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Systematic Review

Comparison of Infection Incidence Between Recurrent Glioblastoma Treatment Strategies: A Systematic Review and Meta-Analysis

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Abstract

Background: The purpose of this study was to evaluate different chemotherapy regimens in the treatment of recurrent glioblastoma.

Methods: In this review, databases including Scopus, Google Scholar, ISI, and PubMed were reviewed using keywords of recurrent glioblastoma, Bevacizumab, infection. In this meta-analysis study, of all articles evaluating recurrent glioblastoma treatments, 19 articles reporting infection were selected, based on inclusion criteria, 11 articles were used to compare the incidence of infection in Bevacizumab based chemotherapy strategies, and seven articles were included in the Bayesian network meta-analysis for comparison between more various chemotherapy regimens. Cochran test was used to determine the homogeneity of the samples. The prevalence was estimated based on Random Effect in Revman software (version 3.5). Bayesian network meta-analysis was performed by NetMetaXL 1.6.1 software and winBUGS 1.4.3.

Results: A total of 11 studies with 776 subjects were evaluated to compare the incidence of infection in bevacizumab-based drug regimens. There was a significant difference between the chemotherapy regimens (P <0.0008) in the subtotal pooled random effect size. The lowest odd ratio of infection incidence was seen in the Bevacizumab+ Irinotecan chemotherapy regimen. Also, in a network meta-analysis of 1,169 patients, Temozolomide plus radiation was ranked as the best treatment to prevent infection (Surface Under Cumulative Ranking Curve (SUCRA) = 73%).

Conclusions: Among the conventional treatment regimens containing Bevacizumab, Bevacizumab + Irinotecan had the lowest incidence of infection. Compared with these diets with those without Bevacizumab, Temozolomide plus radiation has the lowest incidence.

***Keywords:** Bevacizumab, Infection, Recurrent Glioblastoma, Treatment Strategies*

1. Introduction

Glioblastoma (GBM) is the most common and malignant central nervous system tumor [19]. This primary tumor is predominantly found in brain white matter of adults and the cerebellum and medulla oblongata of children [29]. Its incidence is 3 to 7 per 100,000 people per year, although geographical variation contributes to its prevalence; it is the highest incidence in Europe (5.5 per 100,000), while the lowest is in South-Central Asia (1.8 per 100,000 people) [24].

GBM accounts for approximately 40% of all primary brain tumors and 80% of all malignant tumors of the central nervous system [23]. The prevalence of GBM in men is two times greater than in women [23]. The prevalence of GBM is highest among people aged 84-75 years [33]. The standard treatment for patients with suspected GBM is tumor resection by the surgery followed by focal radiotherapy and concomitant chemotherapy [31]. This type of tumor has clinical symptoms, including cognitive impairment, personality changes, headache, sensory impairment, and imbalance in walking [1]. Risk factors involved in the development of GBM include family history, multiple endocrine neoplasia, injuries due to brain metastasis, abnormalities of the female sex hormones, high body mass index (BMI), and viruses such as human cytomegalovirus (HCMV)[2, 3, 8, 20, 25, 37]. Standard care of newly diagnosed patients with GBM consists of total surgical resection accompanied by postoperative radiation with complementary and adjuvant Temozolomide (TZM) therapy [35]. There are still minimal chemotherapy treatments for recurrent GBM. Treatment choices for recurrent GBM are already limited and show misleading outcomes such as toxicities like an infection. This study aimed to evaluate the incidence of infection in various chemotherapy regimens used in recurrent GBM treatment.

2. Materials and Methods

2.1 Search Strategy

The present study is a meta-analysis study investigating the relationship between infections incidences in recurrent GBM based on received chemo-radiotherapy regimens. The current study was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Fig. 1). Two independent researchers performed qualitative evaluation and data extraction to prevent bias, search, selection of studies, and selection. The required data were collected from databases such as ProQuest, Science Direct, PubMed, Springer, Web of Science, EMBASE, Cochrane, EBSCO, Chemical Abstracts, Online Library Wiley, and Google Scholar search engine. To maximize the search consistency, we used the search terms ‘‘recurrent glioblastoma’’, ‘‘Bevacizumab’’, and ‘‘infection’’ with all possible OR and AND operators combinations.

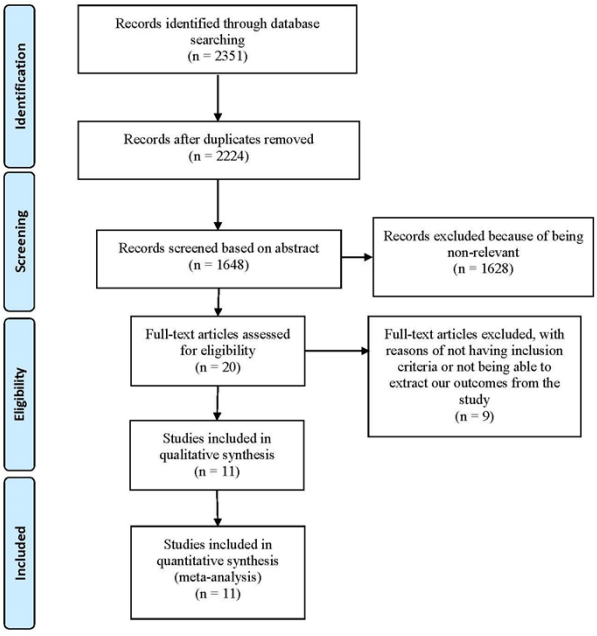

Figure 1. *PRISMA diagram flow*

2.2 Study Selection and data extraction

The main inclusion criteria in this study were retro-prospective, cohort, and clinical trials reporting the incidence of infection in subjects with recurrent glioblastoma. Exclusion criteria include lack of relevance to the issue and inadequate data.

Qualitative evaluation, selection of relevant articles, and extraction of their data were performed by two researchers separately. Selected articles were evaluated by researchers using the Strobe Checklist (STROBE). Any disagreements were referred to as the third assessor. The checklist consists of 22 different sections and evaluates various aspects of the methodology, including sampling methods, variables measurement, statistical analysis, adjusting for confounders, mentioning the validity and reliability of the tools and the study's objectives. Based on the study collections in the first step, 2351 related articles were found; 1628 articles were excluded as non-relevant. Of the remaining, 127 were duplicated because of being extracted by two researchers. The infection rate was not the main outcome of many of these studies and was not reported in the abstract. So abstract review did not help to select articles.

Next, the full text of the remaining articles was reviewed, of which 11 studies entered the study. (Figure 1) A checklist including the author's name, year of publication, type of study, sample size, mean age, study treatment regimens, and the number of infection incidence in each group was used. To estimate the standard error of event rate, Pooled Prevalence estimates were used based on the study of Cowling et al. (1999), assuming 100% test sensitivity and specificity in reporting infection incidence [10].

2.3 Data analysis

To combine the results of the studies, logarithm (OR) was used in each study. Convergence has been reached at 40,000 iterations for all projections, and autocorrelation has been tested and verified. We produced a median estimate of the odds ratio (OR) and stated it at 2.5th to 97.5th centiles of distribution (95 percent credible interval (CrI)). Modeling of the Markov chain Monte Carlo (MCMC) has been used to measure the relative rating likelihood of each treatment group. ''Rankograms" of the surface under the cumulative ranking curve (SUCRA) have been reported to provide a quantitative ranking of treatment group safety. A SUCRA is a quantitative description of the likelihood of safety; that is to say, a SUCRA of 90 percent means that interest treatment has achieved 90 percent of the safety of that treatment compared to other groups. The Bayesian network meta-analysis was done employing NetMetaXL 1.6.1 and winBUGS 1.4.3.

Weighted mean was used to combine the prevalence of different studies. The heterogeneity of studies was calculated using the Q test and I_2 index. Given the significance of Index I and the heterogeneity of the studies together, the Random model effects were used to combine the results of the studies, which was performed in Revman software (version 5.3). The significance level was set at 0.05.

3. Results

In the present study, the incidence of infection in different studies was studied based on the chemotherapy regimen used. A total of 11 studies were studied with 776 subjects (Table 1). Subtotal analysis was performed to compare this incidence between different chemotherapy regimens. Of the five studies administering the Bevacizumab (BV) medication alone, 76 out of 312 patients had experienced infections (OR = 2.83, 95% CI (1.34-5.97)). The BV + adjuvant therapy, which included other drugs, as Temozolomide (TZM) and Lomustine (CCNU), included three studies, in one study (Readon 2011), OR was not calculated. Finally, three studies with 97 subjects and 30 cases of infection were found in this group (OR = 3.86, 95% CI (5.79 to 2.33)). 5 studies of BV + Irinotecan (CPT-11) reported 27 out of 274 infections (OR = 2.11, 95% CI (1.58-2.81)). BV + CPT-11 + Carboplatin or Cetuximab administration was observed in two studies with 83 subjects and 15 cases of infection (OR = 4.24, 95% CI (3.52-5.11)). There was a significant difference between the study regimens (P <0.0008) in the sub-total pooled random effect analysis. The lowest OR incidence of infection was seen in BV + CPT-11 (figure 2).

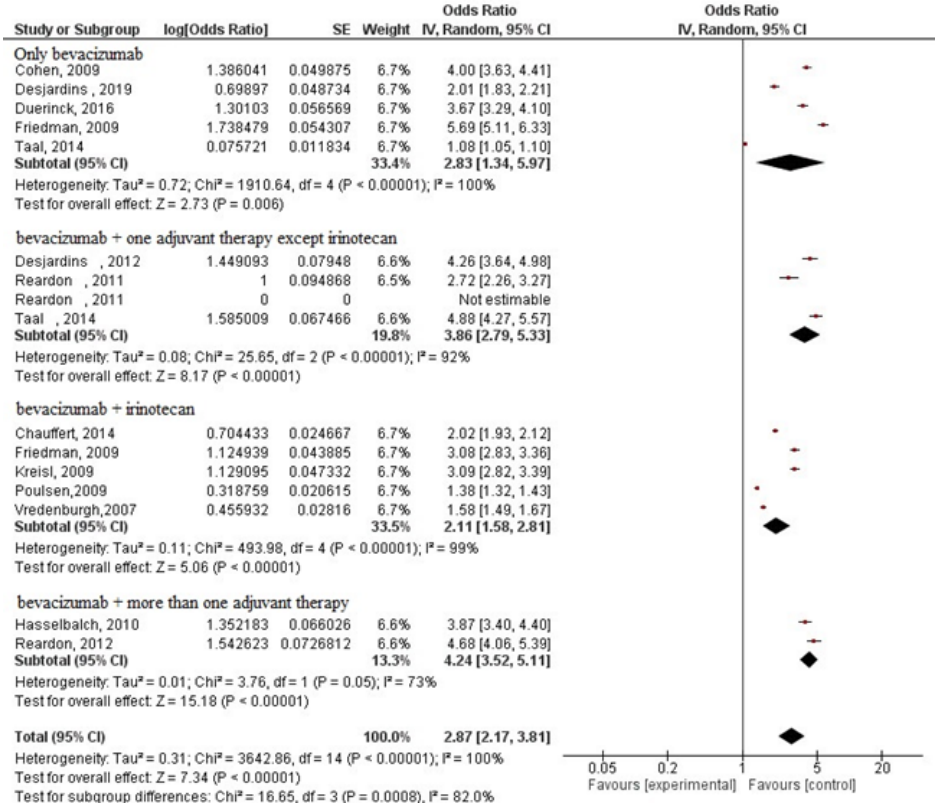

Figure 2. *Pooled random effect estimation of infection incidence and pairwise comparisons*

3.3 Best treatment for infection prevention

According to primary outcome of network meta-analysis of 1,169 patients, TZM plus Radiation were ranked as the best treatment for prevention of infection (Surface under Cumulative Ranking Curve (SUCRA) = 73%) with significantly lower OR than adjuvant TZM (OR=0.27 (0.10 – 0.64)), BV (OR=0.11 (0.00 – 0.99)), and BV+CCNU (OR=0.04 (0.00 – 0.44)) (Table 2 and 3). (Fig. 3).

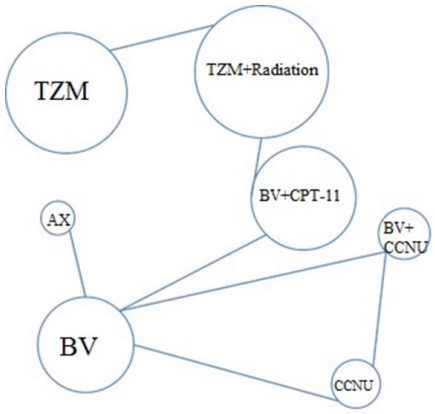

Figure 3. *Demonstrates the network graph of all eligible comparisons for the infection incidence. (BV, Bevacizumab; TMZ, Temozolomide; CPT-11, Irinotecan; CCNU, Lomustine; AX, Axitinib)*

Table 1. Characteristics of studies included in this meta-analysis

Author, year, citation	Regimen	Number of patients	Number of infections that reported	Mean age
Chamberlain, 2004 [6]	Cyclophosphamide	40	1	51.2
Rich, 2004 [30]	Gefitinib	57	2	54
Stupp, 2005 [32]	TMZ + Radiation	286	6	NR
	Adjuvant TMZ	287	21	
Vredenburgh, 2007 [36]	BV + CPT-11	35	1	56.5
Cohen, 2009 [9]	BV	84	46	54
Friedman, 2009 [17]	BV	84	1	NR
Kreisl, 2009 [22]	BV + CPT-11	48	1	53
Poulsen, 2009 [26]	BV + CPT-11	52	7	46
Chamberlain, 2010 [5]	BV	50	3	54
Hasselbalch, 2010 [18]	Cetuximab + BV + CPT-11	43	15	NR
Reardon, 2011 [27]	BV + TMZ	10	1	51
	BV + ETP	13	0	42.95
Desjardins, 2012 [14]	BV + TMZ	32	9	51
Reardon, 2012 [28]	Carboplatin + CPT-11 + BV	40	9	51
Cuppini,2013 [11]	BV + CPT-11	68	0	53
	BV	32	0	53
Chauffert, 2014 [7]	BV + CPT-11	60	8	60.55
	TMZ + Radiation	60	4	60.55
Taal, 2014 [34]	BV	50	10	56.25
	CCNU	46	7	56.25
	BV + CCNU	52	20	56.25
Duerinck, 2016 [16]	Axitinib	22	0	54.5
	BV	20	1	54.5
Duerinck, 2018 [15]	Axitinib	50	0	NR
Desjardins, 2019 [13]	BV	74	18	NR

BV, Bevacizumab; TMZ, Temozolomide; CPT-11, Irinotecan; VP-16, Etoposide; CCNU, Lomustine; NR, not reported

Table 2. SUCRA of each regimen

Treatment	SUCRA
Temozolomide + radiation	0.7362
Axitinib	0.6991
Bevacizumab + Irinotecan	0.6058
Lomustine	0.4963
Bevacizumab + Irinotecan	0.4773
adjuvant Temozolomide	0.4625
Bevacizumab	0.4091
Bevacizumab + Te-mozolomide	0.3642
Bevacizumab + Lomustine	0.2494
SUCRA, surface under cumulative ranking curve	

Table 3. League table of estimated effects of biologic therapy regimens in network meta-analysis on infection rate, OR<1 means better results

TZM + radia-tion								
49.73 (0.00 – 433100.00)	BV + VP-16							
0.63 (0.01 – 326.48)	0.02 (0.00 – 6798096.53)	Axitinib						
13.47 (0.00 – 9850.00)	0.19 (0.00 – 6.23)	11.85 (0.00 – 35350.00)	BV + TZM					
0.43 (0.11 – 1.40)	0.01 (0.00 – 757575.76)	0.67 (0.00 – 52.96)	0.03 (0.00 – 1613423.69)	BV+ CPT-11				
0.27 (0.10 – 0.64)	0.01 (0.00 – 404530.74)	0.40 (0.00 – 53.58)	0.02 (0.00 – 785545.95)	0.62 (0.13 – 3.21)	adjuvant TZM			
0.16 (0.00 – 1.91)	0.00 (0.00 – 504032.26)	0.25 (0.00 – 10.43)	0.01 (0.00 – 1108647.45)	0.38 (0.02 – 3.19)	0.64 (0.01 – 8.06)	CCNU		
0.11 (0.00 – 0.99)	0.00 (0.00 – 322788.90)	0.19 (0.00 – 5.12)	0.01 (0.00 – 751314.80)	0.27 (0.02 – 1.56)	0.44 (0.01 – 4.22)	0.72 (0.22 – 2.10)	BV	
0.04 (0.00 – 0.44)	0.00 (0.00 – 118357.20)	0.07 (0.00 – 2.49)	0.00 (0.00 – 327761.39)	0.10 (0.00 – 0.79)	0.17 (0.00 – 1.95)	0.28 (0.09 – 0.70)	0.38 (0.15 – 0.93)	BV+ CCNU
BV, Bevacizumab; TMZ, Temozolomide; CPT-11, Irinotecan; VP-16, Etoposide; CCNU, Lomustine								

4. Discussion

4.1 Infection rates are lowest when Temozolomide is combined with radiotherapy

In the present study, we investigated the incidence of infection following consumption of different medication regimens in recurrent glioblastoma. Our study showed that Temozolomide (TZM) plus radiation has the lowest incidence of infection compared to different treatment regimens. Although this drug has previously been used to treat the disease, the newly developed regimens have shown higher rates of infection; but not all aspects of the matter are apparent. As shown in the study by De Bonis et al., There was a hypothesis that postoperative infection in patients with glioblastoma increased their chances of survival [12]. Their study, which evaluated the effect of postoperative infection in patients with glioblastoma, concluded that postoperative infection in patients with glioblastoma could increase the chance of survival in these patients [12]. However, this discussion needs further studies on the type of treatment received after surgery, as we were looking for the same.

4.2 Temozolomide mechanism of action

TZM as an alkylating agent can eliminate abnormal cells, but other healthy cells in the body can cope with the environmental stress caused by TZM due to their genome repairability. In understanding the pathophysiology of glioblastoma and advances in treatment, cancer remains incurable because, despite conventional therapies, including removing the tumor with surgery followed by radiation therapy plus TZM treatment, patients usually die in the 12 to 15-month timeframe. TZM is an alkylating antitumor drug belonging to a class of Imidazotetrazinones antitumor. TZM has cytotoxic activity in cell lines and tumor cells. It results in the formation of asymmetric DNA adducts and the induction of apoptosis. In addition to tumor growth-inhibiting, Temozolomide modifies immunization and reduces the tumor cell metastasis potential [4].

4.3 Temozolomide combined with radiotherapy could increase the mean lifetime after surgery

The mean lifetime after surgery and resection of 78% of the tumor volume was 12.5 months. In contrast, the time with TZM chemotherapy reached 16 months. Since 2005 TZM has been used as a therapeutic drug for GBM [1]. Stupp et al., in a study of patients receiving combination therapy of Temozolomide with radiotherapy for two years, reported that the mean life expectancy of patients treated with radiotherapy alone is less than patients receiving combination therapy. This combination therapy has been recognized as a standard treatment because of the increased survival in the treatment groups with TZM concomitant with radiotherapy [32].

However, TZM induces impairment of lymphopenia and T-cells in some cases. Many opportunistic infections were documented in the literature in connection with this toxicity but were not well specified.

4.4 Bevacizumab and incidence of infection

For the treatment of recurrent glioblastoma, Bevacizumab (BV), an anti-vascular endothelial growth factor (VEGF) antagonist, was approved in 2009 by FDA [21]. Our meta-analysis results showed that BV with CPT-11 had the lowest incidence of infection among conventional treatment regimens using BV. VEGF is one of the essential angiogenic-specific regulators. Vascular endothelial growth factors perform their biological action on target cells by interacting with tyrosine kinase receptors present in the cell's plasma membrane. These receptors become dimerized and autophosphorylated upon binding to their ligand, which eventually leads to intracellular cascade events. Vascular endothelial growth factor A is critical in the selection process and works by activating both 1-VEGFR and 2-VEGFR receptors.

4.5 Bevacizumab mechanism of action

The use of antibodies against VEGF and its receptor or the use of tyrosine kinase inhibitors has had good results in clinical studies related to the treatment of tumors. Mast cells accumulate in the tumor medium under the influence of tumor-derived chemokine uptake and produce molecules such as growth factors, histamine, heparin, VEGF, IL-8, and proteases that contribute to the formation of new vessels and metastases. BV is a cancer drug that inhibits the growth and spread of cancer cells in the body. BV is used to treat brain tumors and cancers of the kidney, lung, colon, rectum, uterus, ovary, and fallopian tubes. It is commonly used in combination with other cancer drugs. The drug's mechanism of action is by blocking VEGF binding to its receptors and binding to all of its isoforms and blocking VEGF-induced angiogenesis. It increases the chance of infection of the skin and subcutaneous tissues, especially in wound healing in the gastrointestinal wall. This drug may alter the immune system and weaken the immune system, so the risk of infection may increase.

5. Conclusion

Although newer treatment regimens may be more effective in treating recurrent glioblastoma, it seems that infection with the Temozolomide drug is less likely to occur. While a combination of BV and CPT-11 may have less infection chance.

Authors' contributions

All authors contributed to the study conception and design. Literature search and data analysis was performed by [Shahab Mahmoudnejad Fenderi], [Ali Teimouri], and [Navid *Ebrahimipour].* The first draft of the manuscript was written by [Ashkan Pouyan] and [Daniel Kheradmand]. Critical review and editing the manuscript was done by [Sajjad Saghebdoust]. The study design, conceptualization and supervision was done by [Mehran Alirezaei]. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

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