

Chemopotentiation by ultrafractionated radiotherapy in glioblastoma resistant to conventional therapy

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ABSTRACT

Introduction. Induced radiation resistance (IRR) and hyper-radiosensitivity (HRS) are well-described phenomena in basic literature, yet few reports have been published in which such phenomena are exploited clinically for the benefit of patients. Glioblastoma is a prime example.

Case and methods. The case of an 82-year-old woman is described whose resected frontoparietal glioblastoma progressed through treatment administered according to standard methods. With review board and patient approval, we continued her treatment using radiotherapy and temozolomide, but drastically modified the radiotherapy fractionation, administering 50 cGy twice daily on each of the first 5 days of a 14-day cycle. Temozolomide was administered on the first 4 days of each cycle. We use the term “ultrafractionated radiotherapy” to refer to the extremely low doses of radiation used in this case.

Results. This modified regimen resulted in regression of the contrast-enhancing areas of disease recurrence identified on MRI, and the patient survived approximately 6 months following recurrence of her disease, having received 5 cycles of additional therapy after prior full-dose treatment.

Conclusions. Ultrafractionated radiotherapy and concurrent temozolomide were efficacious and tolerable in this patient whose glioblastoma previously progressed through conventional treatment. Additional studies of this approach are warranted. Free full text available at www.tumorionline.it

Introduction

Glioblastoma multiforme (GBM) is widely recognized as the most common adult malignant brain tumor. Contemporary therapy generally follows the approach described by Stupp *et al.* in their landmark paper describing concurrent radiotherapy and temozolomide followed by adjuvant temozolomide thereafter¹. Though this treatment represents the single greatest improvement in GBM outcome, the survival is still abysmal, at approximately 17 months for patients treated with such an approach². Median progression-free survival and overall survival differ by only 2.4 months, implying an extremely rapid progression from recurrence to patient demise².

In 1997, a group led by Joiner described 2 related phenomena observed in mammalian cell culture, which they termed hyper-radiosensitivity (HRS) and induced radiation resistance (IRR)³. Their work describes an area of the mammalian cell survival curve following various doses of radiation in which survival *increases* with *increasing* dose of radiation per fraction, up to a maximum of approximately 100 cGy⁴. This aspect was termed IRR. Conversely, lower dose fractions of radiation were associated with improved cell kill to fraction sizes as low as 30 cGy; a phenomenon they termed HRS⁴. Despite these phenomena, successive doses of radiation overwhelm the IRR and result in tumor death, as well as normal tissue toxicity.

Key words: chemopotentiation, ultrafractionated radiotherapy, glioblastoma.

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Though the potential to exploit HRS for the purpose of improving patient survival while minimizing treatment toxicity seems obvious, few published studies have sought to do so in clinical practice. The first such clinical trial identified was published in 2004 by Arnold and colleagues at the University of Kentucky⁵. This paper describes the use of 80-cGy fractions of external-beam radiotherapy (XRT) as a locally chemopotentiating agent in the management of squamous cell carcinoma of the head and neck. This study found an overall 90% response rate and a complete response rate of 13% to 2 cycles of therapy⁵. Later that year, a group in the United Kingdom published a work describing superior responses to dermal metastases from various primary tumors treated with 3-times-daily fractions of 50 cGy *vs* 150 cGy fractions delivered once daily⁶. The latter trial did not employ chemotherapy. Two additional clinical works describe an HRS-type approach combined with chemotherapy in gastrointestinal⁷ and epithelial tumors⁸, with discernible benefit.

At present, no prior works have described the efficacy of ultrafractionated radiotherapy as a chemopotentiator in central nervous system malignancies. Nonetheless, the notion that HRS and IRR apply in this setting has been previously contemplated. The human glioblastoma cell line T98G was shown to exhibit HRS in cell culture studies done by Short and colleagues⁹. Nonetheless, subsequent *in vivo* studies failed to confirm such findings¹⁰. However, the trial attempting to confirm the *in vitro* findings did not incorporate chemotherapy. Thus, we propose an alternative in which ultrafractionated radiotherapy may prove useful as a local chemopotentiator, as has been seen in other clinical trials^{5,7}, rather than suggest its use as a single-modality treatment.

Case and methods

The patient studied is an 82-year-old Caucasian woman who was diagnosed with GBM after experiencing new onset ataxia in June 2008. She was evaluated in a tertiary center, and an awake, image-guided craniotomy was performed to remove the right frontal tumor, rendering a gross total resection. Completeness of resection was confirmed with both image guidance at the time of surgery and postoperative imaging demonstrating no gross residual tumor. Pathology demonstrated an astrocytic neoplasm displaying cytological pleomorphism, mitotic figures, microvascular changes, and pseudo-palisading necrosis, rendering a diagnosis of GBM/WHO grade IV astrocytic neoplasm.

On July 29, 2008, the patient started treatment according to Stupp's protocol¹, employing 200-cGy daily fractions of XRT and 75 mg/m² daily temozolomide delivered concurrently. Treatment employed intensity-modulated radiotherapy (IMRT) to cover the preoperative

edema with a minimum 2-cm margin for the first 46 Gy, followed by a 14-Gy boost encompassing the preoperative gross tumor volume and a modest margin. On September 11, 2008, the patient received her final fraction of XRT, and was observed by the nursing staff to have a simple-partial seizure involving clonic movement of the left lower extremity prior to leaving the clinic. Emergent MR imaging was obtained, which revealed 3 distinct contrast-enhancing nodules lying along the edges of the resection bed. The largest of the nodules was approximately 9 mm in greatest dimension. Surrounding the nodules were areas of increased signal on the fluid-attenuated inversion recovery (FLAIR) sequence, consistent with peritumoral edema.

The patient was started on dexamethasone and levetiracetam and was allowed to return home to await further planning. A single-patient protocol was submitted to the local institutional review board for emergent approval, with parameters as described below.

Treatment with dose-intense temozolomide was based on an adaptation of the method described by Dall'Oglio¹¹, using escalating doses with each new cycle, based on tolerance to the prior cycle. A minimum 14-day respite was mandatory between completion of conventional chemo-radiotherapy and initiation of protocol treatment. Thereafter, treatment proceeded on 14-day cycles. Temozolomide was administered during the first 4 days of each 14-day cycle. The initial dose was 100 mg/m² daily. If blood counts obtained on the first day of the second and subsequent cycles were within acceptable parameters, the patient could be advanced to a dose of 125 mg/m²/day for the first 4 days of the cycle. If blood count parameters were below the limit of acceptability, but not less than 75% of the limit, a dose reduction of 25 mg/m²/day was used, and treatment was continued.

Acceptable hematological parameters were based on the aforementioned study by Dall'Oglio¹¹, and included an absolute neutrophil count of $\geq 1500/\mu\text{L}$, an absolute lymphocyte count of $\geq 500/\mu\text{L}$, and a platelet count of $\geq 100,000/\mu\text{L}$. In the event the patient's hematological parameters were less than 75% of the limit, a treatment break of 1 week was mandated, followed by re-evaluation and re-initiation of treatment as indicated by subsequent counts. In no case was a dose of less than 75 mg/m²/day, nor more than 125 mg/m²/day used.

Given the propensity of GBM to spread via neural tracts, and the belief that ultrafractionated doses are relatively less toxic than conventional radiotherapy, the protocol specified that treatment be delivered to the whole brain at a dose of 50 cGy, twice daily, on days of chemotherapy, and on the day following the last dose of chemotherapy in each cycle (day 5). In the event chemotherapy was withheld, radiotherapy was also withheld, as radiotherapy was to function as a local chemopotentiator. Radiotherapy fractions were administered with a minimum 6-hour interfraction interval;

however, in rare cases (e.g., linear accelerator maintenance) a 4-hour interfraction interval was permitted, with the primary investigator's approval. Treatment fields encompassed the entire brain, extending inferiorly to the bottom of the C2 vertebral body. Electronic compensators (a "dose-painting" technique) were used to deliver a homogeneous dose normalized to 50 cGy maximum per fraction. Great effort was made to keep all brain surfaces within the 95% isodose line.

The patient was informed that she could discontinue treatment at any time; however, the protocol limited treatment to a maximum of 8 cycles, which would be followed by maintenance temozolomide, as described by Stupp¹. MRI of the brain was performed at approximate monthly intervals during the patient's treatment.

Radiographic analyses for this manuscript were performed by a single diagnostic radiologist who had no involvement in the clinical care of the patient. Analytic contouring was carried out in meticulous fashion, with utmost attention to detail. Immediate analyses for clinical purposes were performed by separate clinical diagnostic radiologists. Volumetric analyses of tumor burden were performed using Varian Eclipse radiotherapy treatment planning software (Varian Medical Systems, Palo Alto, CA, USA). Great care was taken to ensure that all lesions were contoured using as similar a window and level setting as could be reasonably achieved. Likewise, all graphical depictions made part of this manuscript have been created with maximally similar window and level settings to ensure an accurate depiction of tumor response.

Results

Treatment was started 18 days after completion of conventional XRT and identification of recurrence. Table 1 details the treatment course specifics, with day 1 representing the first day of treatment on protocol. After 4 cycles of treatment, blood counts necessitated a 1-week break. The patient returned for 1 additional cycle, and then elected to discontinue treatment so as not to interrupt her Christmas holiday.

Images demonstrating the initial areas of recurrence are shown in Figure 1. Three predominant nodules of tumor regrowth are observed, all of which lie along the edges of the resection cavity. During the time between this initial scan and the first scan after the initiation of protocol therapy, subtle progression was observed; however, we are quick to note that most of this time was spent not in active treatment but awaiting protocol preparations and institutional review-board approval. Subsequent imaging done on an approximately monthly basis demonstrated a subjective decrease in the intensity of the lesions' contrast enhancement as well as an objective decrease in the volume of the T1 post-contrast tumor volume on MRI. Figure 2 includes a panel of

Table 1 - Progression of patient's hematological parameters and adjustments made, as mandated by protocol

Protocol day	Chemotherapy	Radiotherapy	ANC	Lymph	Plt
1	100 mg/m ² /d	50 cGy b.i.d. x5 d.	6700	700	126
15	125 mg/m ² /d	50 cGy b.i.d. x5 d.	5500	700	104
29	100 mg/m ² /d	50 cGy b.i.d. x5 d.	4000	900	81
43	75 mg/m ² /d	50 cGy b.i.d. x5 d.	4500	600	81
57	HOLD CHEMO	HOLD XRT	4500	600	75
64	75 mg/m ² /d	50 cGy b.i.d. x5 d.	5800	600	85
78	DISCONTINUE	DISCONTINUE	4900	600	81

ANC, absolute neutrophil count; Lymph, absolute lymphocyte count; Plt, platelet count; XRT, external-beam radiotherapy.

4 such images. Great care has been taken in preparing this graphic to ensure that the window and level are as close as possible, and that the slices portrayed are as nearly identical as possible to ensure that perceived changes in the tumor nodules are not due to artifact.

Contrast-enhanced nodule-contouring by a diagnostic radiologist not involved in the clinical care of the patient demonstrated regression as well, though there was some progression of hyperintense FLAIR signal, suggesting the possibility of evolving edema. The volumes of both T1 contrast-enhanced changes and FLAIR hyperintensity are presented in Table 2.

Clinically, the patient became intermittently nauseated and dehydrated secondary to the nausea and resultant poor fluid intake. This was effectively managed with 5-HT₃ blockers and IV fluid rehydration as needed. Symptoms were more significant during weeks of active treatment and less troublesome during the intervening weeks. With the exception of progressive fatigue, the patient remained near her pre-study level of functioning, staying fully cogent, often making witty and intellectually complex remarks, in spite of her fatigue. Fatigue was partially assuaged with controlled-release methylphenidate. At the end of the fifth cycle, the patient elected to discontinue protocol therapy, indicating that she felt she would enjoy the upcoming holiday more if she were not as fatigued. Approximately 6 weeks after discontinuing protocol therapy, the patient elected hospice/palliative care, and she expired slightly more than 6 months after diagnosis of her recurrence.

Discussion

Glioblastoma represents one of the greatest remaining oncological challenges. The single most revolutionary study in decades witnessed an improvement of a mere 2.5 months in overall survival¹. Thus, even subtle improvements in treatment efficacy are worthy of further evaluation. That said, we are quick to note that this is a carefully developed single-patient study and should be viewed in the context of its obvious limitations. Still, the data presented are compelling in their own right and warrant further study of this approach.

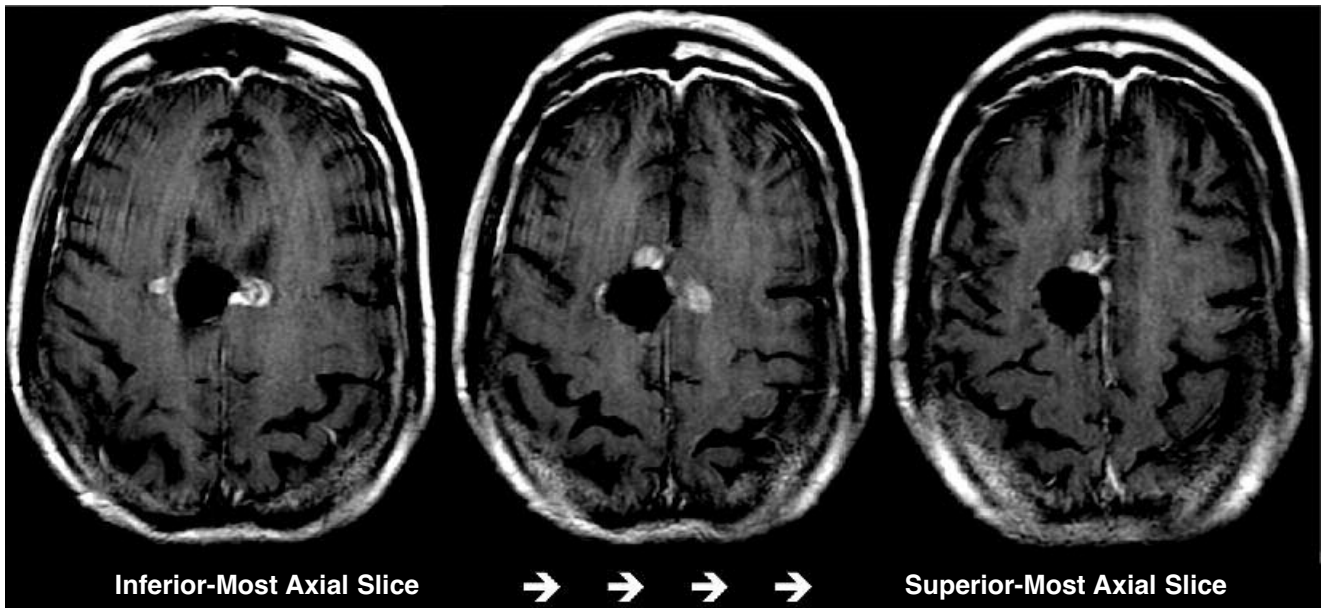


Figure 1 - T1-weighted axial post-contrast MRI demonstrating tumor nodules at the initial diagnosis of recurrence. Three predominant nodules are seen anterior and lateral to the resection cavity. Images shown are consecutive from inferior to superior; 6-mm slice thickness.

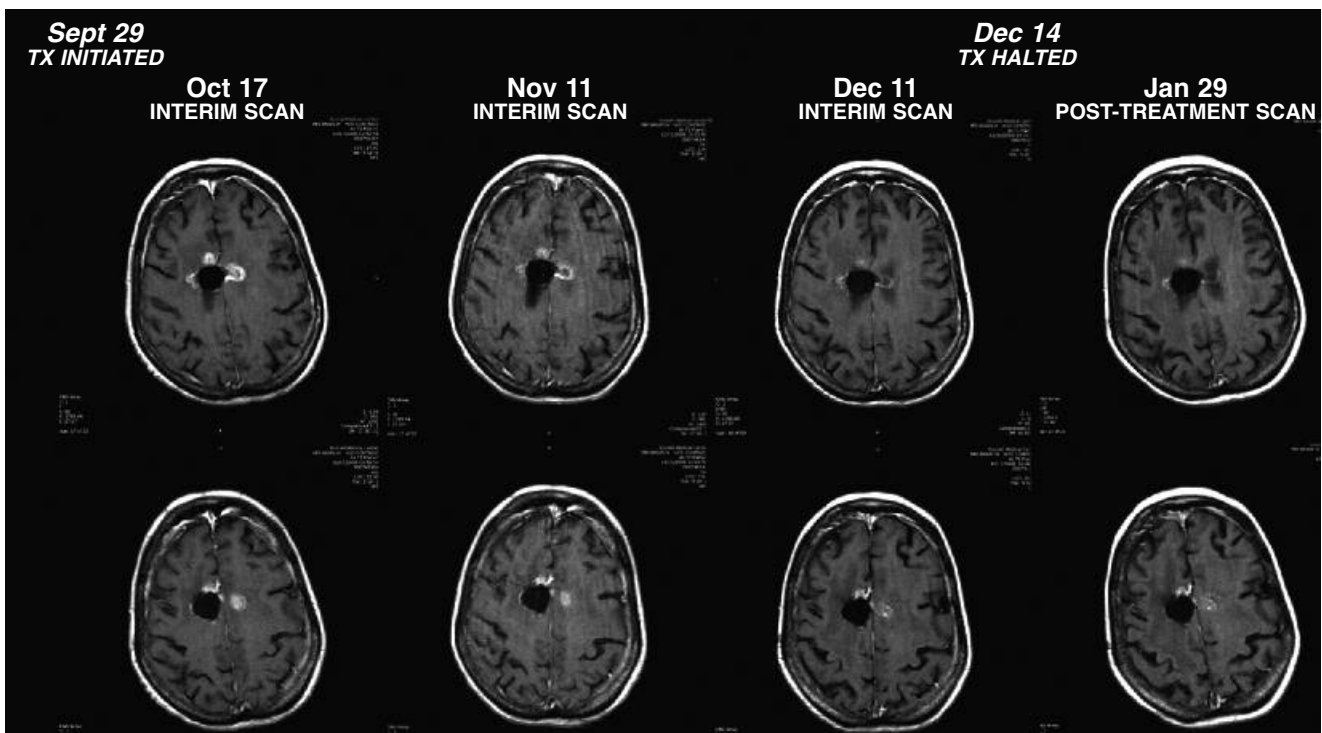


Figure 2 - T1-weighted axial post-contrast images are presented for each date shown (2 adjacent slices each date), demonstrating a decrease in the intensity of the post-contrast signal, representing regression of gross recurrent disease.

One must consider the unique features of this case to fully appreciate the merits of the approach described. Foremost is the patient's age of 82 years and the fact she had completed a gross total resection followed by full-

dose chemo-radiotherapy ending less than 3 weeks prior to initiation of this protocol. This emphasizes the tolerable nature of this approach.

With regard to efficacy, we are pleased both by the pa-

Table 2 - Comparison of contrast-enhancing tumor volume (T1 contrast) and MRI-evident edema (FLAIR) by study date

	Day -17	Day 19	Day 44	Day 74	Day 94	Day 123
T1 contrast	1.52 cm ³	2.64 cm ³	2.45 cm ³	1.34 cm ³	0.90 cm ³	0.81 cm ³
FLAIR	48.3 cm ³	83.6 cm ³	98.6 cm ³	109.0 cm ³	130.3 cm ³	140.9 cm ³

Note that day 1 is considered the first day of active protocol treatment, and as such, day -17 would be the day on which recurrence was first diagnosed. Following initiation of protocol therapy, one can observe a steady trend toward regression of gross disease and significant early edema formation, followed by less dramatic progression of edema.

patient's extended survival of 6 months post-recurrence, and by the fact that she had a radiographically demonstrable response to therapy. For clarity, the patient's disease progressed while she was treated with 75 mg/m² temozolomide daily along with 200-cGy fractions of radiation, but regressed when the dose of radiation was altered to 50 cGy twice daily. While temozolomide dosing was altered, in retrospect, this was less significant a change. It seems apparent that altered radiotherapy dose fractionation was the greatest contributor to this response.

The fact that the patient's FLAIR hyperintensity increased most dramatically in volume following initiation of protocol therapy argues in favor of an inflammatory response to subclinical tumor deposits. Nonetheless, we have considered that it could also represent more slowly progressive disease. We further regard the latter possibility as less likely, given the fact that objective regression was seen in the grossly evident disease.

Finally, we acknowledge that any amount of radiation administered to a patient previously treated with 60 Gy would be associated with a significant risk of radiation necrosis. This was acknowledged both to the internal review board prior to their approval and was discussed extensively with the patient before beginning protocol treatment. The patient acknowledged and accepted this risk, and the review board deemed it reasonable. It is critically important that future studies of this approach include this aspect of informed consent as well. To that end, we reiterate that the dose delivered under this protocol was an additional 25 Gy total. Given the fact that our understanding of ultrafractionated radiotherapy's toxicity is rudimentary at best, future endeavors such as this must be carried out with utmost caution.

Clearly, a case study cannot prove this hypothesis on its own. Nonetheless, ultrafractionated radiotherapy as a chemopotentiator of temozolomide is logical and

worthy of further investigation in future clinical trials for patients with glial neoplasms. It may simultaneously allow for enhancement of the therapeutic effect and minimization of treatment-related toxicity. To seek after such endpoints needs little justification.

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