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Short-course hypofractionated proton beam therapy, incorporating ^{18}F-DOPA PET and contrast-enhanced MRI targeting, for patients aged 65 years and older with newly diagnosed glioblastoma: a single-arm phase 2 trial

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Abstract

Background: Older patients (aged ≥65 years) with glioblastoma have a worse prognosis than younger patients and a median overall survival of 6-9 months. 3,4-Dihydroxy-6-[^{18}F]fluoro-L-phenylalanine (^{18}F-DOPA) PET sensitively and specifically identifies metabolically active glioblastoma for preferential targeting. Proton beam therapy potentially improves quality of life (QOL) by sparing more healthy brain tissue than photon radiotherapy. With improved targeting and the dosimetric advantages of proton beam therapy, we aimed to test whether hypofractionated proton beam therapy could improve survival and QOL in older patients with glioblastoma.

Methods: In this single-arm phase 2 trial, we enrolled patients aged 65 years and older with an Eastern Cooperative Oncology Group performance status score of 0-2 and newly diagnosed WHO grade 4, malignant glioblastoma from two Mayo Clinic campuses (Phoenix, AZ, and Rochester, MN, USA). Radiotherapy target volumes were defined by ^{18}F-DOPA PET and MRI regions of contrast enhancement. Patients were given dose-escalated hypofractionated proton beam therapy (35-40 Gy equivalents in five or ten treatments) plus oral concurrent temozolomide (75 mg/m^2 daily on days 1-7 for the five-treatment regimen or on days 1-14 for the ten-treatment regimen), and 1 month after completing radiotherapy patients were given adjuvant temozolomide (150-200 mg/m^2 on days 1-5 for six 28-day cycles). The primary endpoint was overall survival at 12 months after enrolment. The primary endpoint and safety were assessed in the intention-to-treat population (defined as all eligible patients who started radiotherapy). This study is registered with ClinicalTrials.gov, NCT03778294, and is now complete.

Findings: Between May 22, 2019, and May 25, 2021, 43 patients were enrolled, of whom four did not receive treatment because of progression (n=2), death (n=1), or insurance denial (n=1), such that 39 patients received treatment (median age 70·2 years [IQR 67·4-74·3]; 11 [28%] of 39 patients were female, 28 [72%] were male, 37 [95%] were White, one [3%] was Black or African American, and one

chose not to disclose their race). As of data cutoff (Jan 30, 2024), median follow-up was 25·4 months (IQR 22·1-29·7). 22 (56% [95% CI 39-72]) of 39 patients were alive at 12 months. Median overall survival was 13·1 months (95% CI 11·1-19·1). Grade 3 baseline-adjusted, treatment-associated adverse events were CNS necrosis (four [10%] of 39) and thrombocytopenia (one [3%]). No baseline-adjusted, treatment-associated grade 4 adverse events or deaths occurred.

Interpretation: We observed improved overall survival compared with historical controls and a promising adverse event profile by using ^{18}F-DOPA PET-guided, dose-escalated, hypofractionated proton beam therapy. These findings have resulted in the opening of a phase 2 study (NCT05781321) investigating this regimen versus standard-of-care treatment in adults of any age with newly diagnosed glioblastoma.

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