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International Journal of Radiation Oncology*Biology*Physics

Available online 8 March 2025

In Press, Journal Pre-proof What's this?

Brief Report

A phase II study of multiparametric MR-guided high-dose response-adaptive radiotherapy with concurrent temozolomide in patients with newly diagnosed glioblastoma: Results from an interim analysis

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https://doi.org/10.1016/j.ijrobp.2025.02.020

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Abstract

Background

Biologically-informed radiotherapy (RT) targeting an adversely prognostic hypercellular/hyperperfused imaging phenotype in patients with newly diagnosed glioblastoma (GBM) may improve outcomes by identifying emerging regions of treatment resistance associated with survival (OS), and is under investigation in an ongoing Phase II trial (XXX) of individualized, response-adaptive RT.

Methods

In this single-arm phase II study, patients with newly diagnosed GBM following resection undergo dose-intensified chemoradiation (chemoRT) targeting the residual hypercellular (TV_{HCV}, 2 SD above mean intensity contralateral normal brain) and hyperperfused tumor volume (TV_{CBV}, 1 SD above contralateral normal frontal lobe grey matter) identified using high b-value diffusion-

weighted and dynamic contrast-enhanced perfusion MRI. The combination of TV_{HCV} and TV_{CBV} (TV_{HCV}/TV_{CBV}) is treated to 50 Gy in 20 fractions (2.5 Gy/fraction), and following mid-RT reassessment, the persistent and developing TV_{HCV}/TV_{CBV} is treated to 30 Gy in 10 fractions (3 Gy/fraction). The primary endpoint is improvement in OS, with planned interim safety analysis.

Results

At interim analysis, 16 of 30 patients were enrolled. Median age was 58 years (range, 29-75) and 69% were male. No patient underwent biopsy only, and 50% had gross total resection; 19% had MGMT methylated tumors. Median TV_{HCV}/TV_{CBV} was 6.9 cc (range, 1.9-42.8) pre-RT and 30% (range, 1-72%) was nonenhancing. By mid-RT, TV_{HCV}/TV_{CBV} was reduced to 4.2 cc (range, 0.8-34.3) and 47% (range, 3-74%) was nonenhancing. The TV_{HCV}/TV_{CBV} persisting from pre- to mid-RT was 2.3 cc (range, 0-24.2), with an additional 1.8 cc (range, 0.3-20.6) newly developing outside of the initial region. All patients underwent adaptive replanning for boost without interruption. Planned interim analysis determined an acceptable rate of neurologic toxicity and safety to continue enrollment.

Conclusion

Individualized, response-adaptive chemoRT using an advanced imaging biomarker to assess emerging and especially non-enhancing regions of treatment resistance in patients with GBM is feasible, with short term safety and longer-term efficacy outcomes anticipated with completion of accrual.

Introduction

Glioblastoma (GBM), the most common and lethal primary brain tumor in adults, almost invariably recurs despite maximal surgery and chemoradiation (chemoRT).[1] Key biologic properties identified by advanced imaging techniques have long been recognized to predict outcome better than anatomic magnetic resonance imaging (MRI), but as of yet, no such imaging biomarker has been integrated into standard treatment for this disease.[2] The development of imaging biomarkers enabling spatial identification and temporal monitoring of a therapy resistant phenotype prior to, during and after treatment is a key step towards improving outcomes in patients with GBM.

In our prior investigations of a multiparametric MR imaging signature incorporating high b-value (b=3000 s/mm^2) diffusion-weighted (DW) MRI and dynamic contrast enhanced (DCE) perfusion MRI, we determined that the combination of these imaging techniques identified largely distinct non-overlapping tumor regions that spatially predict eventual tumor progression better than either technique alone, and nearly always contain treatment-resistant disease that will progress.[3,4] Moreover, the adversely prognostic hypercellular tumor regions (identified with high b-value DW-MRI) and hyperperfused tumor regions (identified with DCE perfusion MRI) were often non-enhancing and not included in standard of care boost tumor volumes. Quality assurance and end-to-end testing of image acquisition and processing enabled the accuracy and

reproducibility required for clinical use on trial.[5] In a phase II single-arm study implementing this multiparametric imaging signature as an integral biomarker to guide patient-specific dose-intensified radiotherapy (RT), we observed favorable survival rates and reduced in-field recurrences.[6] However, patients with suboptimal response in this advanced imaging signature during the course of RT had worse OS, independent of O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, extent of resection, and age.[7]

In the present phase II clinical trial (XXX), we hypothesize that a hyperperfused/hypercellular MRI signature identifying treatment resistant tumor regions before and during radiation therapy can be targeted with response-adaptive, dose-intensified chemoRT to improve survival in patients with GBM. We report the results of the planned interim safety analysis of this ongoing study.

Section snippets

Brief eligibility criteria

This phase II, single-institution, single arm trial was approved by the institutional review board and registered at ClinicalTrials.gov. Informed consent was required and obtained for all patients. Adult patients with newly diagnosed, histologically-confirmed supratentorial WHO grade IV glioma were eligible. The combined hypercellular tumor volume (TV_{HCV}) and hyperperfused tumor volume (TV_{CBV}) for this study was required to be less than 5 cm in longest diameter. Patients unable to undergo MRI …

Patient characteristics

Between October 2020 to March 2022 at the time of interim analysis, 16 of a planned 30 patients were enrolled (4 additional patients enrolled by 6 months after the 12^{th} patient completed RT). The median age was 58 (range 29-75), 8 (50%) underwent gross total resection, and 3 (19%) patients had MGMT promoter methylated tumors. The majority (63%) were of recursive partitioning analysis (RPA) class IV (Table 1). …

Imaging volumes

No breaks for adaptive replanning occurred. The median combined pre-RT TV_{HCV} and TV_{CBV} …

Discussion

Individualized, response-adaptive chemoRT using an advanced imaging biomarker to assess emerging and especially non-enhancing regions of treatment resistance in patients with GBM is feasible, with short term safety demonstrated in the scope of this planned early interim analysis, and longer-term efficacy outcomes anticipated with completion of accrual. To our knowledge,

this is the first clinical trial in patients with glioblastoma utilizing an integral imaging biomarker to individualize …

Funding

This study was supported in part by NIH P01 CA059827, Cancer Center Support Grant P30 CA046592, and Michigan Pandemic Research Recovery Grant …

Disclosures

Michelle Kim is supported by NIH/NCI R50CA276015 and reports research funding from Blue Earth Diagnostics; Denise Leung reports honoraria from Spectrum Health System and participation on the Advisory Board of Servier Pharmaceuticals; Wajd Al-Holou reports consulting fees from Servier Pharmaceuticals; Daniel Wahl reports grants from NIH/NINDS/NCI, Sontag Foundation, V Foundation, Rogel Cancer Center, Damon Runyon Cancer Foundation, IVY Foundation, consulting fees from Bruker Inc, Servier Inc, …

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