Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://dx.doi.org/10.21608/zumj.2022.135444.2560 Volume 28, Issue 6, November 2022(1254-1260)

Manuscript ID ZUMJ-2204-2560 (R2)
DOI **10.21608/zumj.2022.135444.2560**

ORIGINAL ARTICLE

Adjuvant Temozolamide Six Cycles Versus Extended Twelve Cycles in Glioblastoma Multiform

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Submit Date	2022-05-11 23:49:47
Revise Date	2022-09-18 20:32:47
Accept Date	2022-07-03 22:52:29

ABSTRACT

Glioblastoma multiforme (GBM) is one of the most malignant CNS tumors. Despite advances in treatment modalities, it remains largely incurable. Several studies show that there is a promising survival advantage in treatment of GBM with extended temozolamide as compared to standard adjuvant six cycles.

The aim is to evaluate the impact of extended 12 versus standard6 cycles of adjuvant temozolamide (TMZ) on overall survival and progression free survival in glioblastoma multiform patients.

Patients and methods: The study was conducted on 40 newly diagnosed cases of glioblastoma referred to Zagazig University Hospital's Clinical Oncology and Nuclear Medicine Department, between January2018and January 2020.Eligible patients are adults between the age of18-65 years. They had normal liver and renal function tests, hemoglobin more than 10gm/dl and Karnofsky Performance Score (KPS) more than70. Patients with recurrent GBM or other active cancer or poor KPS were excluded.

The patients were divided into 2 groups: group A included 20 patients treated by radiotherapy at a dose 60Gy/30fraction concurrently with TMZ for 6cycles (conventional TMZ) compared with group B which included 20 patients treated by the same concurrent chemo-radiotherapy regimen followed by 12 cycles of adjuvant TMZ (extended TMZ).

RESULTS: The median progression free survival (PFS) was7.3 months and 5.6 months in extended TMZ and conventional TMZ respectively. Median overall survival (OS) was 12.4 months versus 10.8 in extended TMZ and conventional TMZ respectively.

Conclusions: the study found that extended TMZ is well tolerated and is associated with increased PFS and OS in treatment of GBM, although being statically not significant. Further studies are needed to evaluate the extended treatment protocol.

Keywords
Temozolamide, Glioblastoma, Overall survival, Radiotherapy

INTRODUCTION

Glioblastoma multiforme (GBM) is one of the most common and malignant forms of brain tumor. The current standard therapeutic approach for glioblastoma multiform (GBM) is multimodal in nature, involving surgical removal, followed by concurrent chemo-radiotherapy. Surgical excision of GBM aims for maximal safe resection of the lesion, which helps to alleviate the mass effect on the brain and prolong overall survival (OS) rate [1].

Postoperative external beam radiation is standard for glioblastoma and as such, efforts have been made to improve efficacy. Three-dimensional conformal radiotherapy, stereotactic radio surgery and proton therapy had been evaluated in several large studies, but none showed additional benefit over standard radiation [2].

Chemotherapy is now a significant part of the standard treatment protocol for GBM despite its moderate effect and controversial efficiency. Nowadays, many studies are searching for more effective chemotherapeutic protocols [3].

Despite this aggressive multimodal treatment and the good improvement in the OS of patients with GBM in the recent decade, the outcome is still poor, due to the heterogeneous nature of GBM and its quick progression with a median survival of about 15 months, which make it highly difficult to establish efficient treatment approaches with uniform results for all patients [4].

The modern post-surgical standard of care for newly diagnosed GBM is based on the results of randomized phase III study .It concluded that local radiation with daily concurrent temozolomide and post-radiation adjuvant TMZ 150-200mg/m2 for 5 days every 28 days for 6 cycles is associated with a significant increase in OS **[3]**.

Several clinical trials with TMZ studied different dose programs . The use of extended 12 cycles of adjuvant TMZ have shown promising survival benefit [5], but there was no improvement in the RTOG0525 trial which randomly assigned patients to receive radiotherapy followed by 6 cycles TMZ or dose dense TMZ for 12 cycles [4].

METHODS

The study was conducted on 40 newly diagnosed cases of glioblastoma referred to Zagazig University Hospital's Clinical Oncology and Nuclear Medicine Department, between January2018 and January 2020.Eligible patients are adults between the age of18-65 years. They had normal liver and renal function tests, hemoglobin more than 10gm/dl and (KPS) more than70. Patients with recurrent GBM or other active cancer or poor KPS were excluded. The patients were randomly divided in 2 groups: group A included 20 patients treated by radiotherapy at a dose 60Gy/30fraction concurrently with TMZ for 6cycles (conventional TMZ) compared with group B which included 20 patients treated by the same concurrent chemo-radiotherapy regimen followed by 12 cycles of adjuvant TMZ (extended TMZ).The adjuvant TMZ dose was150 -200mg/m^2 for five days every four weeks.

Written informed consent obtained from all participants, the study was approved by the research ethical committee (IRB) of faculty of medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Treatment Details

Patients received adjuvant three-dimensional conformal radiotherapy, conforming the recommended dose to the target volume ,and decreasing normal tissue exposure through patient's immobilization, CT planning, target volume and critical structures delineation, beam design and shaping of field with multi leaf collimator, dose calculation, plane optimization, and verification. The radiotherapy started within 3-6 weeks after surgery and a dose 60 Gy is given concurrently using temozolomide (TMZ) daily 75mg/m2 during radiotherapy (RT). The treatment delivered by photon beam using linear accelerator machine(Linac, Elekta 151204,precise plan, release 2.12, 477.08). with three-dimensional conformal Radiotherapy is planned in two phases. In the first phase the clinical target volume [CTV] includes the gross tumor volume plus edema plus 2cm safety margin. In the second phase CTV includes gross tumor volume +2cm safety margin. Planning target volume is generated by adding 5mm margin to CTV in the two phases, radiation dose is 50 Gy in the first phase followed by 10Gy in the second phase.

Monitoring for the adverse effects

During RT, all cases were observed every week for acute radiation complications. Patients may complain from transient worsening of neurologic manifestations due to edema, radiation dermatitis and alopecia which need medical management and reassurance.

After RT, the performance status was determined by physical and neurologic examination every month and complete blood count as well as liver and kidney function test before each cycle of adjuvant TMZ. the Follow up brain MRI was done every 3 months .response evaluation was done by Macdonald DR etal criteria[5]

STATISTICAL ANALYSIS

Data were collected and coded using Microsoft Excel software, then imported for analysis into SPSS software version 20.0**(**Statistical Package for the Social Sciences). Qualitative data were represented as numbers and percentages ,and quantitative continuous data were represented as mean ± SD. Difference and association of qualitative variables was tested by Chi square test (X^2). Differences between quantitative independent groups were tested by t test. Kaplan-Meier estimator was used for survival analysis. P value <0.05 indicates significant results and <0.001 indicates high significant result.

RESULTS

Table [1] shows no statistically significant difference between the 2 groups regarding

demographic data, manifestations, lesion site and extent of surgical resection.

Regarding the treatment outcome (Table [2]);5% of patients showed complete response[CR] in both groups, while 25%of patients in group A and 30% of patients in group B showed progressive disease[PD]. Partial response[PR] occurred in 55% in group A and was 40% in group B. Stable disease[SD] was presented in 15% of group A and 25% of group B with no statistically significant difference or association between the 2 groups. Extended adjuvant TMZ was associated with improvement in overall survival (OS) and progression free survival (PFS) (median OS was12.4 months versus 10.8 in conventional adjuvant TMZ, (P value 0.3) and median PFS 7.3 months versus 5.6 for group A of conventional adjuvant TMZ(P value 0.2),while this improvement is stastistically insignificant .Fig[1],table [3]

Toxicity :table [4]

There was no stastistically significant difference between both groups regarding toxicity .

Grade 1 non-hematological toxicity (nausea) was detected in 8 patients in both arms, Grade2 non-hematological toxicity (nausea), was detected in 9 and 10 patients in E-TMZ and C-TMZ arms respectively and no patients complained from grade 3 non-hematological toxicity

G1-2 vomitting was detected in 4 patients of arm A and 3 patients of arm B

two patients had grade 2 hematological toxicity(thrombocytopenia) in groupA, while three patients in group B. grade 1 anemia was shown in one patient only in both groups.two patients had grade 2 neutropenia in both groups.

Table1: demographic and clinical data distribution

			GROUP A	GROUP B	t/ X^2	P
Age			54.45±6.48	52.05±8.33	1.016	0.316
KPS			71.50±5.87	69.0±7.67	1.441	0.121
Sex	Female	N	9	7		
		%	45.0%	35.0%		
	Male	N	11	13	0.41	0.51
		%	55.0%	65.0%		
Initial presentation	Convulsion	N	5	5		
		%	25.0%	25.0%		
	Speech difficulties	N	1	0		
		%	5.0%	0.0%		
	Hemiparesis	N	12	12	3.33	0.5
		%	60.0%	60.0%		
	Personality changes	N	0	2		
		%	0.0%	10.0%		
	Blurring of vision	N	2	1		
		%	10.0%	5.0%		
Surgery	Biopsy	N	4	8		
		%	20.0%	40.0%		
	Near total resection	N	7	5	2.19	0.13
		%	35.0%	25.0%		
	Subtotal total resection	N	9	7		
		%	45.0%	35.0%		
Total		N	20	20		
		%	100.0%	100.0%		

No statistically significant difference between the 2 groups regarding demographic data, manifestations, lesion site and extent of surgical resection.

Table2: outcome distribution

			Group		X^2	P
			A	B		
RESPONSE	CR	N	1	1		
		%	5.0%	5.0%		
	PD	N	5	6	1.06	0.78
		%	25.0%	30.0%		
	PR	N	11	8		
		%	55.0%	40.0%		
	SD	N	3	5		
		%	15.0%	25.0%		
STATUS	DIED	N	10	9		
		%	50.0%	45.0%		
	LIVE	N	10	11	0.1	0.75
		%	50.0%	55.0%		
Total		N	20	20		
		%	**100.0%**	**100.0%**		

Table3: OS and PFS

	Group A	Group B	T	P
OS	12.40±5.76	10.85±3.91	0.995	0.326
PFS	7.30±2.36	5.65±1.85	1.301	0.201

No significant difference founded

Table (4): Toxicity.

Toxicity	Group A 20		Group B 20		Test*	p-value (Sig.)
	No.	%	No.	%		
Hematological						
Anemia						
G1-2	1	5.0%	1	5.0%	0.0	1.0 (NS)
Neutropenia						
G1-2	2	10.0%	2	10.0%	1.02	0.59 (NS)
G3	0	0.0%	1	5.0%		
Thrombocytopenia						(NS)
G1-2	2	10.0%	3	15.0%	0.23	0.89 (NS)
G3-4	1	5.0%	1	5.0%		
Non-Hematological						
Radiation dermatitis						
	2	10.0%	3	10.0%	0.22	0.63 (NS)
Nausea						(NS)
G1	8	40.0%	8	40.0%	0.25	0.88 (NS)
G2	9	45.0%	10	50.0%		
Vomiting						
G1-2	4	20.0%	3	15.0%	0.17	0.67 (NS)
Headache						
G1-2	3	15.0%	2	10.0%	0.22	0.63 (NS)

No significant difference founded

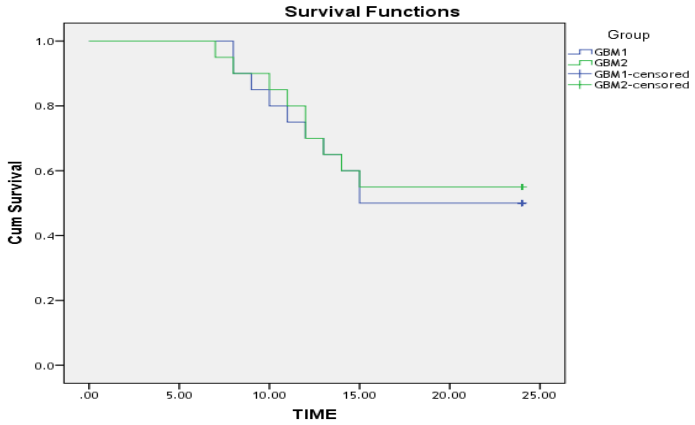

Figure (1): Kaplan-Meier plot Overall survival (OS)showing significant relation between overall mean OS in extended temozolamide(GBM1)was 12.4Months while that for Six cycles (GBM2)was 10.8 months.

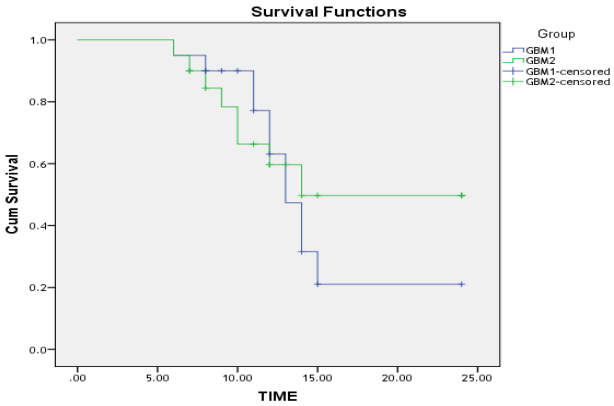

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Figure (2) Kaplan Meier plot survival and (showing significant relation between progression free survival in extended temozolamide(GBM1)was 7.3 Months while that for Six cycles (GBM2)was 5.6months

DISCUSSION

The current standard of care of GBM after surgery is concurrent TMZ and radiotherapy followed with adjuvant 6 cycles TMZ. Although this protocol improves treatment outcome, the prognosis of GBM is still poor. About 70%ofpatients progress during the first year [6].

Recently the recognized efficacy of TMZ in the adjuvant treatment of GBM encourages researchers to study dose modification to improve the outcome and survival. This can be achieved either by increasing dose in each cycle or extended adjuvant TMZ. The concept of this modification is the sustained depletion of **6methyleguaninmethyltransferase** [MGMT] by increasing the exposure of TMZ[9].

In the present study as regard survival outcomes median OS was 12.4 months versus 10.8 in extended TMZ and conventional TMZ respectively (No significant difference founded [Pvalue0.3].

Median PFS was7.3 months and 5.6 months in extended TMZ and conventional TMZ respectively No significant difference founded.[P value 0.2] which was similar to

RTOG 0525 trial in which patients randomized to recive 6 cycles versus 12 cycles TMZ of dose dense schedule [75-100mg/m2 given for 21days][7].However, neither median OS[16.6 VS14.9 months; p=0.63] nor median PFS[5.5 VS 6.7 months;p=0.06] was improved. Grade 3 toxicity was significantly higher in dose dense arm [53% versus 34%;P less than0.001]

Refae et tal randomized 59patients to 6 cycles of adjuvant TMZ or more than 6 cycles(median11 cycles range[8-23] .Both PFS and OS were statistically better in extended group

.Median PFS was12.1months in the arm treated by 6 cycles vs18.8 months in the arm treated with extended TMZ,p=0.015.Median OS was 18.1 months in the first arm vs 24.1 months in the second arm[10]this results was comparable to the present study may be due to prolonged adjuvant TMZ more than 12 cycle.

Menal etal randomized 40 patient received 6 cycles conventional temozolamide[C-TMZ] versus 12 cycles extended temozolamide[E-TMZ] median OS was 15.4 months versus 23.8 in C-TMZ and E-TMZ arm respectively [p=0.044][11].extended duration of TMZ was safe and well tolerated and rates of Grade 3 or higher hematological toxicity was less than 10% which was similar to the current study as Overall, 0% and 5% in C-TMZ and E-TMZ respectively had hematological toxicity more than grade3 during concurrent chemo- radiotherapy.

Overall, 5% and 15% of patients in C-TMZ and E-TMZ respectively had hematological toxicity during adjuvant treatment[11].

Retrospective multi-institutional trial by Hau P et al in which patient receiving at least 12 cycles of TMZ resulted in median overall survival was 30.6 for GBM patient[12].

Baragello et al showed that median OS 28 vs 8 months in patient treated with more than 6 cycles TMZ group [A] vs patients treated with only six cycles group [B] respectively and median PFS 20 VS 4 months in group A vs group B[13].with

Significant survival benefit to extended treatment

The result of retrospective comparative study by Roldan Urgoiti et al was median survival of 16.5 months in group treated with six cycles TMZ vs 24.6 months in group treated with extended 12 cycles TMZ with tolerated toxicity [8].this results were similar to the results of the current study.

In Bhandari RCT, the median overall survival was 23.8 in extended 12 cycles TMZ group compared to15.4 months in 6-cycles TMZ group with no statistical significance. The 2-year OS rates were 35% in 12 cycles arm compared to12.9% in the six cycles arm. The median PFS was 18.7 months in the 12-cycle group compared to16.4 months in the 6-cycles group [14]. this results were nearly similar to the results of the current study.

CONCLUSION

The current study suggest that extended adjuvant TMZ was safe and well tolerated and is associated with increased PFS and OS in treatment of GBM, although being statically not significant. Further studies are needed to evaluate the extended treatment protocol **.**

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

Funding information

None declared

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To Cite:
Elsebai, E., Elsheikh, M., Hefzi, N. Adjuvant Temozolamide Six cycles Versus Extended Twelve cycles In GLioblastoma multiform. *Zagazig University Medical Journal*, 2022; (1254-1260): -. doi: 10.21608/zumj.2022.135444.2560