Original Article

Comparative study of concurrent conventional chemoradiotherapy versus hypofractionated chemoradiotherapy in newly diagnosed glioblastoma multiforme postoperative patients

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ABSTRACT

Purpose: To assess the treatment response and toxicity profile among two groups of newly diagnosed glioblastoma multiforme (GBM) postoperative patients receiving conventional radiotherapy (RT) versus hypofractionated RT with concurrent temozolomide (TMZ) in both.

Materials and Methods: A total of 50 patients randomly allotted into two arms (25 in each). Dose received 60 Gy (2 Gy/#) in conventional fractionation RT versus 50 Gy (2.5 Gy/#) in hypofractionated RT with concurrent TMZ 75 mg/m^2 orally daily in both arms, respectively. Follow-up was done at 1, 3, 6, and 12 months after completion of treatment to evaluate toxicities, treatment response, and progression-free survival (PFS).

Results: All patients were well tolerated with treatment; no major adverse effects were monitored in two arms. There was no statistical significant difference in treatment response, which was found 64% versus 60% in arm A and arm B, respectively, at 3 months of follow-up ($P = 0.768$). Toxicity profiles were also noted similar in both arms. The 6-month PFS was 84% and 80% in arm A and arm B, respectively ($P = 0.71$) and 12-month PFS was 60% and 52% in arm A and arm B, respectively ($P = 0.69$).

Conclusion: Among the patients followed, this study showed that hypofractionated RT regimen was not inferior to conventional RT regimen.

KEY WORDS: Conventional radiotherapy, hypofractionated radiotherapy, newly diagnosed postoperative glioblastoma multiforme

INTRODUCTION

According to Globocon 2020 data, India was a single country, which contributing to 6.86% of the global cancer burden. Brain and central nervous system (CNS) tumors were the 20th most common cancer in world and the 14th most common cancer in India by incidence. It was the 13th most common cause of cancer-related death in the world and the 10th most common cause of cancer-related death in India. In India, deaths due to brain and CNS tumors were 26,656 in 2020, which was 3.1% of total cancer deaths.[1]

Incidence of brain and CNS tumors increases with age according to studies. Brain tumors divided into two categories: (1) primary brain tumors and (2) secondary brain tumors. Among them, secondary brain tumors are more common than primary type. Secondary brain tumors come from breast carcinoma, lung carcinoma, cervical carcinoma, testicular tumors, etc., Overall, brain and CNS tumors are slightly more common in females than males. In high-grade gliomas, includes anaplastic and GBM. Among them, anaplastic glioma contributes about 25% and rest about 75% are GBM. Histologically, these tumors have increased cellularity, nuclear atypia, and marked mitotic activity. However, in GBM, vascular proliferation and necrosis were also present. The incidence of brain tumors increases with age.[2]

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Farmers and petrochemical workers have been shown higher incidence of this tumor. A variety of chemical exposures have been linked, as reviewed by Brem SS *et al.*[3] There is also association of hereditary diseases, such as neurofibromatosis type 1 and 2, Von Hippel Lindau disease, and tuberous sclerosis. Maximum safe surgical resection followed by adjuvant chemoradiation with TMZ followed by adjuvant TMZ is the current standard of care of patients with newly diagnosed GBM patients.[4,5] A radiation dose of 60 Gy delivered at 2 Gy per fraction is considered optimal for tolerance with acceptable neurotoxicity.[6]

In adults, high-grade gliomas include anaplastic glioma and GBM; both types carry poor prognosis.[7] Even with aggressive radiotherapy (RT), chemotherapy, and seemingly complete surgical resection, the mean survival is typically less than 2 years.[8,9]

MATERIALS AND METHODS

This was a randomized prospective study conducted at Regional Cancer Centre, Bikaner. Randomization was done using computer software (https://www.randomizer.org). The study protocol included 50 patients of histologically-proven postoperative newly diagnosed GBM patients, who were enrolled from December 2018 to March 2020. Inclusion criteria included age 15–65 years, operated cases, KPS status 70 or more, without any hematological, renal, or liver functions abnormality, no previous history of RT treatment for GBM, and no concurrent other malignancies.

All 50 patients were randomly assigned to two arms either conventional CTRT (arm A) or hypofractionated CTRT (arm B), 25 patients in each arm. Patients in arm A received a total 60 Gy in 30 fractions (2 Gy per fraction, EQD2 = 60 Gy), administered daily (5 days per week) for 6 weeks (conventional fractionated RT) and arm B received total 50 Gy in 20 fractions (2.5 Gy per fraction, EQD2 = 52.08 Gy), administered daily (5 days per week) for 4 weeks (hypofractionated RT) at linear accelerator (LA) (3DCRT). Treatment volume included surgical bed including edema. External beam RT was given on LA machine with photon energies of 4–6 MV. All patients received concurrent chemotherapy (TMZ 75 mg/m^2 daily day 1–42 in arm A and day 1–28 in arm B). Adjuvant chemotherapy with TMZ 150 mg/m^2 daily D1–D5 was delivered for both arms, every 4 weeks, total 6 cycles. TMZ was discontinued if the absolute neutrophils count was $<1000/mm^3$ and platelet count $<75,000/mm^3$. Steroids, antiemetics, and other supportive treatment were used as per individual patient requirement.

Arm A

Dose: 2 Gy per fraction, 1 fraction per day, 5 days a week

Total tumor dose: 60 Gy; total number of fractions: 30

For treatment purpose, 2 panning target volume (PTV) volumes created

PTV 50 (low risk) - 2 Gy per fraction; total 25 fractions, 50 Gy dose

PTV 60 (high risk) - 2 Gy per fraction; total 30 fractions, 60 Gy dose, with TMZ 75 mg/m^2 daily (Day 1–42)

Arm B

Dose: 2.5 Gy per fraction, 1 fraction per day, 5 days a week

Total tumor dose: 50 Gy; total number of fractions: 20

For treatment purpose, 2 PTV volumes created

PTV (low risk) - 2.5 Gy per fraction, total 18 fractions; 45 Gy dose,

PTV (high Risk) - 2.5 Gy per fraction, total 20 fractions; 50 Gy dose, with TMZ 75 mg/m^2 daily (Day 1–28).

In high risk, PTV volume includes postoperative volume with edema, with 2 cm margin for CTV and additional 0.5 cm margin for PTV. In low risk, PTV volume includes postoperative volume only, with 2 cm margin for CTV and additional 0.5 cm margin for PTV.

Patients were under monitoring during RT treatment. In each monitoring, patients were assessed for treatment-related toxicities and morbidities. After completion of RT, patients were called for follow-up visit at 1, 3, 6, and 12 months for evaluation of treatment response, toxicities, and PFS. Contrast-enhanced magnetic resonance imaging (MRI) brain was done at 3, 6, and 12 months after completion of treatment. The response measured by Response Evaluation Criteria In Solid Tumors criteria. In this study, only acute toxicities were studied by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The primary objective of the study was to compare the efficacy of hypofractionated RT over conventional RT regimen in terms of DFS. The secondary objectives were treatment-related toxicities and tumor response due to RT schedules. Results of both arms were analyzed and compared in terms of DFS, tumor response, and treatment-related toxicities. This study was medically and ethically approved by our institutional ethical team.

RESULTS

The baseline patients and tumor characteristics are shown in Table 1. The treatment response on different follow-up visits is shown in Tables 2-5 to evaluate local control. Treatment-related toxicities are depicted in Figure 1 and PFS in Figure 2.

In this study, surgery included complete removal, partial removal, and tumor decompression. Complete removal of tumor means entire tumor removed; partial removal means

Table 1: patients characteristics and the column head is Characteristics

Patients characteristics	Arm A	Arm B	*P*
Age (years)			
Median age	35	43	
Range	15-65	20-65	
Gender			
Male	14	21	0.064
Female	11	4	
Anatomical site			
Frontal lobe	7	8	0.082
Parietal lobe	3	1	
Occipital lobe	2	2	
Temporal lobe	2	4	
Multi lobes	11	10	
Socioeconomic background			
Urban	8	9	0.076
Rural	17	16	
KPS status of patients			
100	0	0	0.776
90	13	14	
80	7	6	
70	5	5	
Surgery			
Complete removal	15	14	-
Partial removal	10	11	
Tumor decompression	0	0	

KPS=Karnofsky performance status

Table 2: Treatment response at 1 month

Treatment response	Number of patients	
	Arm A (25; 100%), *n* (%)	Arm B (25; 100%), *n* (%)
Regressive disease		
CR	4 (16)	5 (20)
PR	8 (32)	8 (32)
Total (CR + PR)	12 (48)	13 (52)
SD	13 (52)	12 (48)
PD	0	0

CR=Complete response, PR=Partial response, SD=Stable disease, PD=Progressive disease

Table 3: Treatment response at 3 months

Treatment response	Number of patients	
	Arm A (25; 100%), *n* (%)	Arm B (25; 100%), *n* (%)
Regressive disease		
CR	0	0
PR	16 (64)	15 (60)
Total (CR + PR)	16 (64)	15 (60)
SD	9 (36)	10 (40)
PD	0	0

CR=Complete response, PR=Partial response, SD=Stable disease, PD=Progressive disease

most of part of tumor removed, but some part of tumor still present; tumor decompression means tumor part that cause pressure effect, removed only.

Treatment response at 1 month was assessed by contrast-enhanced computed tomography (CECT) scan of the brain due to institutional protocol.

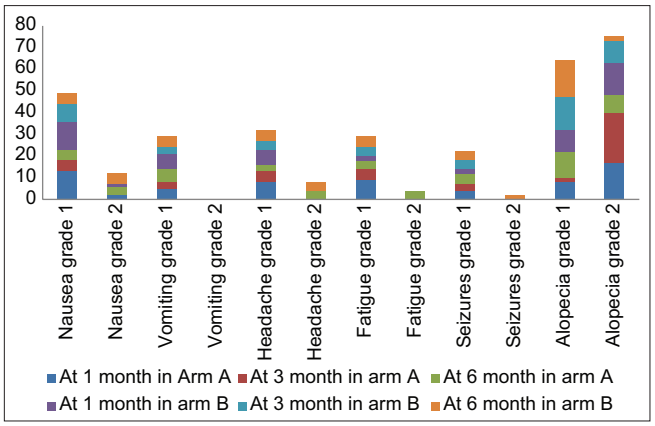

Figure 1: Treatment-related toxicities in arm A and arm B

Most of the patients had KPS status 90 in both arms, median age was 35 years in arm A and 43 years in arm B, and most of the patients had involvement of multilobes in both arms [Table 1]. A total of 50 patients (25 in each arm) were received concurrent chemoradiotherapy (CTRT). The first follow-up was done at 1 month after completion of chemoradiotherapy; CECT brain was done at 1-month follow-up to assess response from RT. 4 and 5 patients had complete response in arm A and arm B at 1 month, which was insignificant; 8 and 8 patients had partial response, 13 and 12 patients had stable disease, and 0 and 0 patient had progression of disease in arm A and arm B, respectively ($P = 0.777$) [Table 2.]

The subsequent follow-up was done at 3, 6, and 12 months. At 3-month follow-up, a total of 16 and 15 patients had regression (all had partial responses), 9 and 10 patients had stable disease, 0 and 0 patient had progression of disease in arm A and arm B, respectively ($P = 0.768$) [Table 3]. MRI brain at 3-month follow-up suggests no complete response compared to CECT brain at 1 month, due to less accuracy of CT scan of parenchymal disease differentiating from edema, compared to MRI. At 6-month follow-up, 13 and 12 patients had partial response, 8 and 8 patients had stable disease, 4 and 5 patients had progression of disease in arm A and arm B, respectively ($P = 0.777$) [Table 4]. At 12-month follow-up, 10 and 7 patients had partial response, 5 and 6 patients had stable disease, 10 and 12 patients had progression of disease in arm A and arm B, respectively ($P = 0.69$) [Table 5]. At this time, 8 and 10 patients expired in arm A and B, respectively, due to disease and other than disease causes. In arm A, 5 out of 8 patients expired due to disease itself, and in arm B, 7 out of 10 patients expired due to disease.

There were no grade 3 and 4 nonhematological toxicities in both arms [Figure 1]. The toxicities were measured by CTCAE Version 4.0. At 6 months, PFS was found 84% versus 80% in arm A and B, respectively ($P = 0.71$), and at 12 months, PFS was found 60% versus 52% in arm A and arm B, respectively ($P = 0.69$) [Figure 2].

DISCUSSION

GBM of the brain is predominantly a locoregional disease, and it is the most common malignant brain tumor in adults.[10,11]

Table 4: Treatment response at 6 months

Treatment response	Number of patients	
	Arm A (25; 100%), *n* (%)	Arm B (25; 100%), *n* (%)
Regressive disease		
CR	0	0
PR	13 (52)	12 (48)
Total (CR + PR)	13 (52)	12 (48)
SD	8 (32)	8 (32)
PD	4 (16)	5 (20)

CR=Complete response, PR=Partial response, SD=Stable disease, PD=Progressive disease

Table 5: Treatment response at 12 months

Treatment response	Number of patients	
	Arm A (25; 100%), *n* (%)	Arm B (25; 100%), *n* (%)
Regressive disease		
CR	0	0
PR	10 (40)	7 (28)
Total (CR + PR)	10 (40)	7 (28)
SD	5 (20)	6 (24)
PD	10 (40)	12 (48)

CR=Complete response, PR=Partial response, SD=Stable disease, PD=Progressive disease

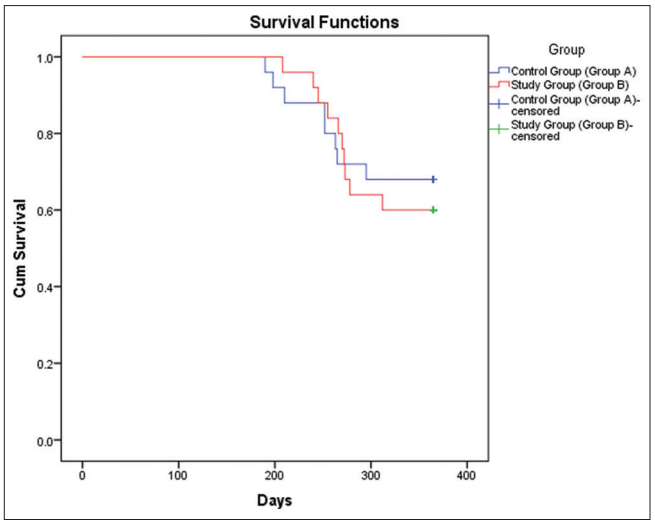

Figure 2: Comparison of conventional RT (2 Gy per fration) v/s hypofractionated RT (2.5 Gy per fraction) regarding progression-free survival (P = 0.69). Control group - Arm A. Study group - Arm B. Mean progression-free survival time for control group - 325.20 (301.19–349.21). Mean progression-free survival time for study group - 323.76 (302.93–344.58). Log rank test P = 0.69

The treatment of GBM is multimodality approach, requiring surgery, RT, and chemotherapy. Most of patients require radiation therapy, that given concurrently with chemotherapy. Cranial RT with concurrent TMZ is the most frequently administered treatment for patients with GBM. The prognosis of the most of patients with GBM is poor, with median survival of 12–14 months according to trials. Therefore, a short course of cranial RT would be preferable, so patients should spend less time going to treatment session. The short course of RT regimen that is as effective as conventional RT would be a best option. The role of adjuvant TMZ after RT has been investigated during the last decade. It seems that there is almost 2–3 months additional overall survival benefit as adjuvant chemotherapy after completion of RT treatment.[5,6]

Stupp *et al.*[12] performed an analysis using with 420 patients treated on brain tumor, with doses ranged from <45 to 60 Gy using 1.7–2 Gy per fraction. A significant improvement in median survival from 28 to 42 weeks in the groups treated with doses of 50–60 Gy was found. This study also showed a significant survival advantage in patients who received 60 Gy compared to those who received 45 Gy (12 vs. 9 months; P = 0.007). Terasaki *et al.*[13] reported on a Japanese study of 26 patients with GBM treated with hypofractionated RT and TMZ. Patients received 45 Gy in 15 fractions over 3 weeks with concomitant and adjuvant TMZ. The PTV included enhancing tumor and postoperative cavity with a 2 cm margin. At a median follow-up of 20 months, the median OS was 15.6 months. No significant increase in toxicity was observed.

A study HART GBM trial[14] published in 2018 evaluated the efficacy of hypofractionation versus conventional RT with concurrent TMZ. The conclusion of HART is comparable to CRT in terms of survival outcome, dose escalation, and reduction in overall treatment time. HART had comparable toxicity and DFS to conventional arm. A study by Perry *et al.*[15] published in 2017 evaluated short course of radiation with and without TMZ in elderly patients with GBM. The conclusion is that, in elderly patients with GBM, the addition of TMZ to short course of radiotherapy results in longer survival than short-course RT alone. In recent study, care is often considered palliative, when patients are not fit and complete resection of tumor cannot be achieved. Patients with a KPS ≤50 have a poor survival prognosis and appear good candidates for short-course RT. It means the patients having good KPS consider for aggressive treatment like short-course RT with TMZ, while patients with poor KPS may consider for RT alone.[16]

This study was started with intension to assess the role of hypofractionated RT in GBM patients. It was observed that hypofractionated RT is not inferior than conventional RT. Overall disease response was almost similar in both conventional and hypofractionated arms. Acute toxicities were similar in both arms. Hence, hypofractionation can be used in patients depending on patient's general condition and patient's age.

Limitations

In this study, CT scan done at 1 month was not useful for the assessment of RT response. In spite of CT scan at 1 month, MRI can be better option than CT scan for assessment, if required. Smaller numbers of patients and relatively shorter follow-up remain the major limitations of this study.

CONCLUSION

This study show noninferiority of hypofractionated RT regimen over conventional RT regimen in terms of overall response

and 6-month PFS in these patients while toxicities were comparable, newly diagnosed postoperative GBM patients.

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Conflicts of interest

There are no conflicts of interest.

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