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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