RESEARCH ARTICLE

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Outcome of Second Line Treatment of Recurrent High-Grade Glioma by re-Irradiation or Bevacizumab-based Chemotherapy: A Cross Sectional Study

Kazem Anvari[1], Mehri Shahabadi[2], James S. Welsh[3], Seyed Alireza Javadinia[4]*, Elham Zarei[5]

Abstract

Introduction: Currently, there is no standard of treatment for the management of the recurrent high-grade glioma. Re-resection, re-irradiation, and chemotherapy are among main treatment options without any proven efficacy. **Aim:** To compare the outcome of second line treatment of recurrent high-grade glioma by re-irradiation or bevacizumab-based chemotherapy. **Methods:** Retrospectively, patients with the recurrent high-grade glioma treated by re-irradiation (ReRT group) (34 patients) or bevacizumab-based chemotherapy (Bev group) (40 patients) as the first-file after the first recurrence were compared in term of first-line progression free survival (PFS), second-line PFS, and overall survival (OS). **Results:** Both groups were similar in term of gender (p=0.859), age (=0.071), type of first-line treatment (p=0.227), and performance status (p=0.150). With a median follow-up of 31 months (m), mortality rate was 41.2% and 70% in the ReRT and Bev groups, respectively. In the Bev and ReRT groups, median OS was 27 m (95% confidence interval (CI) 20-33.9 m) vs. 132 m (95% CI 52.9-211 m) (p<0.0001), median first-line PFS was 11 m (95% CI 7.14-28.7 m) vs. 37 m (95% CI 8.42-65.75 m) (p<0.0001), and median second-line PFS was 7 m (95% CI 3.9-10 m) vs. 9 m (95% CI 5.5-12.4 m) (p=0.564), respectively. **Conclusion:** The PFS is similar after the second line treatment of recurrent primary central nervous system malignancies either by re-irradiation or bevacizumab-based chemotherapy.

Keywords: Recurrent high-grade glioma- re-irradiation- bevacizumab

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Introduction

Recurrence of high-grade gliomas including glioblastoma multiforme (grade IV) and anaplastic astrocytoma (grade III) is an unavoidable situation and even after aggressive surgical resection of primary tumor and subsequent adjuvant re-chemoradiation, the prognosis of these patients is dismal with the median survival of 11 months (Chapman et al., 2019; Hervey-Jumper et al., 2014; Zuniga et al., 2008). Currently, there is no standard of treatment for the management of the recurrent high-grade glioma.

Re-resection, re-irradiation, and chemotherapy are among main treatment options without any proven long-term benefits (Niyazi et al., 2011). Re-resection is generally discouraged in patients with recurrent high-grade glioma and should be considered only in highly selected patients (Hervey-Jumper et al., 2014; Robin et al., 2017). Either re-irradiation using newly developed radiotherapy techniques such as interstitial irradiation (Archavlis et al., 2014) and stereotactic radiosurgery (Kong et al., 2008) or chemotherapy using temozolomide re-challenge (Jauch et al., 2007) and bevacizumab with or without irinotecan (Chen et al., 2020; Zuniga et al., 2008) are two commonly adopted methods for the treatment of recurrent high-grade glioma. However, there is no consensus on the preferred approach. The current study aimed to compare the outcome of second line treatment of recurrent high-grade glioma by re-irradiation or bevacizumab-based chemotherapy.

Materials and Methods

In this cross-sectional study, patients with recurrent high-grade glioma who were treated by re-irradiation or bevacizumab-based chemotherapy at the Omid and Emam Reza Education Hospitals, both affiliated to the Mashhad University of Medical Sciences, Mashhad, Iran, during 2018-2020 were enrolled, retrospectively.

*[1]Cancer Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. [2]Consultant Physician, Mashhad University of Medical Sciences, Mashhad, Iran. [3]Loyola University Chicago, Edward Hines Jr., VA Hospital, Stritch School of Medicine, Department of Radiation Oncology, Maywood, IL, USA. [4]Non-Communicable Diseases Research Center, Sabzevar University of Medical Sciences, Sabzevar, Iran. [5]Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran. *For Correspondence: Javadiniaa941@mums.ac.ir*

Inclusion criteria were primary diagnosis of central nerve system gliomas based on histologic confirmation, unifocal recurrence of high-grade glioma based on either pathologic or imaging evaluations, and treatment at the second-line by -irradiation or bevacizumab-based chemotherapy. Patients who received neither both irradiation and bevacizumab-based chemotherapy, concurrently as the second-line, nor other chemotherapeutic regimens, initially were excluded.

After approval of the protocol of the study by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1398.082) and obtaining a written informed consent form from the patients or the legal guardian, documents of patients were assessed retrospectively in order to assess the overall and disease-free survivals.

The overall survival (OS) was defined as the time interval between the time of first pathology report confirming the diagnosis of high-grade glioma and the time of the death or last visit. The first-line progression free survival (PFS) was defined as the time interval between the time of the first pathology report confirming the diagnosis of high-grade glioma and the time of the recurrence/disease progression based on the imaging or pathologic evaluation. Also, the second-line PFS was defined as the time interval between the time of the first recurrence/disease progression and secondary disease progression. Presence of a newly enhancive lesion or an increase in the size of a preexisting lesion were considered as the tumor recurrence or progression.

Data were analyzed using SPSS 21 by chi square test. Moreover, survival analysis was performed using the Kaplan-Meier method and log-rank test. Cox regression analysis was used to predict the factors affecting the survival. All analysis were interpreted at the level of $p<.05$.

Results

Both groups were similar in term of gender (p=0.859), age (=0.071), type of first-line treatment (p=0.227), and performance status (p=0.150) (Table 1). As it is shown in Table 1, diagnosis of grade 3 astrocytoma at initial diagnosis and subsequently, the diagnosis of high-grade transformation at the recurrence was significantly higher in ReRT group (p=0.012 and p=0.018. respectively).

With a median follow-up of 31 months (m), mortality rate was 41.2% and 70% in the ReRT and Bev groups, respectively. In the Bev and ReRT groups, median OS was 27 m (95% confidence interval (CI) 20-33.9 m) vs. 132 m (95% CI 52.9-211 m) (p<0.0001), median first-line PFS was 11 m (95% CI 7.14-28.7 m) vs. 37 m (95% CI 8.42-65.75 m) (p<0.0001), and median second-line PFS was 7 m (95% CI 3.9-10 m) vs. 9 m (95% CI 5.5-12.4 m) (p=0.564), respectively (Figure 1).

Cox regression analysis showed that the only factors affecting the survival was the type of first-line treatment and therefore biopsy and/or surgery and then adjuvant chemoradiotherapy decreased the probability of death comparing to using non-surgical approaches at the first

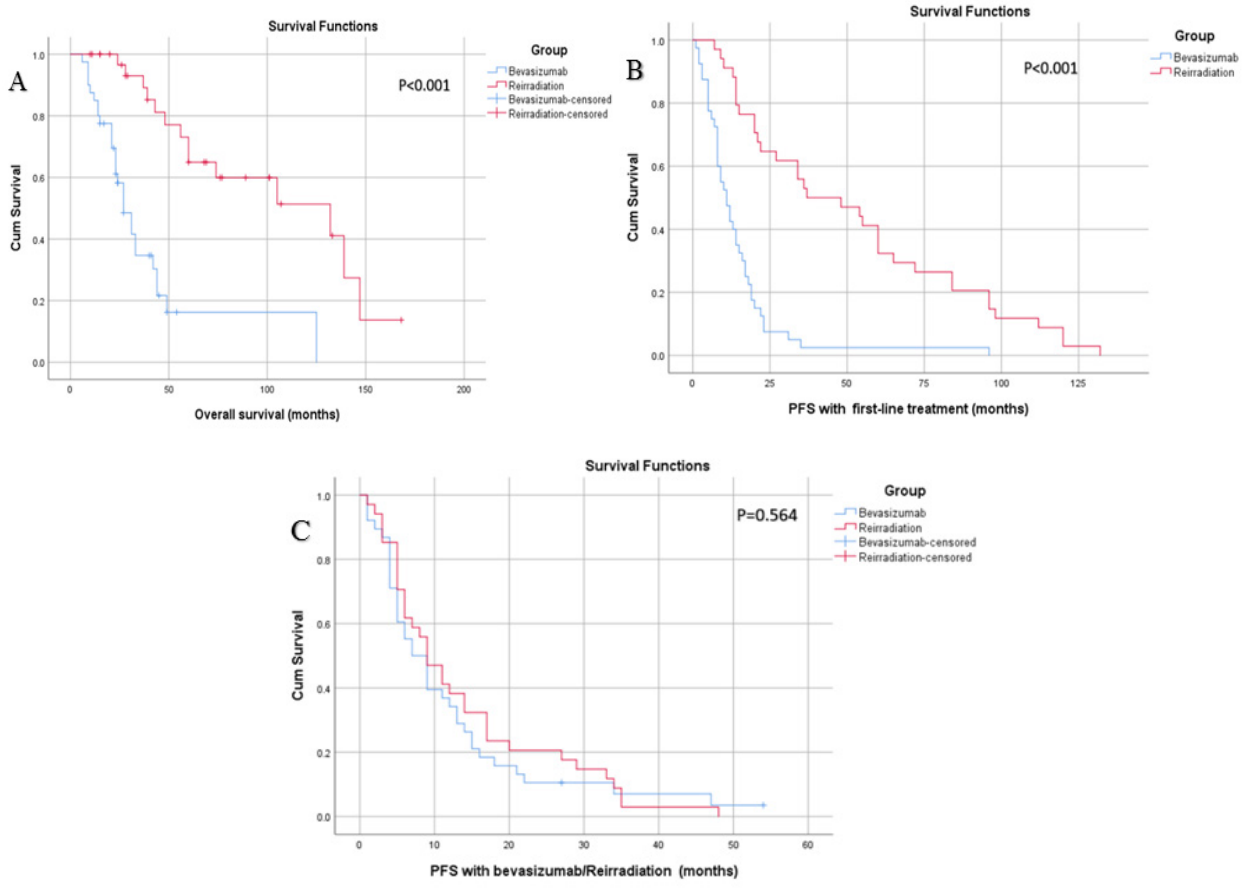

Figure 1. Overall survival (A), primary (B) and secondary (C) progression free survival of patients in two groups.

Table 1. Demographic Data of Patients

	ReRT group Num (%)	Bev group Num (%)	All	P value
Gender				
Male	18 (52.9)	22 (55)	40 (54.1)	0.859
Female	16 (47.1)	18 (45)	34 (45.9)	
Age				
<50 years old (yo)	27 (79.4)	24 (60)	51 (68.9)	0.071
>50 yo	7 (20.6)	16 (40)	23 (31.1)	
Diagnosis at the presentation				
Other grade III and II gliomas	16 (47.1)	7 (17.5)	23 (31.1)	
Anaplastic astrocytoma	6 (17.6)	13 (32.5)	19 (26.7)	0.012
Glioblastoma multiform	12 (35.3)	20 (50)	32 (42.2)	
Diagnosis at the recurrence				
High grade transformation	16 (47.1)	7 (17.5)	23 (31.1)	0.018
Anaplastic astrocytoma	5 (14.7)	6 (15)	11 (14.9)	
Glioblastoma multiform	13 (38.2)	27 (67.5)	40 (54.1)	
ECOG performance score				
1	15 (44.1)	21 (52.5)	36 (48.6)	0.15
2-3	19 (55.9)	16 (40)	35 (47.3)	
4	0	3 (7.5)	3 (4.1)	
First line treatment				
BiopsyàCRTàCT	16 (47.1)	15 (37.5)	31 (41.9)	0.227
Gross total resectionàCRTàCT	18 (52.9)	55 (55)	40 (54.1)	
RT(+/-CT)	0	3 (7.5)	3 (4.1)	

line (HR 0.003, 95%CI 0.001-0.07, p=0.001 for both groups) (Table 2).

Discussion

The current study assessed the efficacy of bevacizumab-based chemotherapy or re-irradiation in the treatment of patients with recurrent primary central nervous system malignancies. Our results showed that both treatments are viable options as the second line of treatment for patients suffering from recurrent primary central nervous system malignancies with similar efficacies. Considering the importance of time interval between two courses of radiotherapy, although, the OS and primary PFS were much higher in patients in Re-RT group.

Currently, patients with high-grade glioma brain receive adjuvant chemoradiation and six cycles of temozolomide following surgical resection of primary lesion (Attarian et al., 2021). However, the treatment approach after recurrence is not clearly stablished. Several treatment options including re-resection, systemic therapies (irinotecan, bevacizumab, and even reintroduction of temozolomide), re-irradiation, and best supportive care are all available considering the performance status of patients, goal of treatments, available options, and complications (Birk et al., 2017). While these treatments can provide some benefits regarding the symptoms relief, none of these responses are neither durable nor associated

Table 2. Cox Regression Analysis on the Factors Affecting the Survival

	Reference	HR	95% CI	P value
Bevacizumab administration	Re-irradiation	2.5	0.7-8.3	0.084
Male gender	Female	0.7	0.1-3.5	0.432
Age<50 yo	Age>50 yo	0.4	0.1-2	0.065
Primary diagnosis of AA	GBM	0.7	0.7-7.1	0.794
Recurrence diagnosis of high-grade transformation	GBM	3.4	0.3-32	0.281
Recurrence diagnosis of GBM	GBM	1.7	0.1-16	0.45
Performance score of 1	4	2.1	0.2-16	0.623
Performance score of 2-3	4	3.2	0.4-24	0.248
First-line treatment of BiopsyàCRTàCT	RT(±CT)	0.003	0.001-.07	0.001
First-line treatment of GTRàCRTàCT	RT(±CT)	0.003	0.001-.07	0.001

with improved survival rates (Laub et al., 2018).

Studies have shown that re-irradiation using techniques such as 3-D conformal radiotherapy (either reduced-dose-rate or conventional rate radiotherapy) (Adkison et al., 2011; Burr et al., 2020; Rong et al., 2011), stereotactic radiosurgery (Kong et al., 2008), and interstitial irradiation (Archavlis et al., 2014) are safe and producing some survival benefits, as it was evident in the current study. Various studies have been performed mostly concentrated on stereotactic radiosurgery due to the ability of this technique in sparing organs-at-risk and delivering the highest doses to tumoral lesion, precisely (Combs et al., 2008; Conti et al., 2012; Greenspoon et al., 2014; Grosu et al., 2005; Minniti et al., 2013). However, there are reports on the utility of 3-D conformal radiotherapy or intensity modulated radiation therapy technique in the reirradiation of high-grade glioma (Aktan et al., 2015; Kaul et al., 2020; Niyazi et al., 2012). In a study by Kaul et al., (2020), 198 patients with recurrent high-grade glioma were treated by reirradiation using intensity modulated radiation therapy technique. Their results showed that median overall survival of patients with glioblastoma and grade 3 gliomas were respectively 6 months and 14 months following relapse. Overall, they showed that reirradiation is safe and is doable event at high doses of 49.4 Gy/3.8 Gy (Kaul et al., 2020).

Bevacizumab-based chemotherapy gains attentions in the management of recurrent primary central nervous system gliomas in the recent decades and has been approved by Food and Drug Administration in 2009 after the publication of AVF3708g (Friedman et al., 2009) and NCI 06-C-0064E (Kreisl et al., 2009) studies showing that it, alone or in combination with other chemotherapeutic agents, was well tolerated and has significant biologic activity in recurrent glioblastoma.

In conclusion, despite the higher OS and primary PFS in patients who received re-irradiation, the secondary PFS following the second line of treatment was similar between two groups regardless of re-irradiation or bevacizumab-based chemotherapy showing similar efficacy.

Author Contribution Statement

Study concept and design: K.A.; acquisition of data: S.A.J. and M.Sh.; analysis and interpretation of data: S.A.J.; drafting of the manuscript: S.A.J., J.S.W., and M.Sh.; critical revision of the manuscript for important intellectual content: K.A. and J.S.W.; statistical analysis: A biostatistician outside of research team help.

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Ethical Statement

The protocol of the study was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1398.082) and a written informed consent form was obtained from the patients or the legal guardian.

Data availability statement

All data generated and analyzed during this study can be accessed through direct communication with the corresponding author and the agreement of all research team members.

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Conflict of interest statement

The authors declare that there is no conflict of interest to be reported.

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