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CTNI-43: A PHASE 1/2 STUDY OF LOW DOSE FRACTIONATED RADIATION THERAPY AS A CHEMOPOTENTIATOR OF SALVAGE TEMOZOLOMIDE FOR HIGH-GRADE GLIOMA

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Cell-survival curves demonstrate low-dose radiation hypersensitivity, with steepest cell kill at 0.3-0.5 Gy/fx. This phase 1/2 study assessed the safety/efficacy of low-dose fractionated radiotherapy (LDFRT) as a chemopotentiator of TMZ in recurrent glioblastoma or anaplastic astrocytoma (AA) patients. Patients with recurrent glioblastoma/AA following standard-of-care therapy, > 12 months from prior RT and >2 months from prior TMZ were eligible for 0.5 Gy RT twice daily x10 fractions with concurrent TMZ (150-200 mg/m2), both delivered in 5 days of a 28-day cycle up to 6 cycles, followed by 6 cycles of adjuvant TMZ. In phase 1, hematologic toxicity was assessed 1 month after initiating therapy. Brain MRIs were obtained every 2 months, or monthly when concerned for progression (defined by RANO criteria). Pseudoprogression consisted of MRI changes irrespective of clinical deterioration/steroid use that stabilized/reversed without oncologic intervention. The primary endpoint, 1-year overall survival (OS), would be considered for future investigation with a lower bound of 80% CI > 28%, chosen from historical data. Secondary endpoints included rates of pseudoprogression and hematologic toxicity. 31 patients were enrolled/analyzed. Grade 3-4 acute
hematologic toxicity was observed in 8(27%) patients. Median follow-up was 9.5(range:0.1-66.3) months. Median OS was 9.6(95%CI 7.0-15.4) months, 1-year OS was 34.5%(95%CI 20.9%-57.0%); lower bound of 80%(CI = 24.8%). 77% of patients experienced pseudoprogression, with a median time from start of LDFRT of 1.9(95%CI 1.7-4.4) months and median duration of 3.6(95%CI 1.6-Not estimable) months. Patients with pseudoprogression had improved OS vs. those without (N = 6; median 10.6 vs 3.9 months, HR = .12[95%CI .03-.40];P < .01). LDFRT for recurrent glioblastoma/AA was safe. High pseudoprogression rates were observed at low RT doses, with improved OS amongst patients with pseudoprogression. LDFRT with TMZ may elicit low-dose RT hypersensitivity in patients with glioblastoma/AA. Further study is needed to optimally apply this radiobiological property to improve clinical outcomes.