

Original Research Article

TO STUDY THE BENEFIT OF BEVACIZUMAB AND IRINOTECAN IN RECURRENT HIGH GRADE GLIOMAS: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Most of High-Grade Gliomas are incurable with Surgery. Regardless of the extent of Surgery, combining radiotherapy (RT) with chemotherapy is highly recommended for High Grade Gliomas. The mean time for Glioblastoma recurrence is approximately 32 to 36 weeks after initial multimodality treatment, and this is most frequently a result of continuous neoplastic growth within 2–3 cm of the original neoplasm. Once tumors progress after first-line therapy, treatment options are limited and the management of recurrent High-Grade Gliomas becomes difficult.

Materials and Methods: We conducted a prospective study in 30 patients with recurrent high-grade gliomas from January 2024 to May 2025. The patients received Bevacizumab and irinotecan, and Response was assessed at 4 weeks and 3 months and graded as per RANOS criteria. Progression-free survival and overall survival were estimated. Adverse reactions were assessed and graded as per NCI-CTCAE version 5.0. Quality of life was assessed using EORTC QLQ-C30 Questionnaire

Results: There is clinical improvement in QoL after starting Bevacizumab and Irinotecan, but the difference failed to reach statistical significance. The median overall survival in our study is 10 months. 43.3% of patients had partial response at the end of 3 months. 43.3% of patients had stable disease at the end of 3 months. 10% of patients had progressive disease at the end of 3 months. 3.3% of patient had complete response at the end of 3 months. Overall Response rate was 46.6% at the end of 3 months. The median progression free survival in our study is 8 months.

Conclusions: There is a promising response rate, median OS and median PFS with tolerable adverse events. There was a non-significant improvement in QoL from baseline to 4 weeks and at 3 months

Keywords: High grade glioma, Bevacizumab, Irinotecan, response rate, Progression free survival, Quality of life.

INTRODUCTION

Gliomas are a heterogeneous group of primary central nervous system (CNS) tumors originating from glial progenitor cells, accounting for 28% of all primary brain tumors and 80% of all malignant primary brain tumors in adults.^[1] High Grade Gliomas (HGG) WHO Grade III and Grade IV are associated with aggressive behavior and poor prognosis. Most HGGs are surgically incurable. Despite maximum safe resection, combining

radiotherapy with chemotherapy (Temozolomide) remains the current standard of care.

Glioblastoma Multiforme (GBM) virtually always recurs after first line treatment, with a mean recurrence time of approximately 32–36 weeks, most frequently within 2–3 cm of the original tumor.^[2] Once tumors progress, treatment options are limited and management is challenging.

Angiogenesis plays a pivotal role in HGG progression,^[3] primarily driven by hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth

factor (VEGF). Anti-angiogenic drugs targeting the VEGF–VEGFR axis including Bevacizumab emerged as promising therapeutic strategies. Irinotecan, a topoisomerase-1 inhibitor with CNS penetration, showed cytotoxic activity against glioblastoma cells including multi-drug resistant lines. Preclinical and early clinical data suggested that Bevacizumab may enhance Irinotecan delivery by reducing interstitial pressure and normalizing tumor vasculature. Phase II trials combining Bevacizumab and Irinotecan showed improved response rates and overall survival compared to historical data with single agent therapy. Multiple Health Related Quality of Life (HR QoL) scales, including cognitive and role functioning were identified as independent prognostic factors for both overall survival (OS) and progression-free survival (PFS) in recurrent HGG.

Aims and Objectives

Aim: To study the benefit of Bevacizumab and Irinotecan in recurrent High Grade Gliomas.

Primary Objectives

- Quality of Life (QoL) improvement in patients with recurrent High Grade Gliomas
- Overall Survival (OS) improvement in patients with recurrent High Grade Gliomas

Secondary Objectives

- Response rates (RANO criteria)
- Progression-Free Survival (PFS) improvement in patients with recurrent High Grade Gliomas

MATERIALS AND METHODS

Study Design: Prospective observational study conducted at the Department of Medical Oncology, Krishna Institute of Medical Sciences (KIMS), Secunderabad from June 2022 to June 2024.

Source of Data: Patients diagnosed with Grade 3 and Grade 4 gliomas post-operative, post-concurrent Chemoradiation therapy, and post-Adjuvant Temozolomide presenting with recurrence or residual progressive disease.

Treatment Protocol: Patients received Bevacizumab 10 mg/kg IV every 2 weeks. Irinotecan was dosed at 350 mg/m² for patients on Enzyme-Inducing Anti-Epileptic Drugs (EIAEDs) and at 125 mg/m² for those not on EIAEDs, administered every 2 weeks based on weight and BSA.

Sample Size: 30 patients

Duration: 2 years.

Inclusion Criteria

- All recurrent high-grade gliomas (Grade III and Grade IV with ECOG performance status ≤ 3)
- Informed consent from the study group
- Adequate Bone Marrow function: WBC $\geq 3,000/\text{cc}$, ANC $\geq 1,500/\text{cc}$, Hb $\geq 10 \text{ gm}\%$
- Adequate Liver functions: SGOT, Bilirubin $< 2.5\times$ the upper normal limit
- Adequate Renal functions: Creatinine $\leq 1.5 \text{ mg}\%$, Creatinine clearance $\geq 60 \text{ cc/min}$

Exclusion Criteria

- ECOG PS > 3
- Uncontrolled hypertension ($> 150/100 \text{ mmHg}$)
- Prior admissions for severe cardiac disease, thrombosis, hemorrhage, stroke, hemoptysis, or colon perforation
- Active infections or concurrent antiplatelet/anticoagulation medications
- Clinical evidence of bleeding diathesis or coagulopathy

Response Assessment & Outcome Measures:

Response was assessed using contrast-enhanced MRI Brain at 4 weeks (or at clinical progression, whichever earlier) and at 3 months, using RANO criteria (Complete Response, Partial Response, Stable Disease, Progressive Disease). QoL was measured using EORTC QLQ-C30 at baseline, 4 weeks, and 3 months. PFS was defined as the time from initiation of treatment to clinical or radiological progression or death. OS was defined as the number of patients alive at the end of the 2-year study period. Statistical Analysis: Categorical variables are presented as numbers and percentages; continuous variables as mean $\pm$ standard deviation. Repeated measures ANOVA was used to compare mean QoL differences at baseline, 4 weeks, and 3 months. Kaplan-Meier method was used to estimate median PFS and OS. IBM SPSS version 26 was used. A p-value < 0.05 was considered statistically significant.

RESULTS

Patient Demographics

30 patients with recurrent High Grade Gliomas were enrolled. The mean age was 51.97 years; 66.7% were ≥ 50 years and 33.3% were < 50 years. Males comprised 66.7% and females 33.3%.

Table 1: Baseline Patient Characteristics

Characteristic	Category	Frequency	Percentage (%)
Age	< 50 years	10	33.30%
Age	≥ 50 years	20	66.70%
Gender	Male	20	66.70%
Gender	Female	10	33.30%
Diagnosis	Glioblastoma Multiforme	19	63.30%
Diagnosis	Astrocytoma Grade 4	6	20.00%
Diagnosis	Oligodendroglioma Grade 3	3	10.00%
Diagnosis	Astrocytoma Grade 3	2	6.70%
ECOG PS	PS 1	2	6.70%
ECOG PS	PS 2	15	50.00%
ECOG PS	PS 3	13	43.30%

Majority of patients had GBM (63.3%); 50% had ECOG PS 2 at enrolment.

Response Rates

At 4 weeks, all 30 patients (100%) had Stable Disease per RANO criteria. At 3 months, response assessment was as follows:

Table 2: Response rates

Response Category	Frequency	Percentage (%)
Complete Response	1	3.3%
Partial Response	13	43.3%
Stable Disease	13	43.3%
Progressive Disease	3	10.0%

Overall Response Rate (CR + PR) at 3 months: 46.6%. Steroid requirement was reduced in 36.6% of patients; one patient was completely off steroids at 3 months with complete radiological response; 60% had stable steroid requirements.

Progression-Free Survival (PFS)

17 patients (56.7%) progressed during the study period; PFS was not reached in 13 patients (43.3%). The median PFS was 8.0 months (95% CI: 5.3–10.7). The estimated six-month PFS rate was 64.7%. Mean PFS was 7.59 ± 3.08 months. PFS was significantly higher in GBM patients (9.10 months) compared to Astrocytoma Grade 4 (5.00 months) and Oligodendroglioma Grade 3 (8.00 months) ($p = 0.023$).

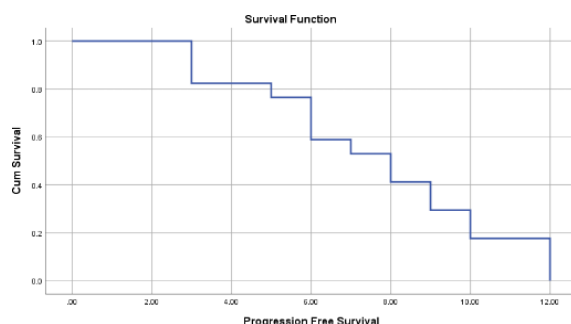


Figure 1: Kaplan-Meier Curve for Median Progression-Free Survival

Table 3: Survival rates

Survival Metric	Estimate	95% CI
Median PFS	8.0 months	5.3 – 10.7 months
Mean PFS	7.59 months	6.1 – 9.1 months
PFS Rate at 6 months	64.7%	—
Median OS	10.0 months	6.5 – 13.5 months
Mean OS	12.54 months	10.5 – 14.5 months
OS Rate at 6 months	53.8%	—

Median OS of recurrent Grade 4 Gliomas from the start of Bevacizumab + Irinotecan: 10 months. Median OS from initial diagnosis of Grade 4 Gliomas: 28 months. OS was significantly higher in GBM patients (14.38 months) versus Astrocytoma Grade 4 (9.60 months) ($p = 0.015$).

Overall Survival (OS)

13 patients (43.3%) died during the study period; 17 patients (56.7%) were alive at the end of the study. The median OS was 10.0 months (95% CI: 6.5–13.5). The estimated six-month OS rate was 53.8%. Mean OS was 12.54 ± 3.69 months.

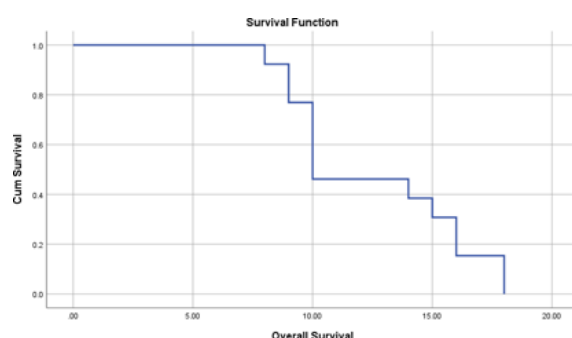


Figure 2: Kaplan-Meier survival curve showing the Median Overall survival

Quality of Life Assessment

QoL was measured using the WHO QLQ-C30 Questionnaire at baseline, 4 weeks, and 3 months. Overall QoL scores showed a trend toward improvement but did not reach statistical significance ($p = 0.059$).

Table 4: Quality of life

Time Point	Mean QoL Score	Std. Deviation
Baseline (pre-treatment)	64.20	5.82
After 4 Weeks	64.87	5.94
At 3 Months	65.27	7.04

Post-hoc analysis showed a significant deterioration in QoL from baseline to 4 weeks ($p = 0.011$); changes between baseline and 3 months ($p = 0.083$) and between 4 weeks and 3 months ($p = 1.000$) were not statistically significant. There was no significant QoL difference by age group or gender. Neurocognitive QoL remained stable throughout (mean = 4.0 at all-time points). Patients who progressed during the

study had a statistically significant QoL deterioration from baseline to 3 months ($p = 0.017$).

Toxicity Profile

Toxicity was graded as per NCI-CTCAE version 5.0⁴. No life-threatening adverse events including febrile neutropenia, GI perforations, intracranial hemorrhages (ICH), thromboembolic events, or wound healing complications were observed.

Table 5: Showing Adverse events

Adverse Event	No. of Patients	% of Patients
Neutropenia (any grade)	14	46.6%
Febrile Neutropenia	0	0%
Thrombocytopenia (any grade)	16	53.3%
Anaemia Grade 1	6	20.0%
Anaemia Grade 2	6	20.0%
Anaemia Grade 3/4	0	0%
Arterial Hypertension Grade 1	10	33.3%
Arterial Hypertension Grade 2	8	26.6%
Arterial Hypertension Grade 3	6	20.0%
Proteinuria Grade 1	16	53.3%
Proteinuria Grade 2	8	26.6%
Diarrhoea Grade 1	14	46.6%
Diarrhoea Grade 2	6	20.0%
GI Perforations / ICH / Thromboembolic Events	0	0%

All cases of Arterial Hypertension were well controlled with medications. The toxicity profile was manageable and consistent with published literature.

DISCUSSION

The outcomes of recurrent HGGs remain extremely poor due to inherent tumor resistance to standard cytotoxic therapies, early tumor invasion into normal brain, and limitations of drug delivery across the blood-brain barrier. Treatment options at recurrence include re-surgery (feasible in 20–30%), reirradiation (with risk of radio necrosis), and systemic chemotherapy, each with limited efficacy. Bevacizumab, through its anti-angiogenic activity (anti-VEGF) reduces VEGF-induced vascular

permeability, leading to decreased interstitial pressure, improved oxygenation, and normalization of tumor vasculature thereby enhancing delivery of cytotoxic agents including Irinotecan. Irinotecan crosses the blood-brain barrier and demonstrates cytotoxic activity against CNS tumor xenografts and multi-drug resistant GBM cells a mechanism distinct from Temozolomide, making it valuable in Temozolomide-refractory disease.

In our study, the overall response rate of 46.6% is consistent with published phase II trials (range 25–57%). The 6-month PFS rate of 64.7% compares favorably to published data (range 29–78.6%), and the median OS of 10 months falls within the reported range of 7.2–11.5 months.

Table 6: Showing Comparison of Survival data and Response rates among various studies in recurrent high-grade gliomas

Study	No. of patients	Overall Response Rates	PFS Rate at 6 months	Overall Survival (Months)	PFS (Months)
Bevacizumab+Irinotecan (Vredenburgh) ⁵	35	57%	46%	9.7	5.75
Bevacizumab→Bevacizumab +Irinotecan (Kreisl) ⁶	85	35%	29%	7.2	4
Bevacizumab Vs Bevacizumab +Irinotecan (Friedman) ⁷	167	28%/38%	43%/53%	9.2 / 8.7	4.2/5.6
Bevacizumab +Irinotecan (Hans Skovgaard Poulsen) ⁸	52	25%	32	7.5	5
Bevacizumab+Irinotecan (Tanja Maesti et al) ⁹	19	47 %	52%	7.7	6.8
Bevacizumab+Irinotecan (Bokstein Fet al) ¹⁰	19	47.4%	25 %	7	4.7
Bevacizumab+Irinotecan (Jairo Legaspi et al) ¹¹	62	38 %	-	9.14	13.84
Bevacizumab+Irinotecan (Present study)	30	46.6 %	76%	10	8

Table 7: Showing Comparison of Survival data with different treatment regimens in recurrent High Grade Gliomas

	Temozolomide in recurrent High Grade Gliomas	Bevacizumab in recurrent High Grade Gliomas	Bevacizumab+ Irinotecan in recurrent High Grade Gliomas
Study	Susan M.Chang et al ¹²	Beatrice Detti Etal ¹³	Present study
Median OS (months)	8	9.5	10
Median PFS (months)	2.5	6.7	8

Regarding quality of life, consistent with Linda Dirven et al,^[15] (2013), Stöckelmaier et al,^[14] (2017), and Coomans M et al,^[16] our study found that treatment with Bevacizumab and Irinotecan did not negatively impact HRQoL a critical consideration in palliative oncology. Patients who progressed showed significant QoL deterioration ($p = 0.017$), underscoring that disease progression, not treatment, was the primary driver of QoL decline. The toxicity profile was manageable and comparable with published experience. The absence of life threatening adverse events support the safety of this regimen in a carefully selected patient population.

CONCLUSION

Summary

This prospective study evaluated 30 patients with recurrent Grade III and Grade IV gliomas treated with Bevacizumab 10 mg/kg and Irinotecan (350 or 125 mg/m² based on EIAED use) every 2 weeks at KIMS, Secunderabad (June 2022–June 2024). GBM was the most common diagnosis (63.3%); 50% of patients had ECOG PS 2 and 43.3% had PS 3 at enrolment.

Key Conclusions

- Overall Response Rate (CR + PR) at 3 months: 46.6%
 - Median Progression-Free Survival: 8.0 months (95% CI: 5.3–10.7); 6-month PFS rate: 64.7%
 - Median Overall Survival: 10.0 months (95% CI: 6.5–13.5); 6-month OS rate: 53.8%
 - Median OS from initial diagnosis of Grade 4 Gliomas: 28 months
 - PFS significantly higher in GBM patients vs. other histologies ($p = 0.023$)
 - OS significantly higher in GBM patients (14.38 months) vs. Astrocytoma Grade 4 (9.60 months) ($p = 0.015$)
 - No statistically significant difference in overall QoL from baseline to 4 weeks or 3 months ($p = 0.059$)
 - QoL deteriorated significantly only in patients who progressed ($p = 0.017$), stable in non-progressors and survivors
 - Neurocognitive QoL remained stable throughout the study period
 - Toxicity profile was manageable; no life-threatening adverse events observed
 - Steroid requirement was reduced in 36.6% of patients at 3 months
- Future large scale randomized controlled trials are required to confirm the efficacy and quality of life benefit of Bevacizumab and Irinotecan in recurrent High Grade Gliomas.

REFERENCES

1. Schwartzbaum JA, Fisher JL, Aldape KD, Wrensch M. Epidemiology and molecular pathology of glioma. *Nat Clin Pract Neurol*. 2006;2(9):494-503.
2. Ammirati M, Galicich JH, Arbit E, Liao Y. Reoperation in the treatment of recurrent intracranial malignant gliomas. *Neurosurgery*. 1987;21:607-614.
3. Zagzag D. Angiogenic growth factors in neural embryogenesis and neoplasia. *Am J Pathol*. 1995;146(2):293-309.
4. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Bethesda (MD): National Cancer Institute; 2017 Nov 27.
5. Vredenburg JJ, Desjardins A, Herndon JE 2nd, Marcello J, Reardon DA, Quinn JA, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol*. 2007;25(30):4722-9. doi:10.1200/JCO.2007.12.2440.
6. Kreisl TN, Kim L, Moore K, Duic JP, Royce C, Stroud I, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol*. 2009;27(5):740-5.
7. Xu T, Chen J, Lu Y, Wolff JE, Huang J, He X, et al. Effects of bevacizumab plus irinotecan on response and survival in patients with recurrent malignant glioma: a systematic review and survival-gain analysis. *BMC Cancer*. 2010;10:252. doi:10.1186/1471-2407-10-252.
8. Poulsen HS, Grunnet K, Sorensen M, Olsen P, Hasselbalch B, Nelausen K, et al. Bevacizumab plus irinotecan in the treatment of patients with progressive recurrent malignant brain tumours. *Acta Oncol*. 2009;48(1):52-8. doi:10.1080/02841860802537924.
9. Mesti T, Moltara ME, Boc M, Rebersek M, Ocivirk J. Bevacizumab and irinotecan in recurrent malignant glioma: a single institution experience. *Radiol Oncol*. 2015;49(1):80-5. doi:10.2478/raon-2014-0021.
10. Bokstein F, Shpigel S, Blumenthal DT. Treatment with bevacizumab and irinotecan for recurrent high-grade glial tumors. *Cancer*. 2008;112(10):2267-73. doi:10.1002/cncr.23401.
11. Legaspi J, et al. Bevacizumab plus irinotecan in patients with recurrent high grade malignant gliomas. *J Clin Oncol*. 2015;33(15 Suppl):e13057. doi: 10.1200/jco.2015.33.15_suppl.e13057.
12. Chang SM, Theodosopoulos P, Lamborn K, Malec M, Rabbitt J, Page M, Prados MD. Temozolomide in the treatment of recurrent malignant glioma. *Cancer*. 2004;100(3):605-11. doi:10.1002/cncr.11949.
13. Detti B, Scoccianti S, Teriaca MA, Maragna V, Lorenzetti V, Lucidi S, et al. Bevacizumab in recurrent high-grade glioma: a single institution retrospective analysis on 92 patients. *Radiol Med*. 2021;126(9):1249-54. doi:10.1007/s11547-021-01381-5.
14. Stöckelmaier L, Renovanz M, König J, Nickel K, Hickmann AK, Mayer-Steinacker R, et al. Therapy for recurrent high-grade gliomas: results of a prospective multicenter study on health-related quality of life. *World Neurosurg*. 2017;102:383-99. doi:10.1016/j.wneu.2017.02.061.
15. Dirven L, Reijneveld JC, Aaronson NK, Bottomley A, Uitdehaag BM, Taphoorn MJ. Health-related quality of life in patients with brain tumors: limitations and additional outcome measures. *Curr Neurol Neurosci Rep*. 2013 ;13(7):359. doi: 10.1007/s11910-013-0359-y.
16. Coomans M, Dirven L, K Aaronson N, Baumert BG, van den Bent M, Bottomley A, et al. EORTC Quality of Life Group and the EORTC Brain Tumor Group. The added value of health-related quality of life as a prognostic indicator of overall survival and progression-free survival in glioma patients: a meta-analysis based on individual patient data from randomised controlled trials. *Eur J Cancer*. 2019;116:190-198. doi: 10.1016/j.ejca.2019.05.012