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CLINICAL-PATIENT STUDIES

Early necrosis following concurrent Temodar and radiotherapy in patients with glioblastoma

Marc C. Chamberlain · Michael J. Glantz · Lisa Chalmers · Alixis Van Horn · Andrew E. Sloan

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Abstract Concurrent temozolomide (TMZ) and radiotherapy is the new standard of care for patients with newly diagnosed glioblastoma. In 51 consecutive patients treated according to this regimen, 7 patients (14%) manifested surgically confirmed early necrosis without evidence of recurrent tumor. This observation suggests that daily TMZ may represent a potent radiosensitizing regimen.

Keywords Glioblastoma · Temodar · Radiotherpy

Introduction

The preliminary report of Stupp et al., and the recently published randomized European and Canadian trial, has substantially altered the algorithm for initial treatment of glioblastoma (GBM) [1, 2]. These studies clearly demonstrated a benefit for chemotherapy (TMZ) in the initial treatment of patients with GBM by showing an improvement in median (14.6 vs. 12 months) and 2-year survival (27% vs. 10%) in patients receiving or not receiving TMZ. As a consequence, this treatment regimen (TMZ given concurrently with radiotherapy followed by 6 monthly cycles of TMZ) has become the new standard of care for patients with newly diagnosed GBM.

This report describes 51 consecutive patients with newly diagnosed GBM treated according to this regimen. Seven patients developed what was initially felt to be early recurrence (shortly after the completion of concurrent TMZ and RT), however at time of re-operation were shown histopathologically to have exclusively treatment-related necrosis without tumor.

Patients and methods

Between January 1, 2005 and June 31, 2005, 65 patients were seen with newly diagnosed GBM at either the H. Lee Moffitt Cancer Center and Research Institute or the University of Massachusetts Medical Center. Of the 65 patients, 14 were greater than 69 years of age and elected to be treated with primary chemotherapy and deferred radiotherapy [3]. The remaining 51 patients (Table 1) were treated according to the Stupp protocol as follows. Temozolomide (Temodar; Shering Plough, NJ) was administered with conventional external beam radiotherapy for 42-consecutive days (75 mg/m^2/a single daily dose) beginning with the first day of radiation. Radiotherapy was administered for 33–34 treatment days, as single 180 cGy fraction per day to a total tumor dose of 59.4–61.2 Gy. Treatment brain volume was as defined by the Radiation Therapy Oncology Group guidelines [4]. Two to three weeks following the conclusion of concurrent chemoradiotherapy, patients were then re-evaluated with MR brain imaging. Patients were then treated if clinically and radiographically stable or improved with TMZ every 4 weeks (200 mg/m^2 as a single daily dose for five

M. C. Chamberlain (✉) · L. Chalmers · A. E. Sloan
Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Avenue, Tampa, FL 33612-0804, USA
e-mail: ChambeMC@moffitt.usf.edu

M. J. Glantz · A. Van Horn
Department of Neurology and Oncology, University of Massachusetts Medical Center, Worcester, MA, USA

Table 1 Patient characteristics

Number	51
Age	
Median	60 years
Range	34–79 years
Gender	
Male	28
Female	23
Initial surgery	
Complete	7 (14%)
Partial	24 (48%)
Biopsy	20 (38%)
Karnofsky performance status	
Median	90
Range	60–100
Location	
Frontal	18
Temporal	10
Parietal	4
Occipital	3
Multilobar	8
Multifocal	4
Thalamus/basal ganglia	4
Recurrence	26 (51%)
During radiotherapy	7
0–3 months after radiotherapy	8
3–6 months after radiotherapy	11
Salvage therapy	
Re-operation	15 (29%)
Chemotherapy	11

consecutive days) for 6 months. Subsequent clinical and laboratory evaluations occurred monthly and neuroradiographic evaluations were every other month.

Results

In total, 26 patients (51% of all patients treated on this regimen) failed both clinically and neuroradiographically within 6 months of completion of radiotherapy. All were considered to have progressive GBM. About 15 patients (29%) underwent re-operation with an image verified complete resection and with the pre-operative plan to enroll in an alternative protocol based on early tumor recurrence. Histopathology was interpreted as necrosis without evidence of tumor in seven patients (13.7%) by two neuropathologists. However, both neuropathologists stated that isolated and viable tumor cells could not be excluded. As such, these patients were not considered candidates for protocol entry, and rather were offered continued TMZ or observation. Time to discovery of treatment-related necrosis from initial surgery ranged from 2–6 months (median 3 months).

Discussion

The observation of early treatment-related necrosis in this small series is notable in several respects. Only 1% of GBM patients treated with conventional fractionated external beam radiotherapy to total doses of approximately 60 Gy manifest radiation-induced necrosis [5]. Moreover, the median time course for appearance of necrosis in such cases is approximately 12–14 months, significantly later than observed in this study. In contrast, nearly 15% of patients with GBM in this study were found to have progressed despite administration of radiotherapy, at the time of their first post-radiotherapy MR brain scan [6]. Thus, patients such as those described in this study would likely be considered radiation failures and offered alternative therapy or no further therapy depending upon patient preference and as clinically indicated.

This study parallels ands expands upon an observation reported recently of early neuroradiographic worsening (as seen in this study) followed by improvement when observed without surgical intervention or other tumor-directed treatment [7]. This pattern of apparent neuroradiographic worsening is problematic with respect to prognostication for patients and their families, and for determination of protocol eligibility for recurrent GBM. Such patients might be considered treatment failures and enter a new treatment trial (as our patients did) with potentially specious results if the apparent progression is temporary and resolves independently of the new therapy. In contrast, some patients, faced with the onerous news of early treatment failure, might mistakenly elect to abandon further treatment (in lieu of palliative care). Unlike the previously mentioned study, the patients in the current study were treated with an aggressive surgical approach permitting pathological correlation for this apparent disease progression. Since all patients in our study who underwent re-operation had a Karnofsky performance status greater than 60, were clinically symptomatic and had greater than 25% enlargement of the tumor by MR, surgical resection was deemed appropriate.

Lastly and perhaps most interesting is the etiology of this phenomenon of early necrosis [8]. Both chemotherapy and radiotherapy were developed as tools to selectively kill tumor and often result in measurable tumor cytotoxicity. However the effectiveness of these therapies in achieving measurable therapeutic effects in GBM are meager. Less than 10% of patients with GBM achieve either a partial or complete neuroradiographic response (defined as greater than 50%

decrease in the diameter of the tumor), the standard oncology measure of therapeutic effectiveness. The patients in this study with early necrosis suggest a potential and perhaps significant chemo- radiosensitization effect in a subset of patients treated with this regimen of concurrent TMZ and radiotherapy that may predict for durable responses and contribute to the regimens observed benefit in patients with newly diagnosed GBM.

An additional, unresolved question is why this regimen of concurrent TMZ and radiotherapy is efficacious in contrast to numerous other trials utilizing up-front chemotherapy for GBM that have been negative [5, 6]. Perhaps the observation of exaggerated early necrosis as reported herein represents one end of the spectrum of positive effects of combined chemoradiotherapy and may in part account for the improved results seen with concurrent TMZ and radiotherapy. Clearly, confirmation of this preliminary observation of unexpected and common early necrosis using concurrent TMZ and radiotherapy in a larger GBM population is required. If these findings are confirmed, the concept of clinically relevant radiosensitization by TMZ may account, in part, for the efficacy of this regimen.

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