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CLINICAL INVESTIGATION **Brain**

PHASE I TRIAL OF HYPOFRACTIONATED INTENSITY-MODULATED RADIOTHERAPY WITH TEMOZOLOMIDE CHEMOTHERAPY FOR PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME

Changhu Chen, M.D.,* Denise Damek, M.D.,† Laurie E. Gaspar, M.D., M.B.A.,* Allen Waziri, M.D.,‡ Kevin Lillehei, M.D.,‡ B. K. Kleinschmidt-DeMasters, M.D.,§ Monica Robischon, R.N.,* Kelly Stuhr, M.S.,* Kyle E. Rusthoven, M.D.,* and Brian D. Kavanagh, M.D., M.P.H.*

Departments of *Radiation Oncology, †Neurology, ‡Neurosurgery, and §Pathology, University of Colorado School of Medicine, Aurora, CO

Purpose: To determine the maximal tolerated biologic dose intensification of radiotherapy using fractional dose escalation with temozolomide (TMZ) chemotherapy in patients with newly diagnosed glioblastoma multiforme.
Methods and Materials: Patients with newly diagnosed glioblastoma multiforme after biopsy or resection and with adequate performance status, bone marrow, and organ function were eligible. The patients underwent postoperative intensity-modulated radiotherapy (IMRT) with concurrent and adjuvant TMZ. All patients received a total dose of 60 Gy to the surgical cavity and residual tumor, with a 5-mm margin. IMRT biologic dose intensification was achieved by escalating from 3 Gy/fraction (Level 1) to 6 Gy/fraction (Level 4) in 1-Gy increments. Concurrent TMZ was given at 75 mg/m^2/d for 28 consecutive days. Adjuvant TMZ was given at 150–200 mg/m^2/d for 5 days every 28 days. Dose-limiting toxicity was defined as any Common Terminology Criteria for Adverse Events, version 3, Grade 3-4 nonhematologic toxicity, excluding Grade 3 fatigue, nausea, and vomiting. A standard 3+3 Phase I design was used.
Results: A total of 16 patients were accrued (12 men and 4 women, median age, 69 years; range, 34–84. The median Karnofsky performance status was 80 (range, 60–90). Of the 16 patients, 3 each were treated at Levels 1 and 2, 4 at Level 3, and 6 at Level 4. All patients received IMRT and concurrent TMZ according to the protocol, except for 1 patient, who received 14 days of concurrent TMZ. The median number of adjuvant TMZ cycles was 7.5 (range, 0–12). The median survival was 16.2 months (range, 3–33). One patient experienced vision loss in the left eye 7 months after IMRT. Four patients underwent repeat surgery for suspected tumor recurrence 6–12 months after IMRT; 3 had radionecrosis.
Conclusions: The maximal tolerated IMRT fraction size was not reached in our study. Our results have shown that 60 Gy IMRT delivered in 6-Gy fractions within 2 weeks with concurrent and adjuvant TMZ is tolerable in selected patients with a T_1-weighted enhancing tumor <6 cm. © 2011 Elsevier Inc.

Glioblastoma multiforme, GBM, Intensity-modulated radiotherapy, IMRT, Chemoradiotherapy, Hypofractionation.

INTRODUCTION

The current standard treatment of glioblastoma multiforme (GBM) is maximal safe surgical resection followed by radiotherapy (RT) with concurrent and adjuvant temozolomide (TMZ) chemotherapy (1, 2). Generally, a total radiation dose of 60 Gy is given within 6 weeks, delivering 2 Gy/daily fraction. Although in a Phase III study, the addition of TMZ to RT increased overall survival by 2.5 months, the 2-year progression-free survival rate remained at only 11% (3). The vast majority of patients die of their disease owing to local tumor persistence or recurrence.

Increasing the radiation dose is an intuitively appealing strategy to explore in an effort to increase the local tumor control. Using a three-dimensional conformal RT technique, investigators at the University of Michigan performed a prospective trial in which the radiation dose was escalated to 90 Gy with conventional fractionation. No significant toxicities were observed (4). More recently, the Radiation Therapy Oncology Group demonstrated, in a large Phase I study (Radiation Therapy Oncology Group 98-03), that radiation dose escalation from 66 to 84 Gy in 2-Gy fractions was well tolerated with carmustine. Acute and late Grade 3-4 RT-related

Reprint requests to: Changhu Chen, M.D., Department of Radiation Oncology, University of Colorado School of Medicine, 1665 Aurora Court, Suite 1032, Mail Stop F-706, Aurora, CO 80045. Tel: (720) 848-0116; Fax: (720) 848-0222; E-mail: changhu.chen@ucdenver.edu

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toxicities did not substantially increase with dose escalation (5). However, the radiation dose escalation with conventional fractionation did not appear to increase either local tumor control or overall survival.

The biologically effective dose (BED) of radiation increases with either the increasing total radiation dose or an increasing fractional radiation dose, with the total dose held constant (hypofractionation). In addition to the possible advantages compared with conventional fractionation in terms of the increased BED, hypofractionation can also be more convenient for the patient, because the overall treatment time is decreased.

The present study was a radiation dose-per-fraction escalation trial to evaluate the feasibility of escalating the radiation fraction size to greater than the conventional 2 Gy/fraction. All patients received 60 Gy of intensity-modulated RT (IMRT) with the fractional dose increased in each sequential cohort. The primary objective of the present study was to assess the maximal tolerated biologic dose-intensification IMRT, given with standard concurrent and adjuvant TMZ.

METHODS AND MATERIALS

The present trial was a prospective Phase I radiation dose-per-fraction escalation study. The University of Colorado institutional review board approved the study, and the trial was registered with ClinicalTrials.gov (NCT00792012).

Eligibility

The eligible patients were ≥18 years old and were required to have histopathologically confirmed GBM. The Karnofsky performance status had to be ≥60, with estimated survival of ≥3 months. The tumor could be supra- or infratentorial in location but could not involve the brainstem. Surgery was required before enrollment. Postoperative, pre-IMRT, brain magnetic resonance imaging (MRI) within 28 days of surgery was mandatory. The surgical cavity plus the T_1-weighted enhancing residual tumor had to be ≤6 cm in the greatest diameter. Multifocal tumor was allowed, but the combined largest diameter of the T_1-weighted enhancing tumor plus the surgical cavity was required to be ≤6 cm. Placement of carmustine wafers at surgery was allowed. Patients could not have received previous TMZ chemotherapy or brain RT. Also, all patients had to have normal liver, kidney, and bone marrow function. All patients signed an institutional review board-approved study-specific informed consent form.

IMRT technique

The IMRT was started within 8 weeks after surgery. Patients were immobilized using an Aquaplast mask (WFR-Aquaplast/Qfix System, Avondale, Pennsylvania). Computed tomography simulation with a 3-mm slice thickness was performed on all patients. Simulation computed tomography and pre-RT brain MRI fusion was performed for target delineation. IMRT with a simultaneous integrated boost was used to deliver a differential radiation dose to different targets. The gross tumor volume was defined as the contrast-enhancing residual tumor on the T_1-weighted pre-RT brain MRI scan plus the entire surgical cavity. The clinical tumor volume was defined as the T_2-weighted abnormality on T_2-weighted brain MRI. Planning target volume 1 (PTV1) was defined as the gross tumor volume plus a 5-mm margin, and PTV2 was defined as the clinical tumor volume plus a 5-mm margin.

All IMRT plans were optimized by forward or inverse planning to ensure maximal dose conformity and rapid dose falloff toward the critical structures (Fig. 1). IMRT was delivered with 6- and/or 10-MV photons, using either multiple static beams or modulated

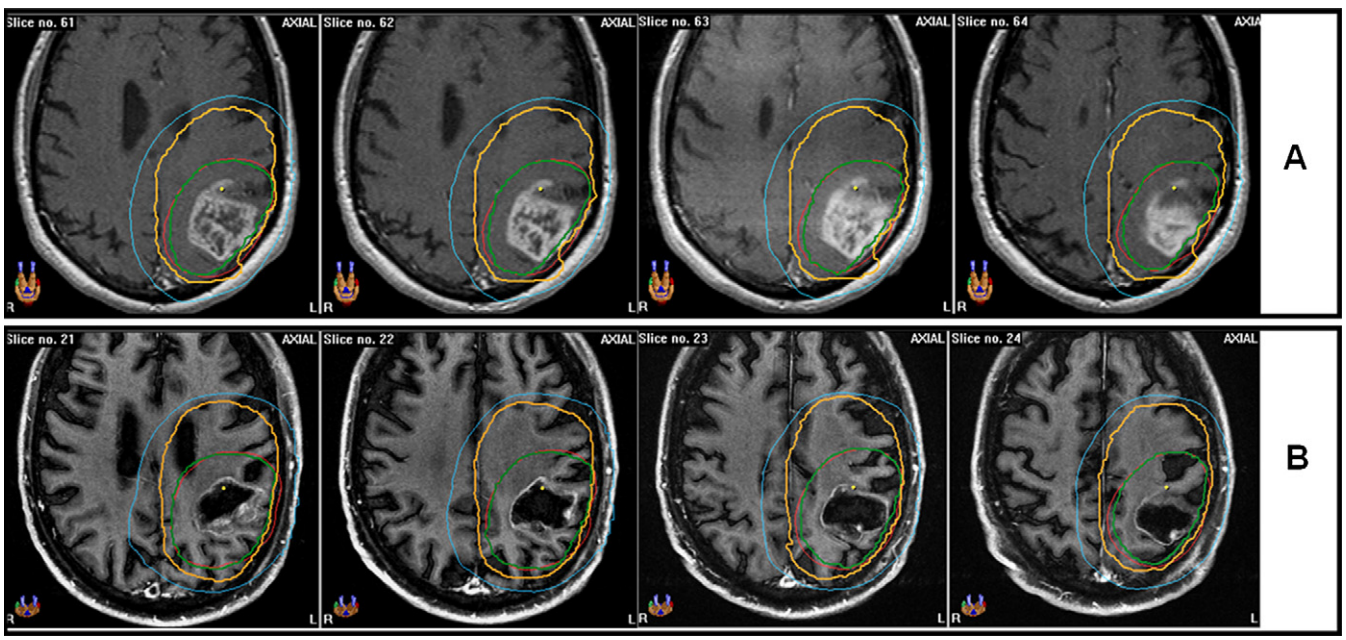

Fig. 1. T_1-weighted contrast-enhanced magnetic resonance image from a patient with needle biopsy-proven glioblastoma. Patient declined craniotomy and was treated at Level 4 (60 Gy in 6-Gy fractions within 2 weeks). Planning target volumes 1 (PTV1; dark green) and 2 (PTV2; brown) outlined; 30-Gy (red) and 60-Gy (cyan) isodose lines also shown. (A) Treatment planning magnetic resonance image with 3-mm slice thickness. (B) Follow-up magnetic resonance image with 5-mm slice thickness performed 3 months after radiotherapy.