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Clinical Study

Hypofractionated intensity modulated radiotherapy with temozolomide in newly diagnosed glioblastoma multiforme

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ABSTRACT

We conducted a phase I study to determine (a) the maximum tolerated dose of peri-radiation therapy temozolomide (TMZ) and (b) the safety of a selected hypofractionated intensity modulated radiation therapy (HIMRT) regimen in glioblastoma multiforme (GBM) patients. Patients with histological diagnosis of GBM, Karnofsky performance status (KPS) $\geqslant$ 60 and adequate bone marrow function were eligible for the study. All patients received peri-radiation TMZ; 1 week before the beginning of radiation therapy (RT), 1 week after RT and for 3 weeks during RT. Standard 75 mg/m^2/day dose was administered to all patients 1 week post-RT. Dose escalation was commenced at level I: 50 mg/m^2/day, level II: 65 mg/m^2/day and level III: 75 mg/m^2/day for 4 weeks. HIMRT was delivered at 52.5 Gy in 15 fractions to the contrast enhancing lesion (or surgical cavity) plus the surrounding edema plus a 2 cm margin. Six men and three women with a median age of 67 years (range, 44–81) and a median KPS of 80 (range, 80–90) were enrolled. Three patients were accrued at each TMZ dose level. Median follow-up was 10 months (range, 1–15). Median progression free survival was 3.9 months (95% confidence interval [CI]: 0.9–7.4; range, 0.9–9.9 months) and the overall survival 12.7 months (95% CI: 2.5–17.6; range, 2.5–20.7 months). Time spent in a KPS $\geqslant$70 was 8.1 months (95% CI: 2.4–15.6; range, 2.4–16 months). No instance of irreversible grade 3 or higher acute toxicity was noted. HIMRT at 52.5 Gy in 15 fractions with peri-RT TMZ at a maximum tolerated dose of 75 mg/m^2/day for 5 weeks is well tolerated and is able to abate treatment time for these patients.

1. Introduction

Glioblastoma multiforme (GBM) is one of the most aggressive and most common glial tumors with an incidence of 5/100,000/year [1]. The median survival is 12.1 months with surgery and radiation therapy (RT) alone [2]. The addition of temozolomide (TMZ) chemotherapy has resulted in a median survival of 14.6 months [2]. Standard RT for GBM was arrived at in the 1970s and consists of 60 Gy delivered in 30 fractions of 2 Gy each for a total of 6 weeks [3–5]. Clearly in the last 10–15 years there have been great advances in imaging of the area to be irradiated as well as advances in the more precise delivery of radiation using three dimensional (3D) conformal and intensity modulated radiation therapy (IMRT) techniques [6]. IMRT is widely regarded as a technique that enables delivery of very conformal radiation to a target while limiting radiation deposition on surrounding structures at risk; IMRT has been considered and used for GBM.

Considering the limited life expectancy of this group of patients and that conventional treatment may occupy a significant amount of their survival time it would be beneficial to evaluate the hypofractionation schedules delivered with the newest RT techniques to try to shorten the time that patients spend receiving treatment, thereby decreasing patients' inconvenience and potentially improving the quality of life of their limited survival time. It is not surprising then that there has been a rekindled interest in exploring hypofractionation regimens that, even if equivalent in effectiveness, would be preferable to conventional ones because of their shorter duration in patients with a terminal disease [7–18]. Moreover hypofractionation is associated with reduced costs compared to standard fractionation delivered with the same algorithm. Hypofractionation has been accepted for elderly or poor performance patients [16,19]. Recently several unconventional fractionation schedules consisting of four to 20 fractions have been proposed for GBM [7–18]. As TMZ has become the standard

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chemotherapy to be given concomitantly to RT and as TMZ may potentiate the effects of RT, including the undesirable ones, it is imperative to assess the safety of TMZ concomitant with the higher dose of radiation per fraction in hypofractionation regimens [2,18,20,21]. Several treatment regimens of concurrent and post-RT TMZ in combination of various RT fractionation schedules have been proposed [2,9,12,14–16,18]. However, the data on safety and efficacy of hypofractionated RT with pre-RT, concurrent and post-RT TMZ is lacking. This paper aimed to evaluate in a phase I study the safety of a chemoradiation treatment using hypofractionation intensity modulated radiotherapy (HIMRT) and an escalating peri-RT TMZ dose.

2. Materials and methods

After approval by the Institutional Review Board, a traditional 3 + 3 phase I study [22] was conducted to assess the scope and tolerability of HIMRT with concurrent and adjuvant TMZ. The study was designed to enroll a minimum of three and maximum of 18 patients. All patients who met the inclusion criteria for study and also consented to participate in the trial were required to sign a written informed consent form. The inclusion criteria for the study were *de novo* GBM and anaplastic astrocytoma, tumors must not involve brain stem or optic chiasm, tumor was diagnosed following biopsy or surgery, age >18 years, Karnofsky performance status (KPS) $\geqslant$ 60, adequate bone marrow reserve, normal renal function, and normal liver function. Patients with prior treatment of their brain tumor were excluded. All patients underwent comprehensive standard pre-treatment evaluation.

2.1. RT

RT was started within 4–6 weeks after surgery or biopsy. IMRT was delivered using a linear accelerator with 6 MV photons. Volumetric CT scans fused to volumetric contrast MRI to delineate the target were used for treatment planning. Gross target volume (GTV) was defined as the contrast enhancing area and/or the surgical cavity. Clinical target volume (CTV) was defined as GTV plus surrounding edema (defined by T2-weighted image). A 2 cm margin was added to define the planned target volume (PTV). Our proposed hypofractionation scheme was designed by calculating a 3 week regimen that would have acute (tumor) effects equivalent to 5906 cGy of conventional (2 Gy) fractionation, assuming alpha: beta ratio of 10. Late effects, assuming alpha:beta ratio of 2, were calculated to be equivalent to 7219 cGy at conventional 2 Gy fractions. A total dose of 52.5 Gy over 15 fractions (3.5 Gy per fraction) over 3 consecutive weeks (5 fractions per week) was delivered to the PTV.

2.2. TMZ

A standard phase I 3 + 3 design was followed for dose escalation. TMZ was administered for 5 weeks: 1 week before beginning RT, for 3 weeks during RT, and for 1 week after completion of RT. The dose escalation study was designed to enroll three patients per cohort in successive dose levels. Three escalating dose levels of TMZ were planned; dose level I was 50 mg/m^2/day for the first 4 weeks and 75 mg/m^2/day for the last 1 week of treatment; dose level II was 65 mg/m^2/day for the first 4 weeks and 75 mg/m^2/day for the last 1 week of treatment; and dose level III was 75 mg/m^2/day over the entire 5 weeks of treatment. Dose limiting toxicity (DLT) was defined as any adverse event qualifying as irreversible grade 3 and any grade 4–5 toxicity as per the revised USA National Cancer Institute Common Toxicity Criteria (version 3.0) [23]. Dose escalation was to be halted when the maximum tolerated dose (MTD) was reached; MTD was defined as one dose level below the dose at which DLT was observed in one-third or more patients. If one of the three patients in a dose cohort experienced DLT, three more patients were added to the cohort. If no DLT was observed in the group after 5 weeks of treatment then an additional three patients were accrued at the next higher dose level. If two of the three patients at any dose level exhibited DLT then the study was to terminate.

Adjuvant TMZ was commenced 4 weeks after completion of RT. The initial dose of 150 mg/m^2/day was used for the first cycle and then increased to 200 mg/m^2/day with the second cycle, provided that toxicity was acceptable. Adjuvant TMZ was continued for 5 consecutive days every 28 days for at least six cycles or until the disease progression or DLT was reached. Avastin (Genentech, San Francisco, CA, USA) was started when there was radiological progression of disease after the completion of HIMRT and concurrent TMZ. Oral trimethoprim–sulfamethoxazole was prescribed during concurrent chemoradiation to mitigate the risk of *Pneumocystis carinii* pneumonia due to TMZ-induced lymphocytopenia. Antiemetic prophylaxis with prochlorperazine and/or a 5 hydroxytryptamine-3 antagonist was typically prescribed prior to concurrent and adjuvant TMZ. All patients continued to receive appropriate treatment of other chronic diseases during and after the protocol therapy.

2.3. Follow-up

All patients were evaluated for any adverse events with laboratory evaluation including serum chemistries and hematologic profile weekly or earlier as needed during the 5 weeks of chemoradiotherapy (primary endpoint). After the initial 5 week period, follow-up visits were arranged monthly or earlier as needed. Neuroradiologic progression (contrast MRI), KPS, hematological analysis and other indicators were evaluated at each follow-up visit. The time to neuroradiological evidence of tumor recurrence or progression, survival time, and time spent in a KPS $\geqslant$70 were evaluated as the secondary endpoints.

2.4. Statistical analysis

Mean, standard deviation, median and range for continuous variables, and frequency for discrete data were calculated for patient demographics. The maximum grade for each type of toxicity was recorded for each patient, and frequency tables were provided. Progression free survival (PFS) and overall survival (OS) were used for survival data analysis. Clinical and/or radiographic PFS was defined as the interval from date of definitive (histological) diagnosis to date of clinical and/or radiographic progression, whichever was earlier. OS was determined from the date of diagnosis to death from any cause. Time spent in a KPS $\geqslant$70 was calculated from date of diagnosis to KPS decline (KPS <70) or censored at the last date the patient was known with KPS $\geqslant$70. Survival curves were estimated using the method of Kaplan–Meier and were displayed graphically.

3. Results

A total of nine patients were enrolled between 2009 and 2012. The median age of the three female and six male patients was 67 years (range, 44–81). Eight patients had a solitary lesion and one patient had multicentric GBM. Gross tumor resection was achieved in two and partial resection in six patients while one patient underwent biopsy. All the lesions were histologically diagnosed as GBM (World Health Organization grade IV). Mean CTV