

## Concomitant Accelerated Hyper-Fractionated Radiotherapy and Temozolomide in the Treatment of High Grade Astrocytoma

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### ABSTRACT

**Purpose:** To evaluate the safety and efficacy of accelerated hyper-fractionated radiotherapy combined with temozolomide in patients with high grade astrocytoma.

**Methods and materials:** Twenty-four patients with newly diagnosed and histologically proven high grade astrocytoma were enrolled into this study. Treatment protocol included radiotherapy delivered in fractions of 150 cGy 3 times daily with at least 4-hour intervals between fractions to a total dose 4050 cGy. The target volume was the tumor plus the edema with a 2-cm margin. A boost of 1800 cGy was given to the tumor plus a 2-cm margin to a total dose of 5850 cGy delivered in 39 sessions over 2.5 weeks. Temozolomide dose was (150 mg/m<sup>2</sup>/dayx7d/wk) given 2 hours prior to radiotherapy, from the beginning till the end of the course.

**Results:** Of the 24 patients included 5 (21%) developed G2 & G3 neutropenia, and 4 patients (17%) developed G2 & G3 thrombocytopenia. Non-hematologic toxicities were: G2 & G3 vomiting in 8 (33%) patients, G2 & G3 fatigue in 13 (54%) patients, G2 skin rash in 4 (17%), and G2 acute radiation reaction in 2 (8%) patients. The twelve months and 18 months survival rates were 67% and 51.5% respectively. Patients aged <45 years and those who underwent debulking surgery had better survival rates (69% & 70%) in comparison to those aged ≥45 years and those who underwent biopsy only (27% & 36%).

**Conclusion:** Temozolomide in a daily dose of 150 mg/m<sup>2</sup> concomitant with thrice daily fractions of 150 cGy for a total dose of 5840 cGy is a safe and tolerable regimen in terms of acute toxicities, however long term follow-up is required for proper assessment of late toxicities. The results achieved are promising and need to be confirmed in a randomized trial comparing accelerated hyper-fractionated radiotherapy with and without temozolomide.

**Key Words:** *Astrocytoma - Hyperfractionated radiotherapy - Temozolomide*

### INTRODUCTION

Malignant gliomas occur more frequently than other types of primary CNS tumors [36]. The standard management of malignant gliomas

involves cyto-reduction through surgical resection when feasible, followed by radiotherapy with or without adjuvant chemotherapy [9,22]. Despite this multimodality approach, the prognosis for this group of patients remains poor, with rare long term survivors [25,13]. Given the poor prognosis of the patients and the lack of viable options, it is imperative that effort be made to explore new therapeutic strategies to improve survival [34]. Hyper-fractionated radiotherapy has a theoretical basis for being more effective in patients with high grade gliomas. The lower fraction size would cause less damage to the normal brain tissue because it has higher capacity for repair and hence would reduce toxicity. Increasing the fraction number would allow more tumor cells to be redistributed into cell cycle phases in which they would be more sensitive to irradiation. Tumor killing becomes less oxygen-dependant at lower fraction sizes, and hyper-fractionation allows for tumor re-oxygenation to occur. Thus a higher tumoricidal dose can be delivered with less collateral damage to normal brain tissue [47]. In addition the purpose of accelerated treatment in patients with anaplastic astrocytoma is to shorten the overall treatment time and hence improve the acceptability of what is considered far too long treatment episode [2]. The safety and tolerability of hyper-fractionated irradiation were confirmed in many randomized trials [1,4,6,8,11,12,14,15,17-20,22,26,30,32,33,37-39,46]. However survival advantage was documented in only two of these trials. The concept of RT concomitantly with chemotherapy has been explored by using several agents with radiosensitizing properties [43,45]. An RTOG phase-1 trial, in which 47 GBM patients were treated

with concomitant RT plus topotecan, reported a median survival of 9.7 months [9]. Similarly, 124 GBM patients treated with concomitant RT plus Tirapazamine a hypoxia-selective cytotoxin, had a median survival of approximately 10 months [7]. Kleinberg et al reported a median survival of 12.8 months for patients treated with concomitant RT plus cisplatin and BCNU [21]. The only trial evaluated RT delivered 3 times daily and concurrent administration of chemotherapy (i.v. nitrosourea therapy) was reported by Ravi et al, [34]. Unfortunately the results of this trial was disappointing because of the unaccepted toxicities. Temozolomide is a novel agent that has demonstrated activity in recurrent gliomas [31,41,35,10,49,48]. It readily crosses the blood brain barrier and achieves effective concentration in CNS with a reported plasma-CSF ratio of approximately 30% to 40% [28,42]. In a large randomized phase II trial in patients with recurrent GBM the efficacy of temozolomide was compared with that of procarbazine. In this trial the 6-month progression free survival rate was 21% for patients treated with temozolomide compared with only 8% for patients treated with procarbazine ( $p < .008$ ) [48]. The rationale of combining temozolomide with RT is based on preclinical data suggesting additive or perhaps synergistic activity. Van Rijn et al. [44] investigated prolonged temozolomide exposure followed by single-dose and fractionated irradiation in two glioma cell lines. No enhancement of cyto-toxicity could be demonstrated in the U251 cell line, but prolonged exposure to temozolomide and fractionated irradiation enhanced cyto-toxicity in the D384 cell line. It has been shown that temozolomide induce a G2-M arrest in glioma cells thus synchronizing the cell in a radiosensitive phase [16]. On the basis of the previously mentioned data, we initiated this study to investigate the safety, tolerability, response rate and survival of concomitant accelerated hyper-fractionated irradiation plus temozolomide therapy in patients with newly diagnosed high grade gliomas.

## PATIENTS AND METHODS

### *Patients' selection criteria:*

This study was conducted in patients with newly diagnosed and histologically proven high grade gliomas (Astrocytoma Gr III and GBM), aged >18 and < 65 years. Patients required to have an Eastern Cooperative Oncology Group performance status < 2 and adequate hemato-

logical, renal and hepatic functions according to all of the following laboratory values: absolute neutrophil count >  $1.5 \times 10^9/L$ , platelet count >  $100 \times 10^9 /L$ , hemoglobin more than 9 gm%, serum creatinine and total serum bilirubin < 1.5 times the upper limit of normal, aspartate amino transferase, alanine aminotransferase, and alkaline phosphatase of less than 2.5 times the upper limit of normal. Initial surgery/biopsy performed < 6 weeks prior to study enrollment. Eligible patients were also required to have no other severe underlying disease (including HIV and chronic hepatitis B or C infection). Exclusion criteria included any medical condition that could interfere with the oral administration of temozolomide or any previous or concurrent malignancies at other sites. Women with child-bearing potential required to have a negative urine or serum pregnancy test.

### *Treatment protocol:*

Radiation was delivered in fractions of 150cGy 3 times daily with at least 4-hour intervals between fractions to a total dose of 4050 cGy. The target volume was the tumor plus edema with a 2-cm margin. A boost of 1800cGy was given to the tumor plus a 2-cm margin to a total dose of 5850 cGy over 39 sessions over 2.5 weeks. Treatment volume was determined on the basis of pre-operative contrast enhanced CT or MRI of the brain. Temozolomide dose was ( $150 \text{ mg/m}^2 / \text{day} \times 7 \text{d} / \text{wk}$ ) given 2 hours prior to RT, from the beginning till the end of radiotherapy course. Prophylactic steroids were administered to all patients. Antiemetics were administered as needed.

### *Pre-treatment evaluation:*

Before treatment, patients underwent: (a) complete history, physical and neurological examination, (b) determination of performance status (PS), including CT scan and/or MRI, (c) hematology and clinical chemistry assessment were checked weekly during therapy and then every month. Neurological examination and CT and/or MRI were re-evaluated at the end of therapy and every 3 months.

### *Statistical methods:*

Toxicity was graded according to the common toxicity criteria [RTOG criteria for evaluation of radiation toxicities (5), and WHO criteria for evaluation of chemotherapy toxicities (29)]. Safety and toxicity were reported for all treated patients. Over-all survival was calculat-

ed from the time of the study until death or lost follow-up according to the Kaplan-Meier method with SPSS statistical software (release 7.5, 1996; SPSS Inc, Chicago, IL).

## RESULTS

### Patients characteristics:

Twenty-four eligible patients were enrolled onto this study. Patients' characteristics are listed in table (1). The median age was 45 years, and the male: female ratio was 1:2. Most of patients had an Eastern Cooperative Oncology Group performance status  $\leq 1$ . Ten patients (41.66%) had undergone de-bulking surgery, none of these patients being considered macroscopically complete resection. Fourteen patients (58.33%) had biopsy only.

### Toxicities

#### Hematologic toxicities:

Of the 24 patients included, 5 (21%) developed G2&G3 neutropenia and 4 patients (17%)

developed G2 & G3 thrombocytopenia (Table 2). None of the patients developed G4 hematologic toxicity.

#### Non-hematologic toxicities:

Non-hematologic toxicities were mild to moderate (Table 3), and were in the form of: nausea/ vomiting, rash, fatigue and acute radiation reaction (brain edema).

#### Survival:

The median duration of follow-up was 15.5 months (ranged between 4 months and 18 months). Using Kaplan-Meier estimates, the percentage survival at 12 months and 18 months were 67 and 51.5 respectively (Table 4). The 18 months survival rates for patients aged  $< 45$  years and those  $> 45$  years, were 69% and 27% respectively, ( $p>0.05$ ). Seventy percent of patients who underwent debulking surgery remained alive at 18 months in comparison to 36% of those who underwent biopsy only ( $p>0.05$ ).

Table (1): Patients Characteristics.

Parameter	Number	%
Total number of patients:	24	
<i>Age (years):</i>		
Mean $\pm$ SD	40.79 $\pm$ 12.43	
Median	45	
<i>Sex:</i>		
Male	8	33.30
Female	16	66.70
<i>Performance Status:</i>		
0	9	37.50
1	10	41.66
2	5	20.84
<i>Prior Surgical Procedure:</i>		
Incomplete resection	10	41.66
Biopsy only	14	58.33
<i>Histopathology:</i>		
Anaplastic Astrocytoma	16	66.70
Glioblastoma Multiforme	8	33.30

Table (2): Hematologic toxicities.

Toxicity	No.	%	GI %	GII %	GIII %
Anemia	21	87.50	3 12.50	0 0.0	0 0.0
Neutropenia	15	62.50	4 16.70	3 12.50	2 8.3
Thrombocytopenia	15	62.50	5 20.80	2 8.3	2 8.3

Table (3): Non-hematologic toxicities.

Toxicity	No.	%	GI %	GII %	GIII %
Vomiting	5	20.8	11 45.8	3 12.5	5 20.8
Fatigue	6	25.8	5 20.0	8 33.3	5 20.8
Skin Rash	17	70.8	3 12.5	4 16.6	0 0.0
Acute radiation reaction	21	87.5	1 4.1	2 8.3	0 0.0

Table (4): Survival rates at one year and 18 months.

Variable	Number of patients	1-year survival (%)	18-month survival (%)	p- value
All patients	24	67	51.5	
<i>Age</i>				
$< 45$	13	77	69	$>0.05$
$\geq 45$	11	55	27	
<i>Prior surgery</i>				
incomplete resection	10	80	70	$>0.05$
biopsy only	14	57	36	

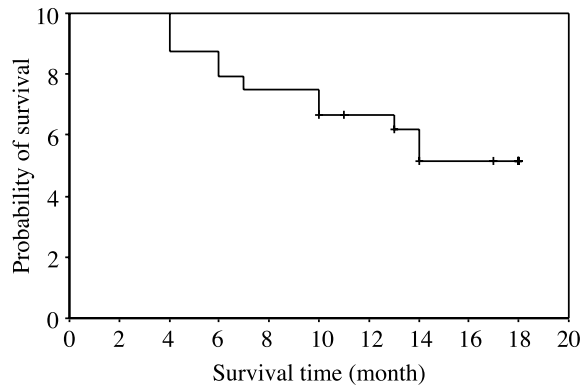


Fig. (1): Kaplan -Meier survival curve

Fig. (2): Patient 1, MRI prior to treatment.



Fig. (3): Patients 1, MRI after treatment.

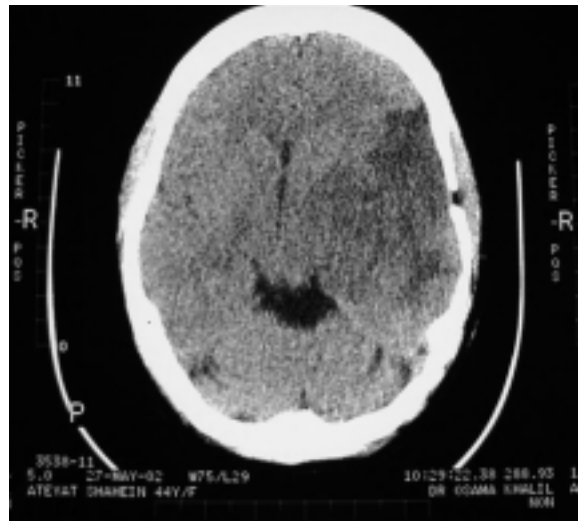
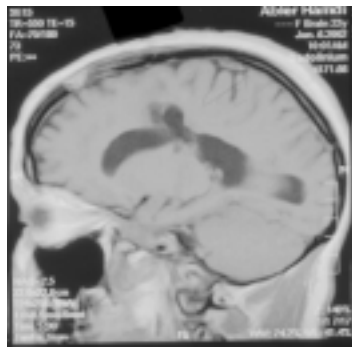


Fig. (5): Patient 2, CT scan after treatment.

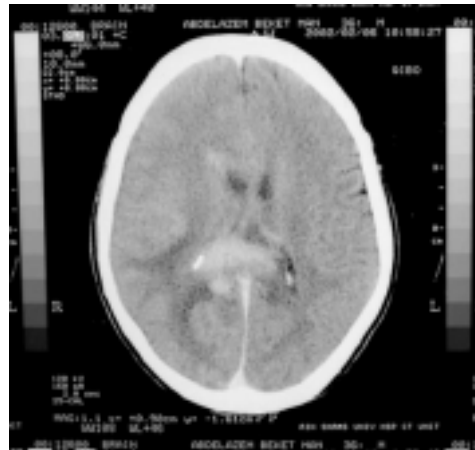


Fig. (6): Patient 3, CT scan prior to treatment.

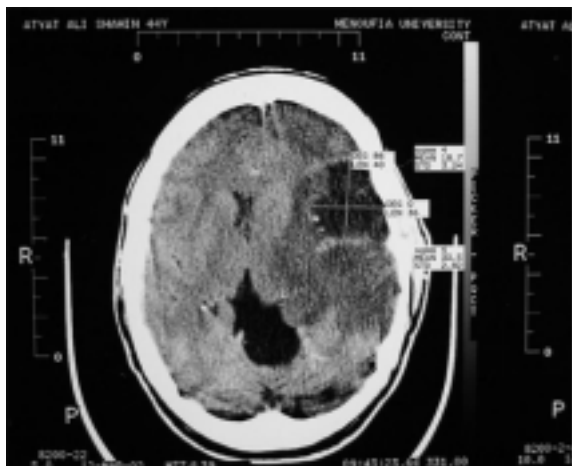


Fig. (4): Patient 2, CT scan prior to treatment.

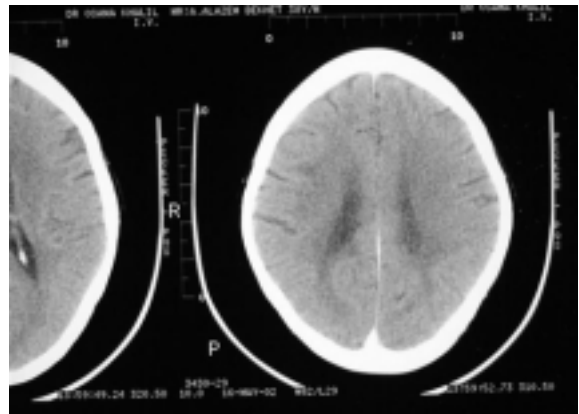


Fig. (7): Patient 3, CT scan after treatment.

## DISCUSSION

Chemotherapeutic potentiation of radiation to enhance tumor cell kill and to lengthen survival of patients who have glioma has been the object of investigation during the last decade. Unfortunately, consistent benefit either been unattainable or modest [23,24,26]. One reason of this is that chemotherapy given to potentiate 30-32 fractions of daily radiation over 6-7 weeks can produce serious systemic dose limiting toxicity. This complications abrogates the amount of drug that can be administrated and thereby the ability to achieve radiation dose enhancement sufficient to slow tumor growth [27].

To overcome this limitation we compressed the treatment schedule into 2.5 weeks to allow for maximal temozolomide dosing. Ravi, et al, [34] investigated the safety of thrice-daily hyper-fractionated radiotherapy given in conjunction with BCNU in high grade glioma. In their study 18 patients with high grade glioma were enrolled. The dose of irradiation was 5040cGy, with a 1440cGy boost in 180cGy fractions delivered thrice daily in two 6-day periods with a 2-week interval. BCNU (200 mg/m<sup>2</sup>) was administrated on the first day of irradiation, then every 7 weeks for 1 year and every 10 weeks for another 1 year. Of the 18 patients included 13 had stable disease, 4 regression, and 1 progression, the median time to progression was 37.8 weeks. The median overall survival was 44.4 weeks. Nine patients had neurologic toxicities, including 2 deaths at 69 and 139 weeks. The authors concluded that this regimen is unacceptably toxic, and speculated that the biologic effect of this combination schedule was responsible for the high degree of toxicity encountered [34]. This could be explained by the relatively high fraction size used (180 cGy), total radiation dose (6480 cGy) and the toxic effect of concurrent administration of i.v. BCNU. In our study radiation was given in fractions of 150 cGy 3 times daily for a total dose of 5850cGy in conjunction with temozolomide, 150 mg/m<sup>2</sup>/dayx7/wk. This regimen was tolerable with no serious acute toxicity. Response to therapy was recorded in our study, as shown in figs (2-7), but was not one of our objectives because it is always difficult to distinguish between the resolution of post-surgical artifacts and the true response to therapy, and also, it is assumed that some patients might have no residual disease to monitor after surgery. Safety

and tolerability of concomitant radiation plus temozolomide was recently reported by Stupp et al. [40], they conducted a trial on 64 patients with high grade glioma. These patients received temozolomide (75 mg/m<sup>2</sup>/dx 7d/wk for 6 weeks) concomitant with fractionated radiotherapy (60 Gy total dose: 2 Gy x 5 d/wk for 6 weeks) followed by temozolomide monotherapy (200 mg/m<sup>2</sup>/d x5 days, every 28 days for 6 cycles). The primary end points were safety and tolerability, and the secondary end point was overall survival. The authors reported that this schedule of concomitant temozolomide and conventionally fractionated radiotherapy is a safe and well tolerated. Non-hematologic toxicities were rare and mild to moderate in severity. During the concomitant treatment phase, grade 3 and 4 neutropenia, thrombocytopenia or both were observed in 6% of patients. During adjuvant temozolomide, 2% and 6% of cycles were associated with grade 3 and 4 neutropenia or thrombocytopenia, respectively. Median survival was 16 months, and the 1 and 2-year survival rates were 58% and 31%, respectively. The authors concluded that this regimen is safe and may prolong the survival of patients with high grade glioma. In our trial we used temozolomide in a daily dose of 150/m<sup>2</sup> from the beginning till the end of irradiation (2.5 weeks). Despite the escalation of the dose of temozolomide (double the dose used by Stupp et al, [40]), the hematologic and non-hematologic toxicities documented in our studies were only mild to moderate. This could be related to the relatively short period of administration of temozolomide (2.5 weeks in our study vs. 6 weeks in Stupp et al study). In addition, the median duration of follow-up was 15.5 months. This period might not be enough for proper evaluation of late toxicities that could happen, especially neurologic. The median survival in our study has not been calculated, as with a maximum follow-up of 18 months, 51.5% of the patients remained alive (This means that the median survival should be  $\geq$  18 months), which is comparable to that achieved by Stupp et al. (15.8 months). This result might help in answering the question raised about whether the improved survival achieved in Stupp et al, study resulted from the combined administration of temozolomide and radiotherapy, or simply because of adjuvant therapy with an active agent. In conclusion temozolomide in a daily dose of 150 mg/m<sup>2</sup> concomitant with thrice daily fractions of 150 cGy for a total dose

of 5840 cGy is a safe and tolerable regimen, in terms of acute toxicities, however long term follow-up is required for proper assessment of late toxicities. The median survival achieved is promising and needs to be confirmed in a randomized trial comparing accelerated hyperfractionated radiotherapy with and without temozolomide.

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