INTRODUCTION: Mounting evidence demonstrates the therapeutic promise of immunotherapies (ITs) for brain metastases (BM). However, there is concern that stringent eligibility criteria in these clinical studies have skewed results against patients with comorbidities. As a result, there remains unclear if these results are truly applicable to the general population, particularly in individuals with end-stage renal disease (ESRD) on dialysis. Therefore, we sought to determine the impact of concomitant dialysis treatment and TMZ on overall survival (OS) of patients with BM. METHODS: Data were collected from TriNetX (TriNetX, Inc., Cambridge, MA), a global research network that aggregates clinical data from 92 healthcare organizations. Independent variables included ‘secondary malignant neoplasm of brain’, ‘pneumolymph’, ‘ESRD’, ‘dependence on renal dialysis’, and ‘dialysis services and procedures’. Patients with BM receiving IT were dichotomized by dialysis use. Cohorts were propensity matched on age, gender, and race. Kaplan-Meier analyses and log rank tests were conducted to assess overall survival (OS) and survival probability over a five-year period. RESULTS: Of the 14,306 confirmed BM patients treated with IT, 95 (6.6%) began dialysis within three months of IT initiation. Propensity matching established 95 patients in each cohort. The dialyzed cohort had a median OS of 277 days with a survival probability of 11.6%, compared to the non-dialyzed group with a median OS of 419 days and survival probability of 40.29% (p=0.109; hazard ratio 1.422, 95% confidence interval, 0.923-2.191, p=0.891). A separate comparison cohort was created to compare ESRD diagnosis with or without dialysis (n=56 and n=106 respectively). The comparison cohorts did not show a difference in median OS and survival probability (p=0.49). CONCLUSION: Despite their health complexities, individuals with ESRD, with or without dependence on dialysis, may nonetheless derive a similar survival benefit from ITs. Therefore, we advocate for greater inclusion of patients with advanced comorbidities in clinical trials to assess for real-world safety and efficacy outcomes.

CSN02012001 STUDY: A PHASE III TRIAL ON ADJUVANT TEMOZOLOMIDE CHEMOTHERAPY WITH OR WITHOUT INTERFERON-ALPHA IN NEWLY DIAGNOSED HIGH-GRADE GLIOMAS

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PURPOSE: The therapeutic efficacy and toxicity of the combination of temozolomide (TMZ) with interferon-alpha (IFN-α) and TMZ alone were evaluated in newly diagnosed high-grade glioma (HGG) patients. PATIENTS AND METHODS: Following surgery, patients with newly diagnosed HGG were eligible and randomized into two groups. All the patients received standard radiotherapy concurrent with TMZ. After 4 weeks' break, patients in group A received standard TMZ (200mg/m² for 5 days) combined with interferon-α (3mIU, subcutaneous, d1, d3, and d5) every 28 days. Patients in group B received standard TMZ. RESULTS: A total of 199 HGG patients were enrolled, with a median follow-up time of 77.9 months. The median overall survival (OS) of patients in the TMZ+IFN group was significantly longer than that in the standard group (TMZ+IFN: 26.67 months, TMZ: 18.83 months, P=0.044). TMZ+IFN also significantly improved the OS in O6-methylguanine-DNA methyltransferase (MGMT) unmethylated patients (TMZ+IFN: 24.33 months) than that in the TMZ group (14.13 months) (P=0.001). In grade 4 gliomas, the difference in PFS survival between TMZ+IFN and TMZ group showed no significant difference (TMZ+IFN:12.00 months, TMZ:12.83 months, P=0.582). However, the TMZ+IFN group had a longer OS than that of the TMZ alone group (TMZ+IFN:20.53 months, TMZ:17.70 months, P=0.044). TMZ+IFN also significantly improved the OS in MGMT promoter unmethylated GBM. Stage 1 was a dose-escalation phase to confirm the dose of TMZ+IFN in this setting. Patients received TMZ at 20, 30, or 40 mg/m²/day x 3 days every 21 days in combination with standard radiation treatment (RT) (2 Gy/day, 5 days/week for 6 weeks). Stage 2 was an expansion phase to enroll up to 20 additional patients at the 30 mg/m²/day of TMZ with RT. A total of 29 patients were enrolled in the study and completed treatment, with 25 patients receiving 30 mg/m²/day TMZ+IFN. The median number of cycles completed by patients was 9 (range 1-18). Consistent with our previous experience, myelosuppression was the most common adverse event. Pharmacokinetics (Cmax and AUC) of TMZ+IFN were broadly linear with respect to dose, and drug half-life was 0.8 hrs. In a sub-group of patients, levels of TMZ+IFN were found to be at least as high as those in plasma. The median progression free survival (PFS) for all patients enrolled was 9.3 (95% CI: 6.4-12.0) months. Eighteen (18/29; 62.1%) patients have died, and median overall survival for all patients enrolled was 19.6 (95% CI: 14.0-22.4) months. These results support the potential benefit of TMZ+IFN as a treatment alternative against GBM tumors with MGMT-mediated resistance to TMZ.

SYST-12

D2C7 CAR: A NOVEL CAR T CELL THAT SIMULTANEOUSLY TARGETS WILDCOY EGR AND ITS MUTANT ISOFORM EGRFVIII FOR TREATMENT OF GLIOMA AND BRAIN METASTASES

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INTRODUCTION: Chimeric antigen receptor (CAR) T-cells represent a classical radiation of immunotherapy, achieving considerable success in hematological cancers but generally failing to control solid tumors, including gliomas, partly due to the lack of a ubiquitously-expressed target antigen. In this study, we engineered a novel CAR T-cell consisting of the D2C7 scfv targeting moiety that binds a shared epitope between EGFR and EGRFVIII. EGRFVIII is the most homogeneous antigen on glial brain tumors, and the mutant EGFR variant, EGRFVIII, is present on a considerable subset of high grade gliomas, CAR T-cells targeting EGFRFVIII alone fail to treat tumors possessing as few as 5-10% EGRFVIII-negative cells. Thus, D2C7 CAR is expected to be superior to the EGRFVIII CAR. METHODS: We retrovirally transduced T-cells with a vector encoding the D2C7 scfv in tandem with intracellular signaling domains of CD28, 4-1BB, and CD3ζ to generate D2C7 CAR. We co-transduced D2C7 CAR or Mock CAR with fluorescently-taged tumor cells expressing either EGRFVIII or EGRFVIII II to validate efficacy and specificity by flow cytometry. To determine in vivo efficacy, EGRFVIII or EGRFVIII -expressing tumors were implanted intracranially in immunodeficient NSG mice. 48 hours later, D2C7 CAR, Mock CAR, or Mock CAR with EGRFVIII were administered intracranially and mice were monitored for survival. RESULTS: D2C7 CAR significantly killed tumor cells that expressed either EGRFVIII or EGRFVIII II, but not cells that lacked EGRFVIII. Intracranial D2C7 CAR administration resulted in significantly prolonged survival of mice bearing EGRFVIII or EGRFVIII II tumors compared to Mock CAR controls. Importantly, D2C7 CAR significantly benefitted mice bearing a heterogeneous mix of EGRFVIII and EGRFVIII II tumors, a model of tumor heterogeneity. CONCLUSIONS: D2C7 CAR is effective against EGRFVIII or EGRFVIII II heterogeneous tumors. Intracranial administration of D2C7 CAR is predicted to safely and effectively treat a large cohort of patients due to the relatively high prevalence of EGRFVIII and/or EGRFVIII II-expressing brain tumors.