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CLINICAL INVESTIGATION **Central Nervous System Tumor**

SEMICONTINUOUS LOW-DOSE-RATE TELETHERAPY FOR THE TREATMENT OF RECURRENT GLIAL BRAIN TUMORS: FINAL REPORT OF A PHASE I/II STUDY

Malika L. Siker, M.D.,* Selim Y. Firat, M.D.,* Wade Mueller, M.D.,†
Hendrikus Krouwer, M.D., Ph.D.,†‡ and Christopher J. Schultz, M.D.*†

Departments of *Radiation Oncology, †Neurosurgery, and ‡Neurology, Medical College of Wisconsin, Milwaukee, WI

Purpose: Semicontinuous low-dose-rate teletherapy (SLDR) is a novel irradiation strategy that exploits the increased radiosensitivity of glial cells in a narrow range of reduced dose rate. We present the final report of a prospective Phase I/II study testing the feasibility of SLDR for the treatment of recurrent gliomas.
Methods and Materials: Patients with previously irradiated recurrent gliomas were enrolled from November 1993 to March 1998. Patients received SLDR, delivered 6 to 8 hours/day at a dose rate of 40 to 50 cGy/hour for a total dose of 30 to 35 Gy given over 12 days using a modified cobalt-60 treatment unit. Acute central nervous system toxicity after SLDR treatment was the primary endpoint. Overall survival was a secondary endpoint.
Results: Twenty patients were enrolled (14 World Health Organization Grade 4 glioma, 5 Grade 2 glioma, 1 ependymoma). No patients developed ≥Grade 3 central nervous system toxicity at 3 months without radiographic evidence of tumor progression. Overall survival after SLDR was 56% at 6 months, 28% at 12 months, and 17% at 24 months. One patient survived >48 months, and 1 patient survived >60 months after SLDR treatment. Re-resection before SLDR treatment significantly improved 1-year overall survival for all patients and patients with Grade 4 glioma.
Conclusion: The delivery of SLDR is feasible in patients with recurrent gliomas and resulted in improved outcomes for patients who underwent re-resection. There were 2 long-term survivors (>48 months). This pilot study supports the notion that reduced dose rate influences the efficacy and tolerance of reirradiation in the treatment of recurrent gliomas. © 2012 Elsevier Inc.

Low-dose-rate radiotherapy, Recurrent gliomas, Reirradiation, Glioblastoma, Resection.

INTRODUCTION

Despite advances in multimodal therapy, most patients with high-grade gliomas develop local recurrence within 12 to 18 months of completing initial treatment (1). Salvage treatment strategies including re-resection, chemotherapy, targeted biologic agents, and reirradiation have all been evaluated (2–15). Although some of these modalities have been reported to be technically feasible and tolerable, improvements in survival compared to historical outcomes have been modest, with median survival less than 1 year after retreatment. The majority of glial recurrences occur within or near the previously irradiated volume, making retreatment with radiotherapy technically difficult and historically contraindicated because of the increased risk of developing radionecrosis (11). Conformal external beam radiation, brachytherapy, and stereotactic radiosurgery have been investigated as salvage therapies for recurrent glioma. These techniques have proved to be safe in carefully selected patients. Limited effective salvage options exist for most patients.

Brachytherapy has been commonly used for treatment of recurrent glioma, and improved median survival has been reported by some institutions compared to historical outcomes (15–22). The efficacy and tolerance of brachytherapy have been attributed to superior dose distribution. An alternative explanation suggests that protracted low-dose-rate (LDR) irradiation is biologically distinct compared to short-term high-dose-rate fractionated irradiation (23). Specifically, protracted LDR radiotherapy may favorably capitalize on a greater capacity of normal tissues to repair radiation-induced sublethal damage compared to tumor, thereby widening the therapeutic ratio. Cell cycle effects, which may include synchronization of tumor cells into sensitive regions of the cell cycle induced by protracted LDR radiotherapy, may also contribute to an improved therapeutic ratio (24, 25). An inverse dose effect, defined as an increase in cell killing within a narrow range of decreasing dose rate resulting in

Reprint requests to: Christopher J. Schultz, M.D. Department of Radiation Oncology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA. Tel: (414) 805-4480; Fax: (414) 805-4369; E-mail: cschultz@mcw.edu

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hyperradiosensitivity, has been identified at approximately 40 cGy/hour, as demonstrated by *in vitro* studies with human glioma cell lines (24–27). Based on these observations, actively proliferating glial tumors may be preferentially more radioresponsive to continuously delivered LDR irradiation than the surrounding quiescent normal brain.

In distinction to other LDR salvage approaches such interstitial or intracavitary (Gliasite) brachytherapy, the delivery of protracted semicontinuous LDR teletherapy (SLDR) in theory is not restricted by treatment volume or tumor location. As such, SLDR would be aptly suited to address the common clinical scenario of large, often diffuse recurrent gliomas. To test the feasibility and tolerability of protracted SLDR, we conducted a prospective Phase I/II study testing the use of SLDR for the treatment of recurrent gliomas. In this report, we present the final, long-term results.

METHODS AND MATERIALS

Initiated in November 1993 and closed in March 1998, this trial was a prospective Phase I/II study of SLDR that aimed to assess the feasibility, acute toxicity, and outcomes of patients with recurrent glial tumors treated with SLDR after previous conventional therapy. It was approved by the Medical College of Wisconsin Institutional Review Board.

Eligibility

Patients needed to be 18 years or older with prior histologically confirmed primary glioma. All patients must have previously received definitive treatment that included cranial irradiation, with or without chemotherapy or resection. All patients had to have pathologically confirmed and/or clinical evidence of recurrence. A neurologic function status (NFS) of 1, 2, or 3 and life expectancy longer than 3 months were required. All patients had to undergo a neurosurgical consultation to consider resectability of the recurrence and neurooncologic consultation to investigate other salvage therapy.

The following patients were not eligible: patients who had recurrent tumors involving the cerebellum, midbrain, pons, or medulla; patients who were to receive standard fractionated external beam reirradiation or systemic therapy during or within 3 months after SLDR treatment; and patients who received systemic therapy within 1 month before treatment or irradiation less than 3 months before treatment.

Pretreatment evaluations

All patients were initially evaluated clinically with neurologic history and physical examination and radiographically with computed tomography (CT) and/or magnetic resonance imaging (MRI) with contrast medium obtained within 4 weeks before starting treatment. The NFS, Mini-Mental State Examination scores, steroid doses, and Karnofsky Performance Score (KPS) were recorded as part of the neurologic history and physical examination.

Radiation therapy technique

The dose rate of 40 to 50 cGy per hour was chosen because this dose rate resulted in an inverse dose rate effect for several experimental tumor lines (28, 29). This dose rate is also similar to the dose rate used in classic LDR brachytherapy applications.

Table 1. Radiation Therapy Oncology Group acute central nervous system toxicity scale

Grade 0	No change
Grade 1	Fully functional status (*i.e.,* able to work) with minor neurologic findings; no medication needed
Grade 2	Neurologic findings present sufficient to require home care; nursing assistance may be required; medications including steroids/antiseizure agents may be required
Grade 3	Neurologic findings requiring hospitalization for initial management
Grade 4	Serious neurologic impairment including paralysis, coma, or seizures >3/week, despite medication; hospitalization required
Grade 5	Death

An Atomic Energy of Canada Limited Eldorado-6 modified cobalt-60 teletherapy unit was used to deliver SLDR. The desired dose rate of 40 to 50 cGy per hour was obtained by placing a custom metal attenuator in the beam. Radiotherapy was delivered 6 to 8 hours/day at a dose rate of 40 to 50 cGy/hour, delivering 30 to 35 Gy over 12 days.

Head immobilization was achieved with a thermoplastic mask fixed to a modified dental chair. Patients were treated for approximately 50 minutes, at which time a 10-minute break was allowed and encouraged for prevention of venous thromboses. No other measures were taken to prevent venous thromboses. Additional break time, as reasonably necessary, was provided during the 6- to 8-hour daily irradiation. During treatment, patients were monitored on a closed circuit video camera and two-way intercom system. A video player, radio, and cable television system were available for patient use in the treatment room during treatments. No routine sedation was necessary, and oral pain medications were used on an as-needed basis.

Simulation and CT-based dosimetry were performed for each patient. The planning target volume included the recurrent primary brain tumor, along with the surrounding edema, with an additional 2-centimeter margin. In situations where CT and MRI imaging were both available for treatment planning, the scan demonstrating the greatest extent of edema was used. Custom blocking was not feasible given the attenuator placement. All field arrangements were therefore parallel opposed rectangular or square fields. Fields were weighted preferentially to the side of the tumor. Dose and dose rate inhomogeneity across the target volume was limited to $\pm 12.5\%$ of the prescription dose.

Surface thermoluminant dosimeter measurements were obtained on the first day of treatment to confirm the total dose and dose rate predicted by the pretreatment computer dosimetry.

Patient assessments

Clinical evaluation with neurologic history and physical examination and radiographic examination with CT or MRI imaging were repeated at 1, 4, 7, 11, and 15 months after completion of SLDR and every 6 months thereafter.

Endpoints

The frequency of developing unacceptable (Grade 3 or greater) acute central nervous system (CNS) toxicity as defined by the Radiation Therapy Oncology Group (RTOG) and shown in Table 1 was the primary endpoint in this study. An observed rate of less