ACT-16

THE POTENTIAL OF HYPOFRACTIONATED RADIOTHERAPY AND BEVACIZUMAB FOR GLIOBLASTOMA TREATMENT

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INTRODUCTION: First-line bevacizumab (BEV) is now available as a treatment option for glioblastoma (GBM) patients with severe clinical conditions in Japan. However, the survival benefits remain controversial. As we have emphasized the combined effect of BEV and radiation therapy, the strategies; 1) first-line add-on BEV to TMZ-radiation for unresectable GBMs and 2) re-irradiation using IMRT under BEV administration for recurrent GBMs, have been positively applied. To elucidate these potential survival benefits, we retrospectively analyzed survival in GBM patients. METHODS: We analyzed survival in 101 patients with IDH-wild type GBM treated from 2006 to 2018. PFS and OS were assessed in two subgroups (TMZ and TMZ-BEV eras), and the correlations of prognostic factors with survival were evaluated. RESULTS: After BEV approval, OS prolongation tendency (median OS: 14.9 vs. 22.1 months; P = 0.52) was observed, and this tendency was clearer in unresectable cases (10.1 vs 16.1 m P = 0.38). Subanalysis showed a significant prolongation of prognosis in the MGMT unmethylated group (12.2 vs 16.7 m; P = 0.04). In 10 patients of recurrent GBMs receiving BEV combined re-irradiation, adverse events of Grade 3 or higher did not occur. All patients showed PR (N=5) or CR (N=5) after treatment. The mPFS and mOS from the recurrence were 4.3 and 9.4 months, however, no local relapse was observed at their second recurrences. CONCLUSIONS: Our treatment strategy has improved the outcome of high-risk cases after BEV approval. These results implied that hypofractionated radiotherapy under BEV administration might be an efficient treatment protocol as a first-line for high-risk cases, such as after partial excision and MGMT unmethylation.

ACT-18

SHOULD THE DOSE OF TEMOZOLOMIDE BE DECREASED FOR PATIENTS WITH HIGH-GRADE GLIOMAS WHO ARE ON HEMODIALYSIS?

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BACKGROUND: The pharmacokinetics of temozolomide in patients with severe renal impairments (creatinine clearance less than 36 mL/min/m2) or in hemodialysis patients has not been investigated. Temozolomide and its metabolic products are mainly excreted in urine, as retention of these in the body may result in increased adverse events in hemodialysis patients harboring a high-grade glioma. METHODS: Eight hemodialysis patients with high-grade gliomas from seven institutions were included in the study. Patient characteristics, treatment schedule, clinical course, pathological/molecular findings, and adverse events were evaluated. RESULTS: The histopathological diagnoses were Isocitrate dehydrogenase (IDH) wild-type glioblastoma in four cases, Not other specified (NOS) glioblastoma in two cases and IDH-mutant anaplastic astrocytoma in one case. Five of the seven patients completed radiotherapy (48–60 Gy) with concomitant temozolomide (75 mg/m2) followed by adjuvant 5-day temozolomide (150 mg/m2) every 28 days. During the entire course of treatment with temozolomide, severe (Common Terminology Criteria for Adverse Events (CTCAE) more than grade 3) lymphocytopenia occurred in 57%(41.7–61%: non hemodialysis patients data, the same as below), neutropenia in 0%(1–15.4%) and thrombocytopenia in 14%(0–16.7%) of the patients. Generally, the frequency and degree of myelosuppression do not increase in hemodialysis patients with high-grade gliomas. Two of the seven (28.5%) patients died of infectious disease despite having no direct correlation to myelosuppression that is similar rate of 21.9% of the death results from infection in hemodialysis patients in Japan. CONCLUSIONS: The high-grade glioma patients under study on hemodialysis did not require decreasing doses of Temozolomide during concomitant radiochemotherapy and maintenance therapy. However, careful clinical and hematological observation is required to avoid critical hematotoxicity and infection.

ACT-21

PRIMARY EXPERIENCE OF NOVOTTF THERAPY FOR THE PATIENTS WITH GBM IN OUR INSTITUTION

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BACKGROUND: Based on EF-14 clinical trial, NovoTTF therapy prolong overall survival in the patients with GBM. However, NovoTTF treatment does not become standard therapy because treatment procedures are cumbersome and potentially impose psychological burden on patients who suffer from dismal disease. In our institution, we can choose NovoTTF therapy as one of the treatment options for GBM patients since June 2018. In this report, we summarized primary experience of this novel treatment. MATERIALS AND METHODS: Adult patients with primary GBM diagnosed after June 2018 were retrospectively reviewed. We investigated the suggestion of NovoTTF, patients' acceptance, the reason of rejection of NovoTTF, and the condition of NovoTTF treatment. RESULTS: Among 22 GBM patients, 12 cases were proposed NovoTTF treatment in actual. In 10 cases who were not proposed NovoTTF, the reasons were 1) poor performance status (KPS 50% or less); 7 cases, oldest-old; 1 case, unavailable care person; 2 cases. In 12 cases who were proposed NovoTTF, 5 cases (42%) accepted and performed this therapy. Remaining 7 cases did not accept NovoTTF because rejection of shaving hair; 1 case, troublesome for daily work; 2 cases, refusal due to cumbersome procedure; 2 cases, unavailable cooperation with care person(s); 2 cases. 5 cases treated NovoTTF were 3 males and 2 females, and the median age was 67yo (range 25yo-69yo). All patients were continued NovoTTF for 1–7 months without major complication. In two cases, minor skin trouble was observed, but easy to handle by putting ointment.

ACT-22

CLINICAL RESULT AND CONSIDERATION OF 70 CASES OF INSULAR GLIOMA

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Our policy for insular glioma has achieved more than 90% removal. The policy influence grade 2 to postpone farther treatment and grade 3 to extend prognosis. In this study, we analyzed our clinical data to be sure how this policy effect to insular glioma. First-onset tumor since 2006 to 2015 were collected and following parameters were analyzed retrospectively, such as the tumor, extension, surgical removal rate, complications, pathological and genomic diagnosis. Of all 70 cases, the average age was 41 years old (24–76). The pathological diagnosis and number of patients were DAmt 20, DAwt 1, AAmt 8, AAwt 5, AO 5, O 18. PFS of each pathological grade(2,3,4) were 55,5m, 42,6m and 4,7m, OS were nr, nr, 32,8 months. 57 cases of IDHmt showed 60,2m of PFS and n.r of OS. 10 cases of IDHwt showed 19,9m PFS and 35,8m OS. The average and median removal rate were 91.4% and 95%. The number of complication case were mild 9 and moderate 2 at 3 months after surgery. The invasion pattern from temporal stem showed that frontal base invasion cases was resulted as poor prognosis comparing with temporal or parietal extension. Number of patients with IDHwt, Oligodedroglial tumor and GBM were relatively low. Surgical complications are mainly caused in the first half of the proficiency process, 15% had paralysis due to LSA infarction. Most of grade 2 cases were treated without post-operative treatment and the prognosis was almost same as grade 3 cases which were treated by chemo and radiation therapy such as 55m, 43m of PFS and n.r of OS. AA wt and GBM showed almost same OS of 32m.We have reconsidered a new classification based on temporal stem extension from surgical point of view. Insular glioma is somewhat different from the other location glioma.

ACT-25

CLINICAL TRIALS BY THE JCOG BRAIN TUMOR STUDY GROUP

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Ongoing brain tumor clinical trials by the Japan Clinical Oncology Group (JCOG) are:JCOG1016, phase III randomized study in patients with anaplastic glioma of radiotherapy with temozolomide versus nimustine hydrochloride (ACNU) followed by temozolomide, is to prove superiority of post-operative radiotherapy with ACNU. JCOG1114, phase III study of high-dose methotrexate and whole brain radiotherapy with or without concomitant and adjuvant temozolomide in patients with primacy CNS lymphoma, is to prove usefulness and get insurance approval of TMZ for primary CNS lymphoma. JCOG1303, randomized phase III study for unresectable WHO Grade II diffuse astrocytoma with radiotherapy alone or chemoradiotherapy with temozolomide, is to prove superiority of STUPP regimen over simple radiotherapy for newly diagnosed and unresectable diffuse astrocytoma. JCOG1308, a multicenter randomized phase III study for recurrent glioblastoma comparing bevacizumab alone with dose-dense temozolomide followed by bevacizumab, is to prove usefulness of dose-dense, 7 days on/7 days off, TMZ, and to approve insurance coverage for recurrent GBM. JCOG1703, a multicenter randomized phase III study for newly-diagnosed maximally resected glioblastoma comparing carmustine wafer implantation followed by Stupp regimen with Stupp regimen alone, is to prove the survival advantage of surgery of GBM using carmustine wafer.