Real-World Outcomes of Irinotecan–Bevacizumab Therapy in Recurrent Brain Tumors: A Retrospective Cohort Study

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Abstract

Aim: Although the irinotecan-bevacizumab (IB) combination is a frequently used treatment option for recurrent high-grade gliomas, predominantly glioblastoma multiforme and other brain tumors, clinical benefit shows heterogeneity among patients. This study aimed to evaluate clinical and prognostic factors associated with early-stage mortality and overall survival (OS) in patients receiving IB therapy.

Methods: Seventy-eight brain tumor patients who received IB treatment between 2015 and 2023 were retrospectively evaluated. The demographic, clinical, and pathological characteristics of the patients were recorded. The timing of IB treatment initiation was categorized according to whether it was started at the first recurrence or subsequent recurrences. Factors associated with early period mortality (≤6 months, defined based on the median survival observed in prior IB studies and consistent with benchmark thresholds used in recurrent glioma trials) were determined using log-linear regression analysis, while independent prognostic factors affecting OS were determined using the Cox proportional hazards regression model.

Results: The mean age of the patients was 53.01±12.78 years, and the mean follow-up period was 9.47 months. The mortality rate within the first 6 months was found to be 44.9%. Early period mortality was significantly associated with multilobular tumor localization (p = 0.037) and initiation of IB treatment at the ≥2nd recurrence (p=0.036). According to log-linear regression analysis, the probability of survival beyond 6 months was approximately 80% lower in patients with multilobular tumor localization (RR=0.198, 95% CI: 0.054–0.735). In patients who started IB therapy at ≥2nd recurrence, this probability was reduced by approximately 77% (RR=0.227, 95% CI: 0.069–0.748). In the multivariate Cox regression analysis, starting IB at ≥2nd relapse (HR: 2.35, 95% CI: 1.09–5.07, p=0.029), the presence of an IDH mutation (HR: 1.98, 95% CI: 1.09–3.58, p=0.025), and age (HR: 1.03, 95% CI: 1.01–1.05, p=0.015) were identified as independent prognostic factors for OS.

Conclusions: This retrospective real-world cohort study demonstrates that the clinical benefit of the IB combination varies according to patient subgroups. Multilobar involvement and initiation of IB therapy at a late line are associated with early mortality and poor survival.

Keywords: *Glioblastoma multiforme; brain tumors; bevacizumab; irinotecan; overall survival*

1. Introduction

Brain tumors, particularly glioblastoma multiforme (GBM), are associated with high mortality and morbidity and remain a significant clinical challenge due to their resistance to treatment. GBM is the most common and aggressive type of brain tumor, with high recurrence rates after treatment. Traditional approaches to GBM treatment, such as surgical intervention and radiotherapy, have limited effectiveness. In this context, the management of treatment-resistant patients poses a major challenge for clinical oncologists, and new treatment strategies need to be developed.

The biological heterogeneity of GBM causes rapid resistance to standard treatments. These characteristics lead to limited treatment options, especially in recurrent disease. In recent years, the

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roles of targeted therapy and immunotherapy in brain tumor treatment have been increasingly investigated[1,2]. However, despite these treatment methods, most patients experience recurrence and overall survival (OS) times are reduced.

In this context, a better understanding of GBM biology has necessitated the development of combination strategies that could increase response rates. The combination of treatment agents such as irinotecan-bevacizumab (IB) is an important option in this field. The vascular structure of GBM and its growth characteristics dependent on angiogenesis make anti-angiogenic treatments a rational target[3].

Bevacizumab, as a vascular endothelial growth factor (VEGF) inhibitor, blocks tumor blood supply and presents an effective treatment option for improving the prognosis of treatment-resistant patients with brain tumors[4]. The use of bevacizumab in GBM aims to improve clinical and radiological response by modulating the tumor's vascular structure. In clinical practice, bevacizumab therapy is frequently preferred in recurrent GBM patients, particularly because it provides rapid symptom control.

However, bevacizumab monotherapy is often insufficient, and combinations with chemotherapy may yield more effective results. In this context, the combination of bevacizumab with chemotherapy agents such as irinotecan offers a promising approach for the treatment of resistant patients[4,5]. It is known that bevacizumab-based therapies in recurrent GBM patients reduce the need for steroids by decreasing peritumoral edema and improve patients' functional status[6].

Irinotecan is a chemotherapy agent that inhibits DNA replication by targeting the S phase of the cell cycle and is used in the treatment of brain tumors such as GBM[4,7]. Studies show that the combination of IB may increase the efficacy of treatment in brain tumors such as GBM. The combined use of anti-angiogenic and cytotoxic effects is considered one of the key mechanisms explaining how this combination increases objective response rates in recurrent malignant gliomas[8].

However, more data is needed on the efficacy of this treatment combination, patient clinical responses, and treatment response predictors. There are a limited number of studies in the literature on the long-term responses to this treatment strategy.

In particular, the heterogeneity of the effect on OS among patient groups necessitates a more detailed evaluation of clinical and prognostic factors[9,10]. The limited availability of real-world data makes it difficult to clearly determine in which patient subgroups the IB combination provides greater benefit in clinical practice. Therefore, this study, which retrospectively analyzes the efficacy of the IB combination in brain tumors and the factors that may influence OS, aims to provide guiding data for patient selection in the management of brain tumors, particularly recurrent GBM.

2. Materials and Methods

Study Population and Patient Selection

This study was designed as a retrospective, observational cohort study that included patients diagnosed with brain tumors and treated with IB between 2015 and 2023. Patients ≥18 years of age with histopathologically confirmed brain tumor diagnosis, complete clinical and radiological follow-up data, and who received IB treatment were included in the study. Patients with incomplete clinical data, insufficient follow-up period, or those whose OS status could not be evaluated were excluded from the study. The demographic characteristics, clinical findings, pathological data, and treatment information of all patients were obtained retrospectively from patient files and electronic record systems.

Treatment and Clinical Evaluation

The start time of IB treatment was classified according to the number of disease relapses as treatment initiated at the first recurrence and treatment initiated at the second or subsequent relapses (≥2nd recurrence). The clinical and radiological responses of the patients were recorded based on the imaging and clinical evaluation results obtained during routine follow-ups.

Table 1

Early period OS-based sociodemographic and clinical characteristics

	OS		
Variables	≤ 6 month (n:35)	> 6 month (n:43)	p
Age	54.74±12.37	51.60±13.07	0.284
Sex			
Female	14(40)	20(46.5)	0.728
Male	21(60)	23(53.5)	
Pathology			
Other pathologies	10(28.6)	12(27.9)	1.000
GBM	25(71.4)	31(72.1)	
Grade			
2	2(5.7)	3(7)	0.626
3	3(8.6)	7(16.3)	
4	30(85.7)	33(76.7)	
Localization			
Single	21(60)	35(81.4)	0.037
Multilobular	14(40)	8(18.6)	
Prevalence of the disease			
Unifocal	29(82.9)	38(88.4)	0.529
Multifocal	6(17.1)	5(11.6)	
R0 resection			
Present	29(82.9)	37(86)	0.942
Absent	6(17.1)	6(14)	
MGMT methylation			
Present	7(20)	7(16.3)	0.897
Absent	28(80)	36(83.7)	
İDH mutation			
Absent	23(65.7)	33(76.7)	0.410
Present	12(34.3)	10(23.3)	
Adjuvan TMZ			
≤ 6 ay	16(45.7)	18(41.9)	0.911
> 6 ay	19(54.3)	25(58.1)	
Recurrent surgery			
Absent	26(74.3)	35(81.4)	0.631
Present	9(25.7)	8(18.6)	
Reirridation			
Present	9(25.7)	14(32.6)	0.682
Absent	26(74.3)	29(67.4)	
IB start time			
1. recurrent	19(54.3)	33(76.7)	0.036
≥ 2. recurrent	16(45.7)	10(23.3)	
ECOG			
0	4(11.4)	12(27.9)	0.216
1	18(51.4)	17(39.5)	
2	13(37.1)	14(32.6)	

GBM: Glioblastoma multiforme MGMT: O^6-methylguanine-DNA methyltransferase, IDH: Isocitrate dehydrogenase, TMZ: Temozolomide, IB: Irinotecan-Bevacizumab, OS: Overall survival

Table 2

Log-linear regression interaction analysis for early period mortality

Predictor	Estimate	SE	Z	p	Rate ratio	95% Confidence Interval Lower	95% Confidence Interval Upper
Intercept	2.3026	0.316	7.281	<.001	10.000	5.3805	18.585
OS (> 6 month) 2 – 1 (≤ 6 month)	1.0296	0.368	2.795	0.005	2.800	1.3601	5.764
Tumor Localization (Multilobular) 1 – 0 (Single lobe)	-0.1054	0.459	-0.229	0.819	0.900	0.3657	2.215
IB start time (≥ 2. rekurrence) 2 – 1 (1. Recurrence)	0.0953	0.437	0.218	0.827	1.100	0.4672	2.590
OS ✻ Tumor Localization (2 – 1) ✻ (1 – 0)	-1.6174	0.668	-2.420	0.016	0.198	0.0535	0.735
OS ✻ IB start time (2 – 1) ✻ (2 – 1)	-1.4816	0.608	-2.437	0.015	0.227	0.0690	0.748
Tumor Localization ✻ IB start time (1 – 0) ✻ (2 – 1)	-0.6831	0.709	-0.964	0.335	0.505	0.1260	2.025
OS ✻ Tumor Localization ✻ IB start time (2 – 1) ✻ (1 – 0) ✻ (2 – 1)	1.5586	1.102	1.415	0.157	4.752	0.5483	41.183

OS: Overall survival, IB: Irinotecan-Bevacizumab

Statistical Analysis

Statistical analyses were performed using JAMOVI software (JAMOVI; URL: https://www.jamovi.org, accessed on 01.10.2024). The distribution of continuous variables was assessed using the Shapiro–Wilk test. Data showing a normal distribution were analyzed using parametric tests, while data not showing a normal distribution were analyzed using non-parametric tests. Student's t-test and chi-square test were used for intergroup comparisons when appropriate. Log-linear regression analysis—a method suited to analyze interactions among categorical variables (early mortality status, tumor localization, and IB initiation timing) by modeling cell frequencies in a contingency table under the assumption of multinomial sampling— and multivariate survival analyses were performed to evaluate factors affecting overall survival. A Cox proportional hazards regression model was created to determine independent prognostic factors affecting overall survival. Variables found to be statistically significant in univariate analysis or considered clinically relevant were included in the multivariate model. Results were presented as hazard ratios (HR) and 95% confidence intervals (CI). A p-value <0.05 was considered statistically significant in all statistical analyses.

3. Results

The mean age of the 78 patients included in our study was 53.01±12.78. The mean follow-up period was 9.47 months (median 7 months, min-max: 0-65). Eighty-four point six percent (n=66) of patients died during the follow-up period. When patients were classified according to early-stage mortality, they were divided into two groups based on GSK status after IB therapy: less than 6 months and greater than 6 months. The mortality rate within the first 6 months was 44.9%. In the comparison based on early-stage mortality, statistically significant differences were found between the groups in terms of tumor localization and time of IB initiation. Multilobar localization and use of IB therapy ≥2nd line were significantly more common in patients who died within the first 6 months (p=0.037 and p=0.036, respectively). No significant differences were observed between the groups in terms of other sociodemographic and clinical characteristics (Table 1).

The log-linear regression analysis created to evaluate the interaction between early-stage mortality and tumor localization and the timing of IB initiation was found to be significant (p<0.001). Patients with multilobular localization had a 5.05-fold lower probability of survival beyond 6 months (RR=0.198, 95% CI: 0.054–0.735). Similarly, the interaction between the start time of IB and the duration of mortality was found to be significant; the number of patients surviving longer than 6 months was 4.40 times lower in patients who started IB in the second or subsequent relapses (RR=0.227, 95% CI: 0.069–0.748). No significant interaction was found between tumor location, time of IB initiation, and time to mortality (Table 2) (Figure 1).

Figure 1

Estimated marginal numbers for the interaction between tumor location and onset time of IB according to early period mortality

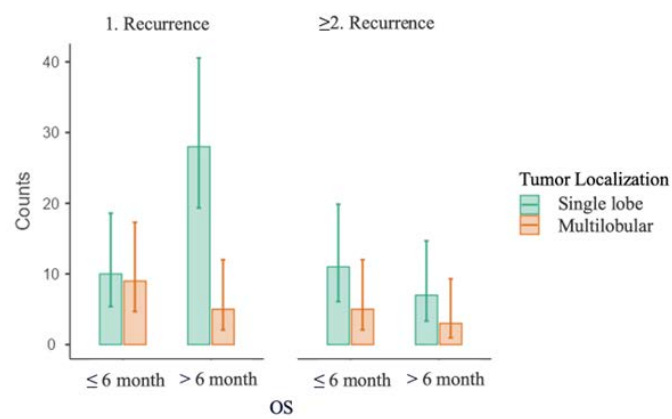
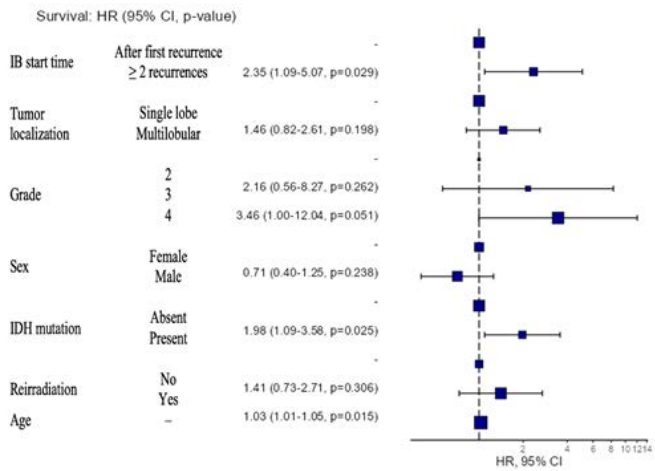


Figure 2

Forest plot representation of multivariate Cox regression analysis for factors affecting OS



In the multivariate Cox proportional hazards regression analysis, the onset time of IB, the IDH mutation status, and age were found to be independently associated with OS. The squares represent hazard ratios, and the horizontal lines represent 95% confidence intervals.

Table 3

Estimated marginal numbers for the onset time of IB and tumor localization according to early period mortality (log-linear regression model)

					95% Confidence Interval	
IB Start Time	Localization	OS	n	SE	Lower	Upper
1. Recurrence	Single lobe	≤ 6 month	10	3.16	5.38	18.59
		> 6 month	28	5.29	19.33	40.55
	Multilobular	≤ 6 month	9	3.00	4.68	17.30
		> 6 month	5	2.24	2.08	12.01
≥ 2. Recurrence	Single lobe	≤ 6 month	11	3.32	6.09	19.86
		> 6 month	7	2.65	3.33	14.68
	Multilobular	≤ 6 month	5	2.24	2.08	12.01
		> 6 month	3	1.73	0.96	9.30

OS: Overall survival, IB: Irinotecan-Bevacizumab

Table 4

Univariate and multivariate Cox proportional hazards regression analysis of factors affecting OS

		All (n,%)	HR (univariable)	HR (multivariable)
IB Start Time	1. Recurrence	52 (66.7)	-	-
	≥2. Recurrence	26 (33.3)	1.24 (0.73-2.09, p=0.430)	2.35 (1.09-5.07, p=0.029)
Localization	Single lobe	56 (71.8)	-	-
	Multilobular	22 (28.2)	1.49 (0.85-2.62, p=0.166)	1.46 (0.82-2.61, p=0.198)
Grade	2	5 (6.4)	-	-
	3	10 (12.8)	1.56 (0.47-5.24, p=0.469)	2.16 (0.56-8.27, p=0.262)
	4	63 (80.8)	1.87 (0.66-5.33, p=0.239)	3.46 (1.00-12.04, p=0.051)
Sex	Female	34 (43.6)	-	-
	Male	44 (56.4)	0.80 (0.48-1.33, p=0.389)	0.71 (0.40-1.25, p=0.238)
IDH mutation	Absent	56 (71.8)	-	-
	Present	22 (28.2)	1.34 (0.78-2.30, p=0.288)	1.98 (1.09-3.58, p=0.025)
Reirridation	Absent	23 (29.5)	-	-
	Present	55 (70.5)	0.87 (0.52-1.47, p=0.604)	1.41 (0.73-2.71, p=0.306)
Age	Mean (SD)	53.0 (12.8)	1.02 (1.00-1.04, p=0.027)	1.03 (1.01-1.05, p=0.015)

IB: Irinotecan-Bevacizumab, IDH: Isocitrate dehydrogenase

In patients who started IB therapy in the first relapse and had a single-lobe tumor, the number of patients showing OS longer than 6 months was higher compared to other groups (Table 3).

In the OS analysis, the time of IB initiation, the presence of IDH mutation, and age were determined as independent prognostic factors according to the multivariate Cox regression model. The risk of death was 2.35 times higher in patients who received IB in the second or subsequent relapses (HR: 2.35, 95% CI: 1.09–5.07, p=0.029). The risk of death was 1.98 times higher in patients with IDH mutation (HR: 1.98, 95% CI: 1.09–3.58, p=0.025). Each additional year of age was associated with a 3% increase in the risk of death (HR: 1.03, 95% CI: 1.01–1.05, p=0.015) (Table 4).

4. Discussion

Our study Concurrent and adjuvant temozolomide-based therapy with postoperative radiotherapy is the standard treatment for GBM and other high-grade brain tumors. However, due to the risk of recurrence and resistance to treatment, these malignancies have significantly limited survival[11]. In our study, the high early-stage mortality in cases receiving IB treatment demonstrates the aggressive nature of the disease and the significantly limited clinical efficacy of systemic treatments administered at advanced stages. Although the strong role of markers such as MGMT promoter methylation in response to standard treatment and long-term outcomes is known, treatment selection in cases of recurrence is often related to clinical course, previous treatments, performance status, and disease extent[12].

Our study found that early mortality emerged as a clinical entity associated with multilobular tumor location and initiation of IB treatment in second or subsequent relapses. The associated low OS levels indicate aggressive tumor biology and increased clinical fragility. Current classification emphasizes the decisive role of molecular features (IDH, 1p/19q, TERT, EGFR, etc.) in diagnosis and prognosis in diffuse gliomas, highlighting the importance of disease heterogeneity in addition to histology[13]. In this context, the interpretation that a multilobular pattern of distribution may be associated with higher tumor burden and aggressive behavior, and that initiation of IB therapy at a later stage may reduce the expected survival time, is clinically consistent.

In our study, the evaluation of treatment response based on clinical and imaging data in real-world conditions highlights the importance of response criteria in high-grade gliomas. Due to the inadequacies of classic radiological criteria, RANO criteria have been proposed as an alternative. Accordingly, a more comprehensive response evaluation approach, including clinical status and steroid requirements, has been suggested[14]. Furthermore, contrast retention may decrease significantly during anti-angiogenic therapies, leading to misleading radiological responses termed “pseudoresponse.” In this context, the increased clinical significance of non-contrast-enhancing tumor components has highlighted the inadequacies of current evaluation criteria and prompted modifications to the RANO criteria[15]. Therefore, it should be considered that some of the heterogeneous survival outcomes observed in our study may be related to differences in patient selection as well as changes in tumor imaging biology under anti-angiogenic therapy. In bevacizumab-based treatment strategies similar to IB, a significant portion of the clinical benefit arises from symptom control and a reduction in peritumoral edema and steroid requirements, rather than changes in tumor burden. Although large phase III studies evaluating the addition of bevacizumab to standard radiotherapy-temozolomide combination showed prolonged progression-free survival, the OS advantage was reported to be limited[16,17]. These phase III data indicate that while anti-angiogenic therapies may increase clinical and radiological response rates, their impact on survival may vary across patient subgroups; thus, patient selection plays a decisive role in real-world data. In our study, the negative prognostic effect of initiating IB in the second or subsequent relapses indicates that bevacizumab-based approaches should be positioned at the appropriate treatment step.

The emergence of age as an independent prognostic factor in multivariate analysis is consistent with current guidelines for adult diffuse gliomas[18]. Increased comorbidity, treatment tolerance status, and neurocognitive impairment in older age, as well as differences in tumor biology, may negatively affect survival. In this context, the prognostic effect of age is a finding that is consistent with real-world data and expected in our study.

The emergence of agents such as regorafenib in the treatment of recurrent glioma in recent years has opened up a more pronounced debate on the efficacy and scope of bevacizumab-based treatment approaches. The REGOMA randomized phase II study demonstrated a statistically significant OS superiority in favor of regorafenib compared to lomustine[19]. In this context, the findings of our study indicate that IB should be rationally positioned based on appropriate patient selection and treatment line rather than being applied as a routine treatment approach in “every recurrent patient.”

The relationship between IDH mutation status and survival in our study is noteworthy. Unexpectedly, IDH mutation was associated with poorer OS in our cohort (HR: 1.98, 95% CI: 1.09–3.58), which stands in contrast to the well-established favorable prognostic role of IDH mutations in diffuse gliomas. This finding should be interpreted with caution and may reflect treatment-line bias, as IDH-mutant tumors tend to occur in younger patients who may have received more extensive prior therapies before IB initiation, thereby entering the recurrent setting with greater treatment burden. Additionally, the limited sample size of this study precludes definitive conclusions regarding this association, and it may not be generalizable. Classical studies have shown that IDH1/2 mutations are a fundamental event in the biology of gliomas and play an important role in prognostic classification, particularly in the diffuse glioma spectrum[20].

The main limitations of this study are its retrospective design and the limited number of patients. Nevertheless, our real-world cohort provides practical insights that may contribute to patient selection in recurrent brain tumors by revealing the relationship between easily accessible clinical parameters, such as multilobar location and the initiation of adjuvant therapy, and early mortality and survival.

5. Conclusions

In conclusion, this retrospective cohort study demonstrates that the efficacy of the IB combination in recurrent high-grade gliomas, predominantly GBM, is heterogeneous and that clinical benefit varies considerably depending on patient selection, relapse stage, and disease extent. Initiating IB therapy in the second or subsequent relapse and the presence of multilobar disease were associated with poorer survival, while age and molecular characteristics also carry prognostic significance. Our findings emphasize the need to evaluate IB therapy in recurrent brain tumors within the framework of an individualized approach and pave the way for prospective, larger-scale studies.

Statement of ethics

The study was conducted in accordance with the principles of the

Declaration of Helsinki and received ethical approval from the Kocaeli University Ethics Committee with the number GOKAEK-2024/20/17 and project code 2024/492.

genAI

No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

Author Contributions:

MS: Study design, research, article writing, PCŞ: Data collection, research, AK: Research, article editing, BM: Statistics, article editing, article writing, TK: Statistics, article editing, article writing, AK: Research, article editing, MU: Research, article editing, TŞ: Research, article editing, MY: Data collection, research, YBT: Research, article editing, DÇ: Research, article editing, UK: Research, article editing, KU: Research, article editing

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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