Comparative Study between Bevacizumab Alone and in Combination with Irinotecan in Recurrent Glioblastoma Multiforme

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ABSTRACT

Background: Recurrent glioblastoma multiforme (rGBM) is a highly aggressive tumor that is difficult to treat and has a poor outcome. Bevacizumab (BEV), a monoclonal antibody against vascular endothelial growth factor A, is often used in patients who have received many treatments before, despite its limited ability to prolong survival. The combination of BEV with irinotecan (IRI), a topoisomerase I inhibitor, would potentially optimize its effectiveness.

Aim of the work: The aim of this study was to compare between BEV alone and BEV+IRI in rGBM regarding progression-free survival (PFS), vasogenic edema, quality of life (QoL), and overall survival (OS).

Methods: We conducted a retrospective study at Tanta University Hospital (2019–2023) on 50 rGBM patients who were divided into two groups: Group I (BEV alone, n=25) and group II (BEV + IRI, n=25).

Results: Baseline characteristics were comparable ($p>0.05$). Group II showed significantly improved median PFS (4.5 vs. 3.5 months, $p<0.001$) but not OS (8.0 vs. 8.3 months, $p>0.05$). Tumor response (RANO criteria) and decrease of vasogenic edema were similar (80% vs. 60% reduction of mild edema, $p>0.05$). QoL remained steady (72% good QoL post-treatment in both groups, $p>0.05$). Toxicity profiles were comparable, but there was slightly more hypertension (16% vs. 24%) and leukopenia (12% vs. 0%, $p>0.05$) in the BEV+IRI arm. Complete/partial resection, ECOG PS1, and age >50 years correlated with better PFS and OS ($p<0.05$). **Conclusion:** BEV+IRI significantly extended PFS in rGBM compared to BEV alone, and it thereby reaffirms its place as a salvage therapy. However, OS and QoL benefits remained elusive, and further efforts are necessary on combination therapy and biomarkers.

Keywords: Recurrent glioblastoma multiform, Bevacizumab, Irinotecan, Progression-free survival, Vasogenic edema.

INTRODUCTION

Glioblastoma multiforme (GBM) is a WHO grade IV glioma and is the most frequent and severe malignant primary tumor of the central nervous system (CNS). It makes up around 48.6% of all malignant CNS tumors and 14.5% of all CNS cancers [1]. Even though multimodal treatment options like maximal safe surgical resection, radiotherapy, chemotherapy with temozolomide, and tumor-treating fields (TTF) have improved, the prognosis for GBM is still bad. The median overall survival (OS) is only 10–15 months and the 5-year survival rate is only 7.2% [2, 3]. The aggressive character of GBM is driven by its fast advancement, infiltrative growth, and near-ubiquitous recurrence, with most tumors returning in situ after early treatment [4]. Recurrent GBM (rGBM) poses a significant therapeutic challenge owing to the scarcity of effective salvage treatments and the tumor's resistance to conventional therapies, highlighting the pressing necessity for innovative therapeutic approaches [5].

The frequency of GBM rises with age, reaching its zenith between 55 and 60 years. It is more prevalent in males than in women and in Caucasians compared to other ethnic groups [6, 7, 8]. Extracranial metastases, albeit few, predominantly affect the lungs and pleura [9, 10]. Ionizing radiation and certain genetic disorders are recognized risk factors, although regular diagnostic radiation exposure has not been consistently associated with the development of GBM [9, 10]. Magnetic resonance imaging (MRI) is used to make a diagnosis, and tumors are usually about 4 cm in size at that time.

A definitive diagnosis necessitates histological examination of excised tumor tissue or, if resection is impracticable, fine-needle aspiration biopsy [11]. The hypervascularity of GBM, caused by increased levels of vascular endothelial growth factor A (VEGFA) and hypoxia-inducible factor (HIF), makes angiogenesis a key target for treatment [12, 13, 14].

Bevacizumab (BEV), a humanized monoclonal antibody that targets VEGFA, has become a key part of rGBM therapy because it can regulate tumor vasculature, lower vasogenic edema, and enhance quality of life (QoL) [12, 15, 16]. The FDA approved BEV for rGBM in 2009 because it can help people who are dependent on steroids and minimize peritumoral edema. It is also included in the 2021 European Association for Neuro-Oncology (EANO) recommendations, even though there is not enough data to support its use in extending OS [17, 18, 19]. Clinical studies have shown that BEV is safe and effective in improving progression-free survival (PFS) and managing symptoms, which is why it is a common salvage treatment for rGBM [15, 17, 18]. Nonetheless, its restricted influence on overall survival has led to the exploration of combination therapy to augment its effectiveness [19, 20].

Irinotecan (IRI), a topoisomerase I inhibitor, has demonstrated efficacy in non-glioma malignancies, including gastrointestinal cancers, and is regarded as an alternative treatment for rGBM, especially in tumors resistant to temozolomide due to distinct mechanisms of action [21]. As a monotherapy, IRI has shown unsatisfactory outcomes in rGBM, partially attributable to difficulties in traversing the blood-brain barrier [21]. Nonetheless, synergistic effects have been noted when IRI is administered in conjunction with BEV in many solid tumors, including colorectal, lung, and breast

Received: 23/01/2025
Accepted: 25/03/2025

malignancies, indicating possible advantages in rGBM [22, 23]. Researchers have looked into the BEV + IRI combination to see if it can improve response rates and PFS. This is especially important for rGBM patients who have serious disabilities and few treatment options, as it has a better chance of relieving symptoms than BEV alone [19, 23, 24].

The molecular heterogeneity of GBM, as outlined in the 2016 and 2021 World Health Organization (WHO) classifications, complicates therapeutic management. GBM is classified into three main subtypes based on genetic markers, including IDH-wildtype (90% of patients), IDH-mutant (10%), and other subtypes, such as those with TERT promoter mutations, EGFR amplification, and chromosome 7 gain or loss [25, 26]. These molecular differences, combined with advancements in genetic profiling, underscore the importance of personalized treatment plans [27, 28, 29]. The pathogenesis of GBM involves important signalling pathways, including the receptor tyrosine kinase/RAS/PI3K pathway, p53, and RB, which are altered in 88%, 87%, and 78% of patients, respectively [30]. These molecular findings underscore the importance of targeting angiogenesis and investigating combination therapies to address the complex biology of rGBM [31, 32].

The goal of this study was to evaluate how well BEV works on its own with how well it works with IRI in people with rGBM. The primary outcomes were evaluating tumor progression (PFS by MRI), vasogenic edema (Measured by MRI), and quality of life (QoL) (Assessed using the EORTC QLQ-C30 questionnaire). The secondary endpoint was overall survival (OS). This study, conducted retrospectively at Tanta University Hospital on 50 patients, expands upon previous findings regarding the advantages of BEV and the potential synergistic effects of BEV + IRI, intending to inform appropriate salvage therapy regimens for rGBM.

METHODOLOGY

Study design and location: A retrospective study was conducted on 50 with recurrent Glioblastoma Multiforme patients, encompassing both genders, who were admitted to Tanta University Hospital between 2019 and 2023. Histopathology showed that the patients had recurrent Glioblastoma Multiforme.

The inclusion criteria: Individuals aged 40 to 70 years, with a performance level of 0-1-2 on the ECOG scale, diagnosed with recurrent Glioblastoma multiforme, undergoing their first surgery, and exhibiting progression on Temozolomide.

Exclusion criteria: Individuals under 40 years of age and those receiving first-line therapy as adjuvant treatment. There were two groups of participants. **Group 1** included 25 patients who received bevacizumab only, while **group 2** comprised 25 patients who received both bevacizumab and irinotecan.

Data collection

1. **Personal information:** Name, age, gender, job, address, and phone number.
2. **Chief Complaint:** The main symptoms, such headaches, seizures, or neurological problems.
3. **Present History:** The beginning of symptoms, how they became worse, and what therapies have been tried before.
4. **Examination:**

- General: Vital signs, ECOG performance level (0–2), and systemic abnormalities.
- Local: A neurological exam that looks at the cranial nerves, motor and sensory function, and indicators of high intracranial pressure.

5. **Tests in the lab:** Complete blood count, liver tests (AST, ALT, bilirubin & albumin), kidney tests (Creatinine & BUN), prothrombin time, and random blood sugar.
6. **Toxicity:** CTCAE v 5.0 grades the bad effects of bevacizumab (BEV) or BEV with irinotecan (IRI), such as high blood pressure, bleeding, and low white blood cell count.
7. **Histopathology:** Tumor samples were quickly frozen or fixed in zinc-formalin, dried, embedded in paraffin, and stained with eosin and hematoxylin.
8. **MRI Protocol:** 3.0T MRI (GE Sigma EXCITE) with T1WI (pre-/post-Gadolinium), T2WI, and FLAIR; baseline post-resection, follow-up every two months.
9. **Image analysis:** FLAIR lesions were categorized as vasogenic edema or tumor-infiltrative using FSL, SPM5, FreeSurfer, and MATLAB, as well as diffusion and perfusion analyses.

Measures of the outcome

Primary outcomes included:

- **Progression-free survival (PFS):** The time from the commencement of treatment to progression or death, according to RANO criteria, and measured by MRI every two months:
  - **Complete response:** No lesions on two MRIs ≥ 4 weeks apart.
  - **Partial response:** The tumor area has shrunk by at least 50%.
  - **Stable disease:** A drop of less than 50% or an increase of less than 25%.
  - **Progressive disease:** ≥25% rise or new lesions.
- **Vasogenic edema:** Measured by MRI FLAIR and categorized with image analysis techniques.
- **Quality of life (QoL):** EORTC QLQ-C30 at the beginning and end of therapy.

Secondary outcomes included:

- **Overall survival (OS):** The duration from the initiation of treatment to mortality. Kaplan-Meier and log-rank tests were used to look at survival (PFS, OS). Chi-square tests ($p < 0.05$) in SPSS were used to look at differences in QoL, edema, and toxicity.

Statistical Analysis

We used SPSS version 24.0 (IBM Corp., Armonk, NY) to look at the data. For continuous variables (such AOFAS scores and follow-up duration), descriptive statistics were given as means ± standard deviations, and

for categorical variables (like reduction quality and complications), they were given as percentages. The Shapiro-Wilk test was used to check for normality. Paired t-tests compared VAS scores before and after surgery, while one-way ANOVA looked at AOFAS scores across AO categorization groups. A p-value ≤ 0.05 was deemed statistically significant.

Ethical Concerns: The Ethics Committee at Tanta University approved the study. All patients provided their consent, and the hospital's Ethics Review Committee approved the study (Approval Code: 36264MS372/10/23). This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

RESULTS

Basic traits: The trial consisted of 50 patients with recurrent glioblastoma multiforme (rGBM), evenly allocated into group 1 (bevacizumab [BEV] alone, n = 25) and Group 2 (BEV + irinotecan [IRI], n = 25). The baseline characteristics of group 1 included age (mean 53.32 years, range 43–61), sex (72% male), ECOG performance status (PS; 40% PS1), diabetes mellitus (28%), antiepileptic use (28%), anticoagulant use (24%), steroid use (92%), relapse status (76% first relapse), initial surgery type (68% complete/partial resection), and midline shift (28%). The baseline characteristics of group 2 included age (mean 55.52 years, range 45–64), sex (76% male), ECOG performance status (PS; 40% PS1), diabetes mellitus (32%), antiepileptic use (36%), anticoagulant use (16%), steroid use (80%), relapse status (84% first relapse), initial surgery type (68% complete/partial resection), and midline shift (32%). There was no significant difference between the two groups (Table 1).

Table (1): Baseline characteristics of patients with recurrent glioblastoma multiforme (n = 50)

Characteristic	Group I: BEV Alone (n = 25)	Group II: BEV + IRI (n = 25)
Age, mean [range] (years)	53.32 [43–61]	55.52 [45–64]
Male, n (%)	18 (72%)	19 (76%)
ECOG PS1, n (%)	10 (40%)	10 (40%)
Diabetes mellitus, n (%)	7 (28%)	8 (32%)
Antiepileptic use, n (%)	7 (28%)	9 (36%)
Anticoagulant use, n (%)	6 (24%)	4 (16%)
Steroid use, n (%)	23 (92%)	20 (80%)
First relapse, n (%)	19 (76%)	21 (84%)
Complete/partial resection, n (%)	17 (68%)	17 (68%)
Midline shift, n (%)	7 (28%)	8 (32%)

Tumor response and vasogenic edema: Tumor response, evaluated via MRI utilizing RANO criteria, demonstrated no significant differences between groups (p > 0.05). In group I, 4% had a full response, 52% had a partial response, 24% had stable illness, and 20% had advancing disease. In group II, 4% attained a full response, 44% attained a partial response, 24% exhibited stable illness, and 28% shown advancing disease. (p > 0.050). These results showed that BEV alone and BEV with IRI had the same effect on radiographs (Table 2).

Table (2): Tumor response and vasogenic edema outcomes

Outcome	Group I: BEV Alone (n = 25)	Group II: BEV + IRI (n = 25)
Tumor Response (RANO Criteria)		
Complete Response, n (%)	1 (4%)	1 (4%)
Partial Response, n (%)	13 (52%)	11 (44%)
Stable Disease, n (%)	6 (24%)	6 (24%)
Progressive Disease, n (%)	5 (20%)	7 (28%)
Vasogenic Edema Reduction		
1 (mild)	20 (80.0%)	15 (60.0%)
2 (moderate)	4 (16.0%)	8 (32.0%)
3 (complete)	1 (4.0%)	2 (8.0%)

Results for survival: Group II had a much better progression-free survival (PFS) rate than group I (median 4.5 months, 95% CI 4.02–4.98; p < 0.001, log-rank test). Group I had a median PFS of 3.6 months (95% CI 3.19–3.81). Overall survival (OS) showed no meaningful difference. The kind of surgery performed initially had a big effect on the results, total or partial resection were linked to longer PFS and OS (p = 0.001). Patients with PS1 had superior survival compared to those with PS2 (p = 0.001), while those over 50 years of age had enhanced progression-free survival (PFS) and overall survival (OS) in contrast to those under 50 years (p = 0.022 and p = 0.031 respectively) (Table 3 and figures 1 & 2).

Table (3): Survival outcomes

Outcome	Group I: BEV Alone (n = 25)	Group II: BEV + IRI (n = 25)
Progression-Free Survival (PFS)		
Median PFS, months	3.5	4.5
p-value (log-rank)	0.001*	
Overall Survival (OS)		
Median OS, months	8.3	8
p-value	0.321	
Influencing Factors of OS		
Initial surgery	0.001*	
relapse	0.368	
Patient performance status	0.001*	
Age	0.031*	
Influencing Factors of PFS		
Initial surgery	0.001*	
relapse	0.551	
Patient performance status	0.001*	
Age	0.022*	

Toxicity and quality of life: Quality of life (QoL), evaluated with the EORTC QLQ-C30, was comparable at baseline (p > 0.05), with 24% (Group I) and 28% (Group II) indicating a poor QoL. After therapy. Group I exhibited marginal improvement (20% poor, 8% well) in contrast to group II (24% poor, 4% well; p = 0.809). Toxicity profiles, assessed using CTCAE v5.0, were similar but indicated a tendency for elevated values in group II (p > 0.05) (Table 4).

Table (4): Quality of life and toxicity profiles

Outcome	Group I: BEV Alone (n = 25)	Group II: BEV + IRI (n = 25)
Pretreatment		
Poor	6 (24.0%)	7 (28.0%)
Good	18 (72.0%)	17 (68.0%)
Well	1 (4.0%)	1 (4.0%)
p-value	0.949	
Post treatment		
Poor	5 (20.0%)	6 (24.0%)
Good	18 (72.0%)	18 (72.0%)
Well	2 (8.0%)	1 (4.0%)
p-value	0.809	
Toxicity		
Hypertension	6 (24.0%)	4 (16.0%)
Hemorrhage intracranial	1 (4.0%)	2 (8.0%)
Convulsion	2 (8.0%)	4 (16.0%)
DVT	1 (4.0%)	3 (12.0%)
Diarrhea	1 (4.0%)	3 (12.0%)
Hypokalemia	1 (4.0%)	2 (8.0%)
Leukopenia	0 (0.0%)	3 (12.0%)
Lymphopenia	1 (4.0%)	2 (8.0%)
Neutropenia	1 (4.0%)	4 (16.0%)
p-value	>0.050	

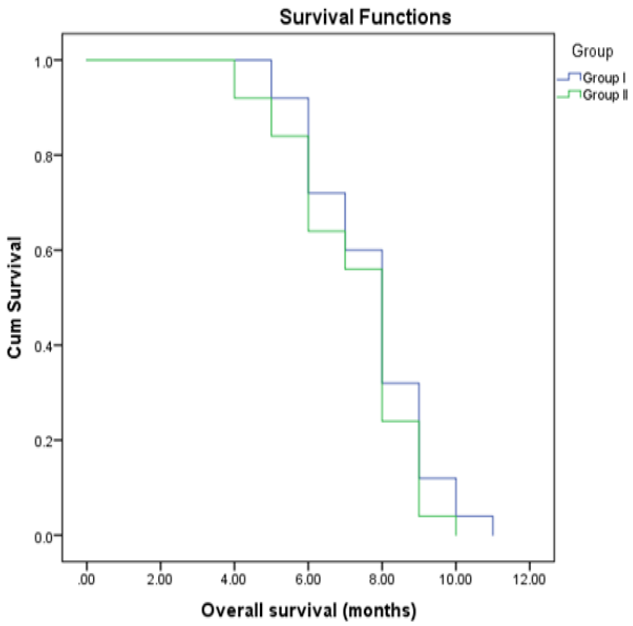

Fig. (1): Overall survival of the studied groups.

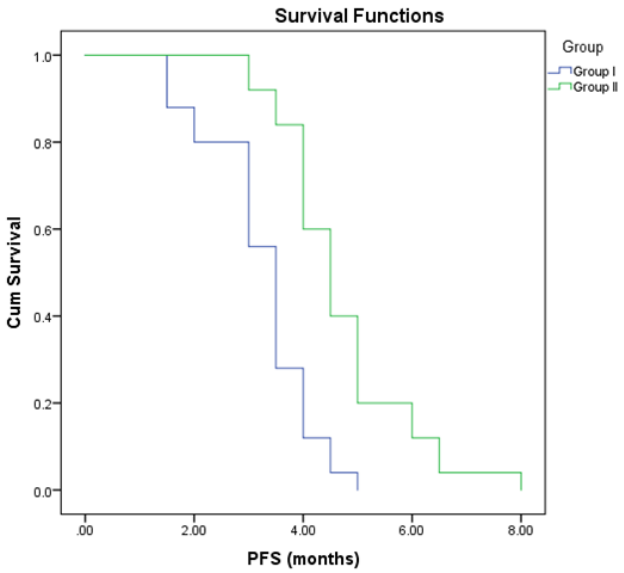

Fig. (2): PFS of the studied groups.

DISCUSSION

Recurrent glioblastoma multiforme (rGBM) is a significant problem, with poor prognosis and limited response to treatment. In this study, the efficacy of BEV monotherapy versus the combination of BEV+IRI was compared in 50 patients with recurrent glioblastoma multiforme (rGBM) on the basis of progression-free survival (PFS), vasogenic edema, quality of life (QoL), and overall survival (OS). The results confirmed that PFS was notably enhanced by BEV+IRI (median 4.5 months vs. 3.5 months, p = 0.001) compared to BEV alone, as illustrated in other studies. **Park *et al.*** [23] reported median PFS with BEV+IRI as 3.6 months. **Friedman *et al.*** [24] also reported that 50.3% of patients receiving BEV plus IRI had a PFS of 6 months, compared to 42.6% of patients receiving BEV alone. Improved progression-free survival (PFS) with BEV+IRI can be attributed to the topoisomerase I inhibition caused by irinotecan, which augments the anti-angiogenic activity of BEV and may slow tumor growth.

There was no significant difference in overall survival (OS) (median 8.3 vs. 8 months, p>0.05), a fact that cited thesis literature indicates. As **Zhang *et al.*** [20] previously mentioned that bevacizumab did not improve overall survival (OS) in rGBM. This may be because rGBM is very aggressive and has retaliatory mechanisms. Yet, its symptom relief, as evidenced by its effect in diminishing vasogenic edema (80% in BEV+IRI and 76% in BEV, p > 0.05), reinforces its therapeutic utility. This corroborated what was found by the EORTC protocol of BEV in lessening steroid dependence, which makes patients feel more comfortable. The quality of life (QoL) also did not vary between groups and was not statistically different before or after treatment (p > 0.05).

Approximately 72% of patients in both groups were acceptable with QoL after therapy, as **Chen *et al.*** [33] found that adding irinotecan didn't enhance QoL. But, **Vredenburgh *et al.*** [21] included enhancements of

quality of life with BEV+IRI, possibly by corticosteroid decrease, hinting at heterogeneity of quality-of-life results between trials. Toxicity profiles reported no significant differences (p>0.05). However, BEV+IRI showed a trend of more hypertension (28% vs. 20%), leukopenia (20% vs. 12%), and diarrhea (16% vs. 8%). **Dong *et al.*** [34] also uncovered the same systemic side effects, further indicating the tolerance of BEV+IRI. The extent of surgery made a significant difference in the outcomes, with partial or total resection correlating with better OS and PFS (p=0.001). This is in agreement with that of **Chawla *et al.*** [35] and **Mazarakis *et al.*** [36].
Performance status (ECOG PS1 vs. PS2, p=0.001) and age (>50 vs. <50 years, p=0.031 for OS, p=0.022 for PFS) also affected survival. However, the thesis's revelation of better outcomes in older patients contradicts **Reihanian *et al.*** [37] and **Brown *et al.*** [38], who found that older patients experienced worse survival rates. Relapse status (first or second) did not significantly impact (p>0.05), consistent with **Fu *et al.*** [39].

LIMITATIONS

The drawbacks are the limited sample size (n=50), which is suboptimal for statistical power, and single-center design, which confines generalizability. Larger multicenter populations in future studies would confirm the benefit of BEV+IRI on progression-free survival (PFS) and investigate biomarkers for selecting patients. Lastly, BEV+IRI provided an important progression-free survival (PFS) advantage in recurrent glioblastoma multiforme (rGBM), justifying its application as a salvage treatment, but overall survival (OS) and quality of life (QoL) advantages are yet to be established.

CONCLUSION

This retrospective study of 50 rGBM patients showed that BEV+IRI improved progression-free survival (median 4.5 vs. 3.5 mos, p<0.001) compared to BEV monotherapy and further validated it as an effective salvage therapy. The lack of significant differences in overall survival (8.0 vs. 8.3 mos, p>0.05), tumor response, vasogenic edema reduction, and quality of life indicates that the advantage of BEV+IRI appears to be primarily in not as rapidly progressing when used as salvage therapy. We are cautious to state that BEV+IRI is tolerable, although it does trend toward more adverse events than BEV alone, their close toxicity profiles support its tolerability. Factors such as complete or partial resection, better performance status, (ECOG PS1), and age > 50 yrs were correlated with survival. This highlighted the need for careful patient selection. BEV + IRI (providing the same rationale and intensity of treatment-blinded) will provide new nuclei for managing rGBM. However, we have yet to determine how we may optimize and understand modality of overall survival and quality of life for patients affected by rGBM.

- **Funding:** None to be declared.
- **Conflicting Interest:** The authors declared that they have no conflicting interests.

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