diagnosed as GBM and received BEV from July 2013 to March 2021 in our institution. Among them, 104 patient, whose clinical courses were followed, were included in this study. (M:F=59:45, median age was 65.5) Results:The patients were divided into three groups by when they used BEV; upfront group at first line therapy, 1st relapse group at second line, and 2nd+ relapse group at more than third line. There were 42, 35, 27 patients in each group. The median overall survival (OS) was 17.6, 24.7, 46.1 month (p<0.0001), median PFS after BEV treatment (PFSpBEV) was 8.8, 5.1, 5.0 month (p=0.2532), and the median survival after BEV treatment (OSpBEV) was 15.0, 9.9, 9.2 month (p=0.4437), respectively. There were 64 patients (22, 25, 17 in each group) who reached progressive disease (PD) after BEV. The median survival after PD (OSpBEVpPD) was 4.5, 5.8, 4.3 month (p=0.1590), respectively. Discussion:At the first onset, we use BEV only when the patients have low PS. Our results showed that OS was significantly longer when BEV was used in the later stage, but there was no significant difference in OS or PFS after BEV treatment. Especially OSpBEVpPD was 4–6 month regardless of the timing of BEV. To improve the treatment outcome of GBM, breakthrough therapy is needed in addition to optimizing the usage of BEV.

Key words: Bevacizumab | Glioblastoma | relapse

ACT-8

CURRENT STATUS AND PROSPECTS FOR THE TREATMENT OF MALIGNANT GLIOMA USING CANCER GENE PANEL TESTS

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Introduction: The cancer gene panel test was covered by insurance in June 2019. Our institution started the test in May 2020 and has experienced 10 cases, so we will report on the current status and future prospects. Methods: The subjects were 10 patients who underwent the cancer gene panel test using FoundationOne CDx. Results:The cases included 8 glioblastomas, an anaplastic astrocytoma, and an anaplastic oligodendroglioma. The total number of tumor mutational burden (TMB) was judged to be low in all cases, and the microsatellite instability test (MSI) showed no instability in all cases (MSI-Stable). The total number of genetic changes detected was 11 ± 5.0, oncogene mutations were 5.3 ± 2.4, and gene mutations of unknown relevance to cancer were 5.7 ± 2.8. Major oncogene mutations were IDH1 mutation in 4 cases, ATRX mutation in 2 cases, TP53 mutation in 6 cases, and BRAF V600E mutation in 1 case. Based on the test results, a 25-year-old man with BRAF V600E mutation was initiated into the NCCH1901 study (Patient-Proposed Healthcare Services). A case with IDH1 mutation (47-year-old male) entered a phase I clinical trial of a mutant IDH1 inhibitor. It is estimated that the chance of finding an appropriate drug by cancer gene panel test is about 10–20%. However, in cases that are resistant to standard treatment, the benefits can be expected if the drugs associated with the cancer gene panel test can be used. Conclusions: Although Malignant gliomas are often TMB-low and MSI-stable and the response rate to molecular-targeted drugs and other therapies is not high, there are some cases that can be salvaged by performing the cancer gene panel test. It is suggested that the active use of cancer gene panel test may contribute to the development of new drugs with high response rates and the improvement of prognosis.

Key words: glioma | cancer gene panel | FoundationOne CDx

PEDIATRIC CLINICAL TRIALS/THERAPEUTIC STUDIES (PEDT)

PEDT-1

INTEGRATED DIAGNOSES OF PEDIATRIC GLIOMAS IN OUR INSTITUTE BY CIMPACT-NOW RECOMMENDATIONS THE ROLE OF RADIATION AND CHEMOTHERAPY IN THE TREATMENTS OF TERATOMATOUS GERM CELL TUMORS

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Purpose:Since many genetic abnormalities in glioma have been revealed in recent years, Integrated diagnoses are necessary in the updated fourth edition of the WHO Classification of Tumors of the Central Nervous System(CNS) published in 2016. The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) was established to provide a forum to evaluate and recommend proposed changes to future CNS tumor classification. We retrospectively classified pediatric gliomas in our hospital in accordance with cIMPACT-NOW recommendations. Methods: This study includes 13 consecutive glioma patients under the age of 18 who underwent surgical resection at our hospital from 2000 to 2021. Histopathological diagnoses and molecular status such as IDH, H3F3A and BRAF were analyzed. Results: There were four females and nine