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A retrospective analysis of irinotecan and bevacizumab combination therapy in recurrent high-grade glioma and glioblastoma multiforme: Single-institute experience

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Abstract

Introduction: High-grade gliomas comprise central nervous system (CNS) World Health Organization (WHO) Grade 3 and CNS WHO Grade 4 gliomas. Recurrence is seen in almost all patients who underwent treatment. Recurrent high-grade gliomas have poor prognosis. There are phase two trials that assessed the role of irinotecan and bevacizumab as combination regimen in recurrent High-grade gliomas and showed overall survival (OS) and progression-free survival (PFS) benefit. We did a retrospective analysis of our institutional experience on treating recurrent high-grade gliomas with combination of irinotecan and bevacizumab.

Materials and Methods: This was a retrospective analysis including 58 patients treated at our center from January 1, 2010 to December 31, 2020. All patients were diagnosed case of CNS WHO Grade 3 and Grade 4 glioma, who received at least one modality of treatment. All patients received inj. Irinotecan 125 mg/m² intravenous (IV) and inj. Bevacizumab 10 mg/kg IV, every 2 weekly. A base line radiological evaluation has been done with magnetic resonance imaging brain with contrast and repeated every 3 months. Patients have been assessed both for PFS and OS.

Results: Median PFS was 6 months (95% confidence interval [CI] 4.395–7.605). Median OS was 8 months (95%CI 5.894–10.106). Six months PFS rate is 49% and 6 months OS is 58%. CNS WHO Grade 3 gliomas responded better to combination therapy as compared with CNS WHO Grade 4 gliomas.

Conclusion: Combination of Bevacizumab and Irinotecan is well tolerated and improves OS and PFS in patients with recurrent high-grade gliomas. The effect of combination systemic therapy is more evident in CNS WHO Grade 3 gliomas as compared with glioblastoma multiforme.

Keywords: Bevacizumab, irinotecan, recurrent high-grade gliomas

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INTRODUCTION

High-grade gliomas are most common primary malignant tumors of brain in adults.^[1] They constitute 35%–45% of primary brain tumors. Glioblastomas constitute majority

of high-grade gliomas. High-grade gliomas comprised of central nervous system (CNS) World Health Organization (WHO) Grade III and Grade IV gliomas. The peak

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incidence happens in fifth and sixth decades of life. These tumors, especially glioblastoma multiforme (GBM), have a poor prognosis. The median survival duration is 8–15 months for a newly diagnosed tumor.^[2] Recurrence is seen in almost all the patients who underwent treatment. In a progressive or a recurrent tumor, the survival ranges between 3 and 6 months. Recurrent high-grade gliomas are resistant to chemotherapy. For a recurrent high-grade glioma or a progressive GBM, currently FDA-approved drugs are Lomustine, Carmustine, Temozolamide, Irinotecan and Bevacizumab, and Bevacizumab. There are phase two trials which assessed the role of Irinotecan and Bevacizumab as combination regimen in high-grade gliomas and showed overall survival (OS) and progression-free survival (PFS) benefit.

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to the vascular endothelial growth factor (VEGF) receptors, that is, FMS related receptor tyrosine kinase 1 and kinase insert domain receptor and competitively inhibits VEGF. GBM is a highly vascular tumor, and expresses high level of VEGF.^[3] Therefore, Bevacizumab works effectively.^[4]

Irinotecan is a topoisomerase-I inhibitor; topoisomerase-I is a critical enzyme needed for DNA replication.^[5] Topoisomerase I and II activities are significantly enhanced in malignant gliomas following DNA damage. Chromatin-bound topoisomerase I and II levels correlate with the induction of apoptosis by DNA-damaging agents, and the induction of apoptosis is associated with a decline in Bcl-2. Irinotecan after carboxylesterase-mediated breakdown produces 7-ethyl-10-hydroxycamptothecin (SN-38).^[6] This is the active metabolite of irinotecan and is more potent than irinotecan. SN38 reduces the expression of anti-apoptotic protein Bcl-2 and increases the expression of proapoptotic protein Bax. Irinotecan can cross blood-brain barrier and glioma cells can convert irinotecan directly to SN38. Irinotecan showed efficacy in GBMs that are multidrug resistant.^[7]

Stark-Vance^[8] studied the efficacy of combination of irinotecan and bevacizumab in malignant gliomas in 2005. This study showed an efficacy rate of 43%. Vredenburg *et al.*^[9] did a phase-two trial which shows that Bevacizumab and Irinotecan is effective in the treatment of recurrent high-grade gliomas.

Based on all this available data, we did a retrospective analysis of our institutional experience on treating high-grade gliomas with combination of irinotecan and bevacizumab.

MATERIALS AND METHODS

Patient characteristics

A total of 58 patients of recurrent high-grade gliomas treated from January 1, 2010 to December 31, 2020 are studied. All patients are known cases of high-grade glioma. All patients underwent prior surgery followed by chemoradiation therapy with concurrent temozolamide followed by adjuvant temozolamide. Patients with previous low-grade glioma recurred with high-grade conversion received a first-line chemotherapy with temozolamide and then on progression switched over to Inj. Irinotecan and Inj. Bevacizumab. All patients should had a previous pathological confirmation of high-grade glioma and a radiological confirmation of progression. We excluded those patients who had hemorrhage on magnetic resonance imaging (MRI), previous history of therapy with Bevacizumab, and previous history of any other malignancy.

Patient evaluation, treatment, and follow-up

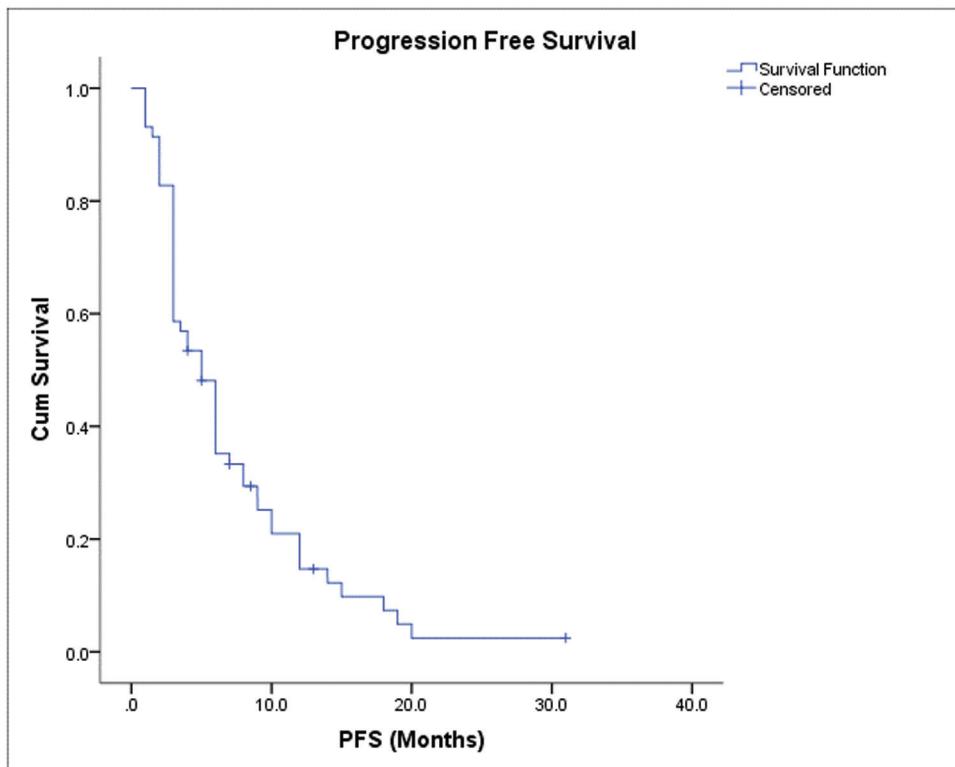
All the patients have a base line MRI, and normal hematological parameters before receiving chemotherapy. Patients received Inj. Irinotecan 125 mg/m² intravenous and Inj. Bevacizumab 10 mg/kg intravenous on day 1, repeated every 2 weeks. Patients were been radiologically reassessed every 3 monthly (after every six doses of systemic therapy) with contrast MRI brain. The systemic therapy has been continued till progression or death.

Response assessment

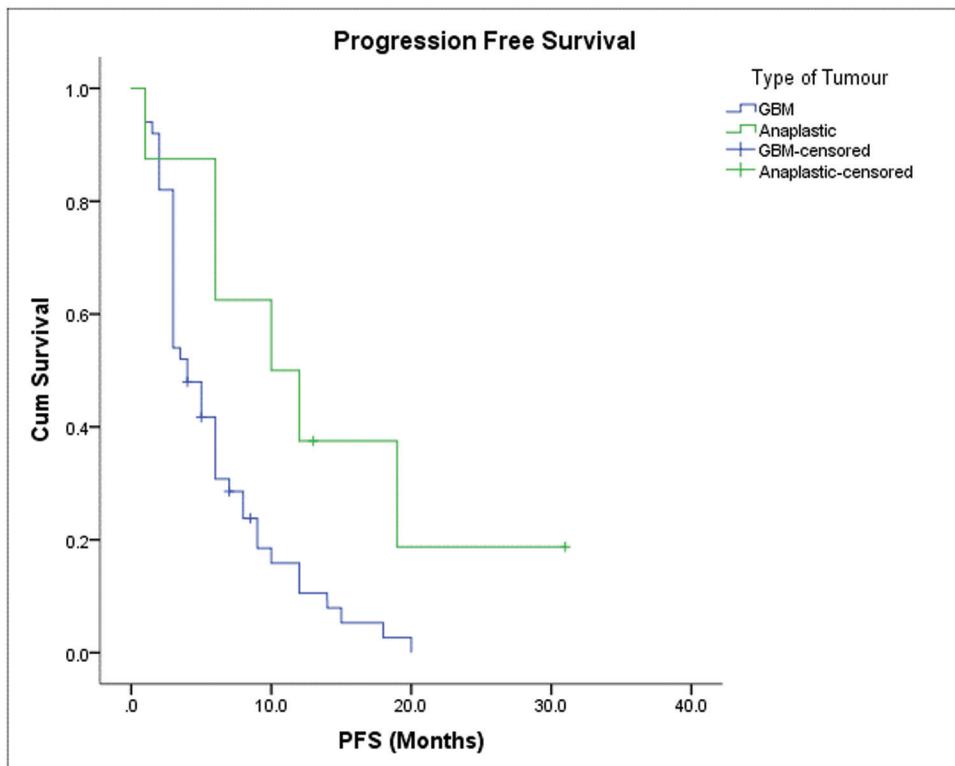
The response to therapy was determined by MRI. A partial response was determined if the contrast images showed a greater than 50% decrease in the area of enhancement and stable or decreased T2 and FLAIR signal. The patient was on stable and on decreased dose of dexamethasone and improved clinically. A complete response was determined by the resolution of all measurable abnormalities on the contrast images, as well as by stable or decreased disease on T2 and FLAIR images. Disease progression was defined as a greater than 25% increase in the area of enhancement, appearance of a new lesion, or deterioration in the patient's clinical status that was thought to be related to tumor progression.

End Points and statistical analysis

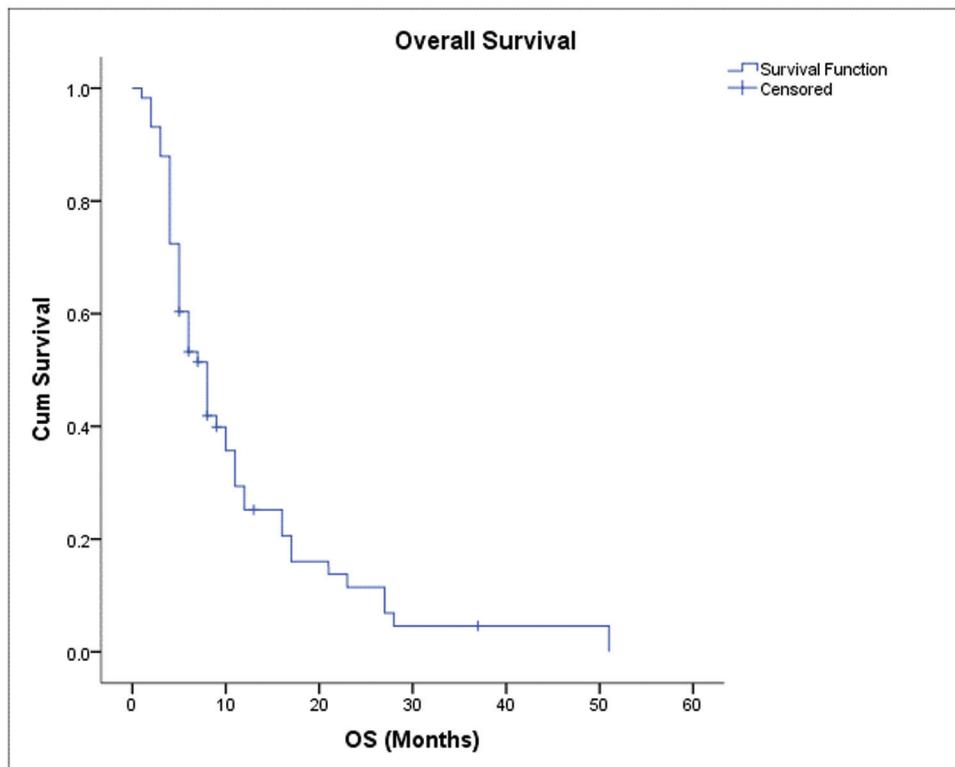
Study end points include treatment response rates, clinical improvement, PFS [Graphs 1 and 2], and OS [Graphs 3 and 4]. Patients were analyzed on intention to treat basis. Kaplan-Meier method was used to analyze the survival outcomes.



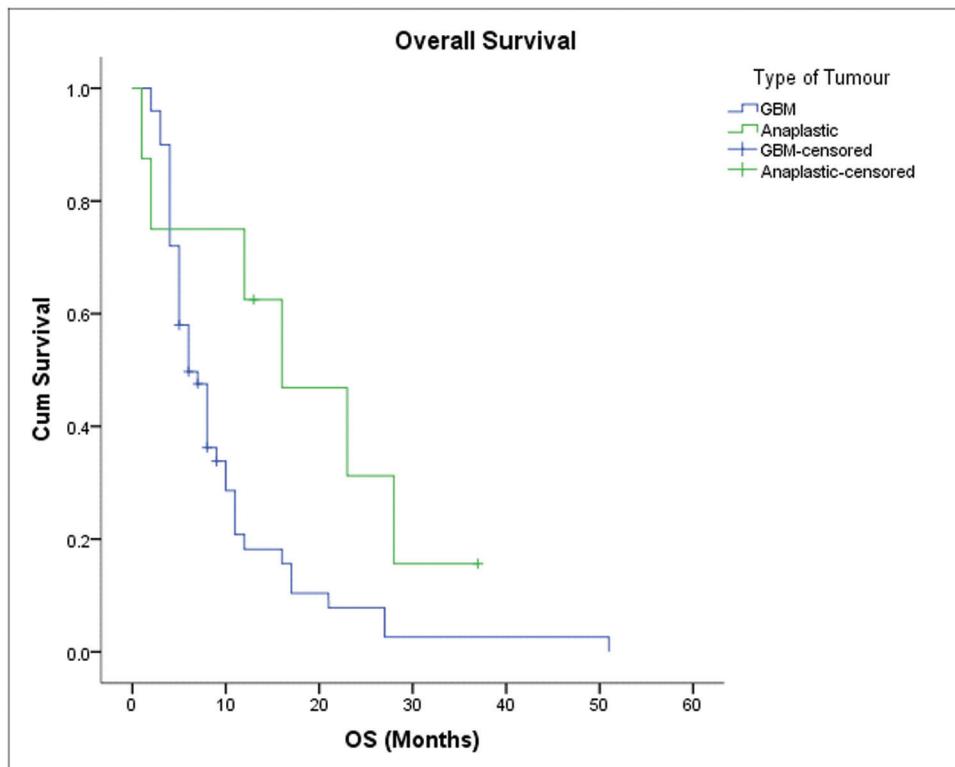
Graph 1: Progression-free survival (censored)



Graph 2: Progression-free survival (type of tumor)



Graph 3: Overall survival (censored)



Graph 4: Overall survival (type of tumor)

RESULTS

A total of 58 patients were analyzed. Patient characteristics are shown in Table 1. Majority of the patients were over 50 years (69%). Eighty six percent of patients were known case of GBM. Approximately 87.9% of patients received Irinotecan and Bevacizumab as second line of treatment. Primary surgery followed by radiation along with concurrent temozolomide and adjuvant temozolomide is considered as first-line treatment. Median follow-up of patients involved in study was 24 months. Median number of prior lines of therapies was 1. Median age of patients in study was 54.5 (21–75).

PFS

Of 58 patients analyzed retrospectively [Table 2], 52 patients, that is, 87.9% patients progressed. Median PFS from the date of initiation of systemic therapy with Irinotecan and Bevacizumab was 6 months with 95% confidence interval of 4.4 months to 7.6 months. Approximately 58.6% patients were progression free at end of 3 months. Approximately 49% patients were progression free at end of 6 months and 20.3% patients were progression free at end of 12 months. On subset analysis, median PFS from the date of initiation of systemic therapy with Irinotecan and Bevacizumab for patients with recurrent GBM was 5 months with 95% confidence interval (CI) of 3.968 months to 6.032 months [Table 3]. Median PFS from the date of initiation of systemic therapy with Irinotecan and Bevacizumab of patients with recurrent anaplastic glioma was 10 months with 95% CI of 2 months to 16 months ($P = 0.017$) [Table 3].

OS

Of 58 patients analyzed [Table 2], 51 patients (87.9%) died at the time of analysis; only seven patients (12.1%) are alive. Median OS from the date of initiation of systemic therapy with Irinotecan and Bevacizumab was 8 months with 95% CI of 5.9 to 10.1 months. Approximately 87.9% patients had 3 months survival, 58% patients had 6 months survival, and 24.1% patients had 12 months survival. On subset analysis recurrent GBM patients had a median OS of 7 months from the date of initiation of systemic therapy with Irinotecan and Bevacizumab with 95% CI of 5.08–8.92 [Table 3]. Recurrent anaplastic glioma patients had a median OS of 16 months from the date of initiation of systemic therapy with Irinotecan and Bevacizumab with 95% CI of 3.1–28.9 months, with P value of 0.039 [Table 3]. The median time period from time of diagnosis to initiation of current treatment was 9.7 months for GBM with 95% CI of 6.9 to 12.5 months. The median

Table 1: Patient characteristics

Age	Frequency	%
< 50	18	31
>50	40	69
Type of tumor		
GBM	50	86.2
Anaplastic glioma	8	13.8
Number of lines of prior therapies		
1	51	87.9
2	3	5.1
3	2	1.7
Performance status		
PS 0–1	42	72.4
PS 2	16	27.6
Survival status		
Alive	7	12.1
Death	51	87.9
Progression status		
Progressed	52	89.7
Not progressed	6	10.3

Table 2: Kaplan estimates of survival

	Six months (%)	Median (months)	# Events
Progression-free survival	49%	6 months	52/58
Overall survival	58%	8 months	51/58

Table 3: Subset analysis

	GBM	Anaplastic astrocytoma	P Value
Median progression-free survival (months)	5 (3.968–6.032)	10(2–16)	0.017
Median overall survival	7(5.080–8.920)	16(3.132–28.868)	0.039

time period from time of diagnosis to initiation of current treatment was 28.63 months for anaplastic glioma patients with 95% CI of 9.2 to 47.7 months. The median OS of GBM patients from initial diagnosis was 17.5 months with 95% CI of 14 to 20.5 months. The median OS of anaplastic glioma patients was 45.1 months with 95% CI of 21.1 to 69 months.

Response rates

Approximately 79.3% of study population (16) patients showed either partial or complete response at 3 months after starting treatment. Approximately 49.2% (28) patients showed either partial or complete response at 6 months after starting treatment.

A case of 43-year-old woman with recurrent right temporoparietal GBM, post-surgery followed by radiation followed by adjuvant temozolomide. At recurrence, she received 6 months of Irinotecan and Bevacizumab [Figures 1 and 2].

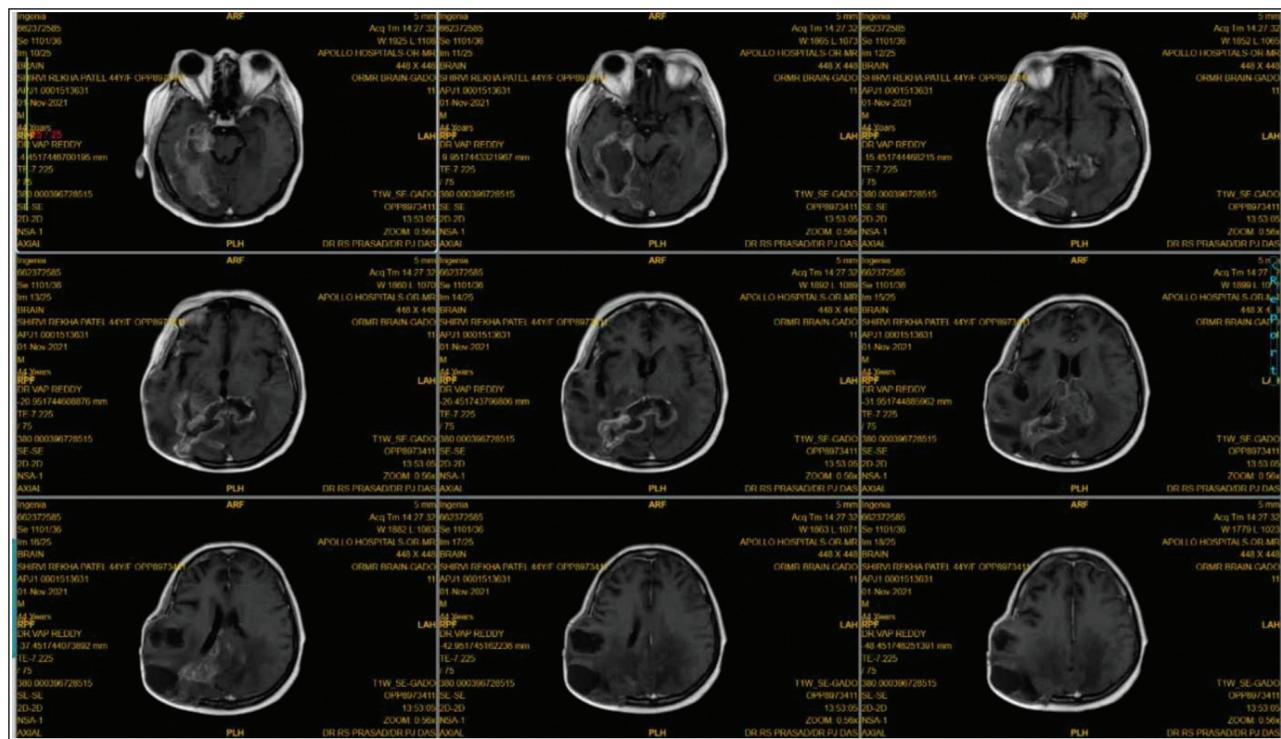


Figure 1: MRI T1 with contrast axial images at the time of recurrence

DISCUSSION

Historically, the data pertaining to recurrent GBM showed response rates of less than 20% and 6 month PFS was less than 30%. While concurrent temozolomide followed by adjuvant temozolomide is considered as primary modality,^[1] the role of temozolamide in a recurrent GBM as second line in patients previously treated with nitrosureas is not clear in view of development of drug resistance.

Other regimens available for treatment of recurrent malignant gliomas are nitrosureas (CCNU and BCNU) either as single agents or in combination regimens, as PCV (procarbazine + lomustine + vincristine). There are phase II data for this regimen conducted by Schmidt *et al.*^[10] This is a study on 86 patients with recurrent GBM. Three patients have partial response, with 0 complete response. Median PFS-17.1 weeks, 6 months PFS – 38.4%. Brandes *et al.*^[11] conducted a study on 40 patients with recurrent GBM, for assessing monotherapy with carmustine monotherapy which showed median PFS of 13.3 weeks and 17.5% PFS at 6 months.

There are many studies mainly Phase II on the efficacy of Bevacizumab as single agent or in combination with other agents in recurrent GBM and grade 3 gliomas. Bevacizumab is approved by FDA for secondary treatment of GBM in the USA.^[12] Tao Xu *et al.*^[13] conducted a systemic review

on effects of bevacizumab plus irinotecan on response and survival in patients with recurrent malignant glioma. This analysis included 411 patients of GBM, and results showed median PFS ranging from 2.4 to 13.4 months across various studies with response rates ranging from 28% to 86%.^[5] This study showed a median OS of 10.96 ± 8.4 months and mean response rate of $18.9\% \pm 20.5\%$. This review showed a statistically significant improved response rates with usage of Irinotecan and Bevacizumab and a moderate effect on OS time.

We did a retrospective analysis at our institute experience on number of recurrent malignant gliomas treated with irinotecan and bevacizumab. Majority of patients had ECOG performance score 0–1; however, 27% of study population had ECOG performance score of 2. All patients received standard of care, surgery followed by adjuvant radiation therapy with concurrent temozolomide followed by adjuvant temozolomide for a period of 6–12 months. Majority of the patients are grade 4 gliomas and very few patients are grade 3 tumors.

Our retrospective study showed an overall median PFS benefit of 6 months and OS benefit of 8 months from the time of recurrence. Median number of bimonthly bevacizumab and irinotecan cycles received in the study population was 12 cycles. In our study, we found that the anaplastic astrocytomas in comparison responded better to

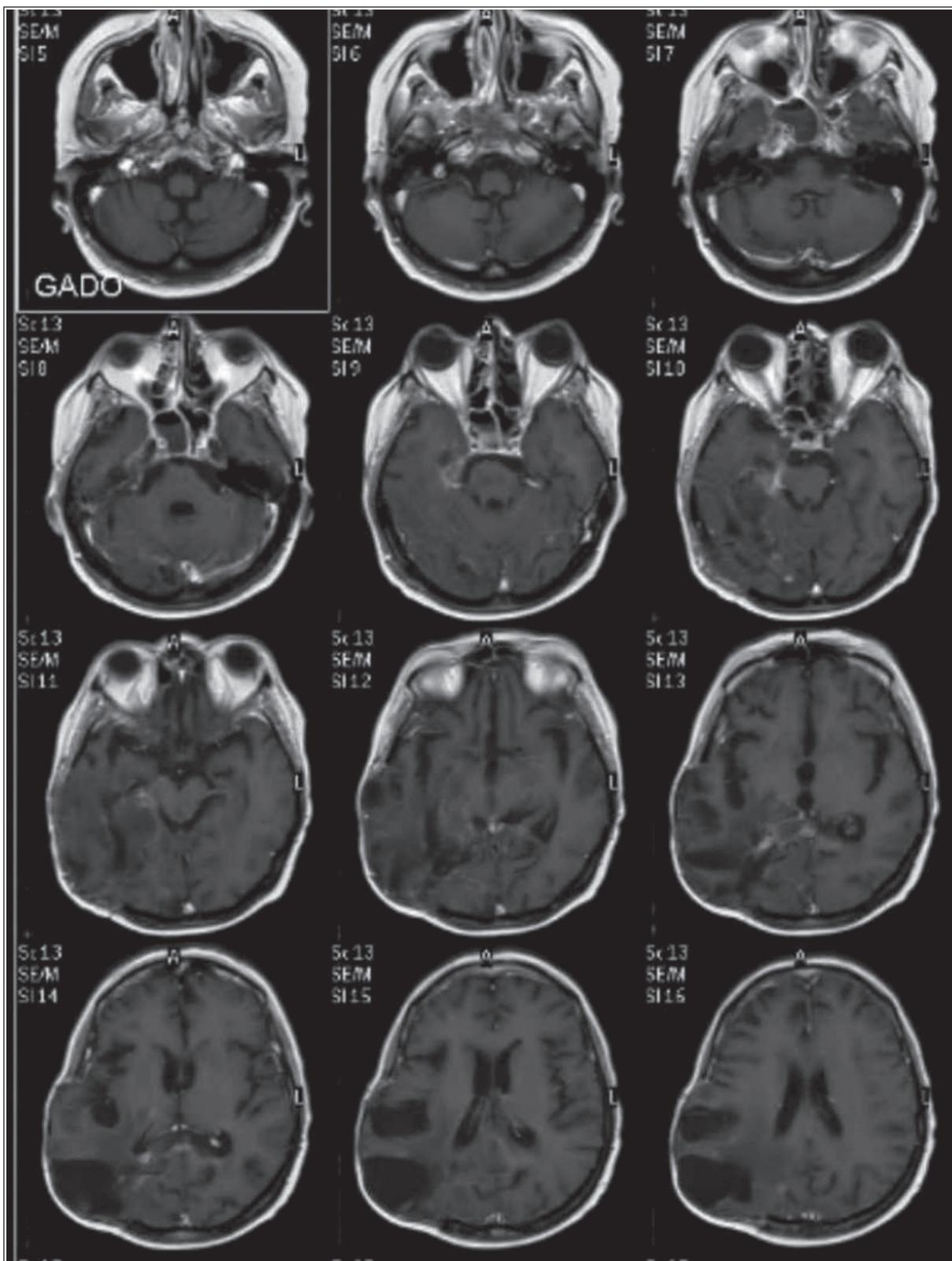


Figure 2: Post-chemotherapy (after six doses—3 months of Irinotecan and Bevacizumab) MRI T1 with contrast axial showing good response

the chemo regimen and have a better PFS and OS. However, because of low number of patients with anaplastic tumors, we are skeptical about this finding.

In Indian scenario, Boppanna *et al.*^[14] from Tata Memorial Hospital conducted a prospective study on 27 patients which showed a median PFS of 145 days and median OS

of 164 days. On the contrary, our study showed better OS and PFS. However, considering the retrospective nature of our data, further prospective studies are required to confirm the same.

Cloughesy *et al.*^[15] did a comparative study on single agent bevacizumab vs. combination of irinotecan and bevacizumab and they found that there is no major improvement in OS with the addition of Irinotecan. OS was 8.9 months for combination and 9.7 months with single agent Bevacizumab.

A network meta-analyses conducted by Mc Bain *et al.*^[16] shows a PFS as high as 4.7 months with usage of Bevacizumab mono therapy with no significant benefit of OS with Bevacizumab. This meta-analysis also showed that Bevacizumab + Lomustine showed better results as compared to Bevacizumab monotherapy or Bevacizumab + Irinotecan combination; however, toxicity profile of Bevacizumab +Lomustine is high. They also suggested that there is no major difference in terms of OS and PFS benefit between Bevacizumab monotherapy vs. combination therapy of Bevacizumab and Irinotecan. When treatments were ranked for OS, FOM ranked first, BEV + LOM second, LOM third, BEV + IRI fourth, and BEV fifth. Ranking does not take into account the certainty of the evidence, which also suggests there may be little or no difference between FOM and LOM. There was better toxicity profile with Bevacizumab monotherapy vs. combination therapies with Bevacizumab.

Nowadays, many biosimilars of Bevacizumab are available along with the innovator. Singh *et al.*^[17] conducted a study on the comparison of safety and efficacy between the innovator, that is, Avastin, Roche and biosimilars, that is, Bevacirel: Reliance Life sciences or Brycta: Zydus Oncosciences. The results showed similar safety and clinical efficacy. This can further facilitate routine use of Bevacizumab as a second line agent in patients irrespective of socioeconomic status.

In view of our study being a single institute study, with less sample size we are not able to compare single agent bevacizumab vs Bevacizumab and irinotecan combination.

In our study, we have not encountered any grade 3 or grade 4 toxicities such as bleeding, thrombocytopenia, and GI perforation. All patients tolerated combination chemotherapy well and no one discontinued treatment because of toxicity.

Recent developments in CNS tumors are mainly based on molecular profiling.^[18] Further studies with correlation of

molecular factors and gene profiling with the behavior of the tumor will help us not only in prognostication, but also in deciding the subsequent therapies.

Limitation of our study includes small sample size, retrospective analysis, less number of patients in anaplastic glioma group, and lack of analysis on toxicity profiles.

Future scope includes a phase III randomized control studies comparing Irinotecan and Bevacizumab with other regimens with respect to OS, PFS, response rates, and toxicity outcomes as well.

CONCLUSION

Combination of Bevacizumab and Irinotecan is well tolerated and improves OS and PFS in patients with recurrent high-grade gliomas. The effect of chemotherapy is more evident in CNS WHO Grade 3 gliomas as compared with GBM.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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