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ORIGINAL RESEARCH

Effectiveness of lomustine and bevacizumab in progressive glioblastoma: a meta-analysis

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Background: Glioblastomas (GBMs) are the most aggressive type of glial brain tumors. Despite aggressive treatment with surgery and chemoradiation, GBMs invariably relapse and tumors are progressive. Controversy remains on optimal treatment of patients with recurrent GBMs. Data from previous trials have suggested that the addition of bevacizumab (BEV) to lomustine (CCNU) might improve overall survival (OS) as compared with that with monotherapies. The aim of this study was to compare the efficacy of BEV in addition to CCNU versus single-agent therapy in patients with recurrent GBM.

Methods: Electronic databases were searched for eligible literature updated in December 2017. Trials assessing the effectiveness of CCNU and BEV in progressive GBM were included, of which the main outcomes were progression-free survival (PFS) and OS. All the data were pooled with the corresponding 95% confidence intervals (CIs) using RevMan software. Sensitivity and heterogeneity were quantitatively evaluated.

Results: Three randomized clinical trials were identified, including 574 patients (combination group: 358, monotherapies group: 216). The combination group treated with BEV and CCNU showed improvement in PFS (OR = 0.49; 95% CI, 0.41–0.59; $p < 0.00001$). No significant differences were, however, found in patients in terms of the OS (OR = 0.84; 95% CI, 0.68–1.03; $p = 0.09$).

Conclusion: Although treatment with CCNU plus BEV prolonged PFS, it did not confer OS advantage over monotherapies in patients with progressive GBM. The encouraging results of the addition of CCNU to BEV warrant investigation in further randomized trials.

Keywords: glioblastoma, bevacizumab, lomustine, meta-analysis, brain tumors, progression free survival

Introduction

Glioblastomas (GBMs) are the most common and aggressive type of glial brain tumors[1] and have a poor prognosis. The current standard of treatment for GBM includes surgical resection followed by combined chemoirradiation with concurrent temozolomide (TMZ).[2] However, GBMs invariably relapse, and when tumor progresses, treatment options are scarce and with poor effectiveness. Previous studies have identified genetically diverse tumors cells, which are used to classify tumors into different subgroups according to their molecular signature,[3–6] to find new targets for specific subgroups of patients.[7–9] Because of the extensive endothelial proliferation that characterizes GBM, soon after the discovery of vascular endothelial growth factor (VEGF) and its significance in the angiogenesis of tumor growth, it has been hypothesized that GBM would provide a good target for antiangiogenic treatments.[10] Previous studies suggested that bevacizumab (BEV), a monoclonal antibody that targets VEGF, alone or in combination with cytotoxic agents, showed interesting results in terms of treatment for recurrent GBM. Preliminary data suggest a beneficial effect of the combination of BEV and lomustine (CCNU) in patients

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with GBM progressing after TMZ-based chemoradiation.[11] Similar to the TMZ therapy, CCNU, an alkylating nitrosurea drug, can be administered at initial diagnosis or at tumor recurrence. However, Piccioni et al[12] demonstrated the equal efficacy of BEV monotherapy, but with no additional benefit of CCNU. Whether BEV should be used as a monotherapy for tumor progression or used by adding to another drug has also remained a matter of debate. Given the lack of clear options, we explored the efficacy of adding CCNU to BEV for GBM patients who progressed after initial therapy.

Methods

Search strategy

Two investigators independently searched the electronic databases PubMed, Embase, and Cochrane Library for relevant literature published up to December 2017. The process was established to find all articles with the keywords "Glioblastoma" AND "Bevacizumab" AND "Lomustine", and relevant Medical Subject Heading terms were utilized. The reference lists of all articles that dealt with the topic of interest were also hand-searched to check for additional relevant publications.

Eligibility criteria

Studies that met the following criteria were included in the meta-analysis: 1) the studies comparing the effectiveness of combination of BEV and CCNU in progressive GBM and 2) the outcomes of interest were survival efficacy, and hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were provided. When we found duplicated or overlapped data in multiple reports, we just included the one with the most complete information.

Quality assessment

Two investigators separately rated the quality of the retrieved studies. We chose the risk-of-bias items recommended by The Cochrane Handbook for Systematic Reviews of Interventions.

Data extraction

Two authors independently extracted the relevant data from each trial. Disagreement was resolved by consensus. From each of the eligible studies, the following information was extracted: the first author's family name, publication year, study type, treatment regimen, and end points of interests. We extracted the corresponding HRs and risk ratios to describe the strength of the association for survival data (overall survival [OS] and progression-free survival [PFS], respectively), with corresponding 95% CIs.

Statistical analysis

The end points of interest in the pooled analysis were OS and PFS data, and the end point outcome was considered as a weighted average of individual estimate of the HR in every included study, using the inverse variance method. If HRs and corresponding 95% CIs were reported, logarithm of HRs and the corresponding logarithm of lower limits and logarithm of upper limits were used as data points in pooling the analysis, whereas if a study did not provide HRs or 95% CIs, the only available data were in the form of K–M curves. Survival data were extracted from amplified K–M curves, according to the methods described by Tierney et al.[13]

A sensitivity analysis was also performed to examine the impact on the overall results, depending on the heterogeneity across the included studies. Heterogeneity across studies was examined using the I^2 statistic.[14] Studies with an I^2 of 25%–50%, 50%–75%, or >75% were considered to have low, moderate, or high heterogeneity, respectively.[15] When there was low heterogeneity among the studies, the fixed-effects model was used; otherwise, the random-effects model was used. A p-value less than 0.05 was considered statistically significant. The statistical analyses were performed using the Review Manager Version 5.3 software (RevMan; The Cochrane Collaboration, Oxford, UK). Findings of our meta-analysis are shown in forest plots. The Begg's and the Egger's tests were conducted to evaluate publication bias.

Results

Overview of literature search and study characteristics

A total of 213 studies were retrieved initially for evaluation. Based on the criteria described in the "Methods" section, eight publications were evaluated in more detail, but some did not provide enough detail of outcomes of two approaches. Therefore, a final total of three trials[16–18] addressed the combination of BEV and CCNU in treating progressive GBM. The search process is described in Figure 1. All included studies in this study were based on moderate- to high-quality evidence. Table 1 describes the primary characteristics of the eligible studies in more detail.

Clinical and methodological heterogeneity

Pooled analysis of PFS with the combination of BEV and CCNU in progressive GBM

Pooling the PFS data from all the three studies[16–18] showed that the combination therapy did prolong the PFS (OR = 0.49; 95% CI, 0.41–0.59; $p < 0.00001$) as compared with that in the monotherapy group (Figure 2).

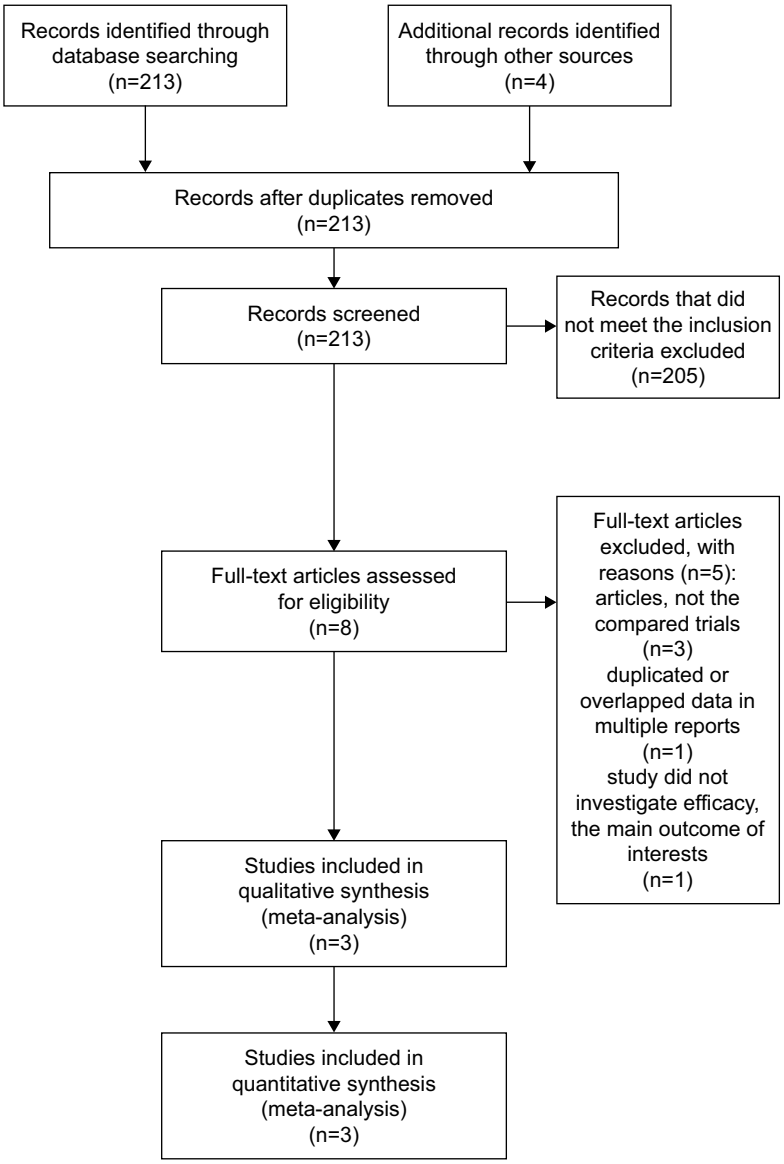


Figure 1 PRISMA flowchart of selection process to identify studies eligible for pooling.

Pooled analysis of OS with the combination of BEV and CCNU in progressive GBM

A fixed-effects model was used to pool the OS data.[16–18] The pooled data showed that the combination of BEV and CCNU did not improve the OS (OR = 0.84; 95% CI, 0.68–1.03; $p = 0.09$) as compared with that in the monotherapy group (Figure 3).

Discussion

GBM is the most common brain cancer in adults. Despite aggressive treatment with surgery and chemoradiation, its prognosis still remains poor.[19] Controversy remains on the optimal treatment of patients with recurrent GBM. GBMs are highly vascularized tumors in which the VEGF signaling

Table 1 Primary characteristics of the eligible studies

Study	Year	Trial	N		Age	
			Combination group	Monotherapies	Combination group	Monotherapies
Wick et al[16]	2017	RCT	288	149	57.1	59.8
Heiland et al[17]	2016	Retrospective study	18	17	50	39.5
Taal et al (1)[11]	2013	RCT	52	50	58	58
Taal et al (2)[18]	2014	RCT				

Notes: Combination group: BEV+CCNU; monotherapies: BEV or CCNU. Taal et al (1): BEV+CCNU 90 vs BEV; Taal et al (2): BEV+CCNU 90 vs CCNU.
Abbreviations: RCT, randomized controlled trial; BEV, bevacizumab; CCNU, lomustine.

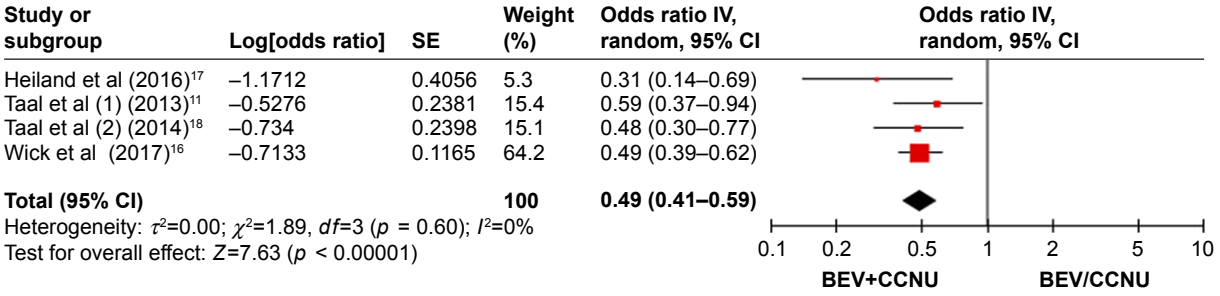


Figure 2 Pooled analysis of PFS with the combination of BEV and CCNU in progressive GBM.
Abbreviations: PFS, progression-free survival; BEV, bevacizumab; CCNU, lomustine; GBM, glioblastoma; CI, confidence interval.

pathway is upregulated. BEV is a humanized monoclonal antibody against circulating VEGF. Although BEV is commonly used, data on timing of administration and optimal patient management upon further progression remain limited. CCNU has been an approved option for recurrent GBM and has also been frequently administered in clinical trials as the standard treatment.[20,21]

Randomized Phase II BELOB trial demonstrated a potential benefit of BEV when added to CCNU chemotherapy in patients with recurrent GBM, although no consensus has been reached on how patients who experience further disease progression after a combined treatment with BEV and CCNU salvage therapy should be treated.[22,23]

In this analysis, we found that the combination of BEV with CCNU did not confer OS advantage over monotherapy alone, but prolonged PFS to some extent. The mechanism by which the combination treatment with BEV and CCNU prolongs PFS still remains undefined. It has been suggested that normalization of the vasculature around the tumor as well as improved regional cerebral blood flow and not necessarily the inhibition of tumor growth are the key components of the antiangiogenic activity.[24–26]

Moreover, results can be explained by the detailed assessment of the patient group and a selection bias with regard to the crossover design of various studies. Furthermore, biomarkers can also affect the outcome after treatment. Taal et al[18] showed that *IDH* mutation status increased the sensitivity to treatment. This raises the question of whether trials on recurrent GBM should identify a subset of patients with *IDH* wild-type tumors or should analyze patients according to *IDH* mutational status. In Erdem-Eraslan et al's study,[10] to identify recurrent GBM patients who benefit from combined CCNU and BEV treatment, gene expression was performed, and it was observed that patients with a specific molecular subtype of glioma, IGS-18, or "classical GBMs" may show more benefit from BEV+CCNU treatment.

The data on adverse effects (AEs) were limited; therefore, it was not possible to assess the AEs in this meta-analysis. In Wick et al's study,[16] the addition of BEV did not improve neurocognitive functioning, and did not lead to poorer neurocognitive function as compared with that observed with CCNU use alone. Heiland et al[17] showed a slight increase in myelosuppression (thrombocytopenia and leukopenia) after the combination therapy. Both the trials showed that the combination therapy can be administered with an acceptable toxicity and no significant negative impact on the clinical performance of the patients compared to monotherapy, and the higher numbers of AEs should be assessed relative to the longer treatment period in the combination group.

Our study still has several limitations. First and the foremost, as this study was a study-level meta-analysis, there is publication bias leading to heterogeneity among the included

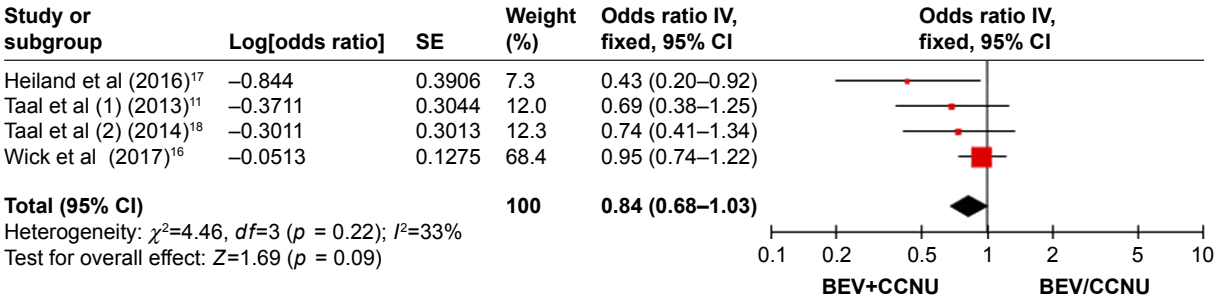


Figure 3 Pooled analysis of OS with the combination of BEV and CCNU in progressive GBM.
Abbreviations: OS, overall survival; BEV, bevacizumab; CCNU, lomustine; GBM, glioblastoma; CI, confidence interval.

studies. The inclusion of retrospective studies was an inherent limitation, and differences in patient comorbidities could not be incorporated in such an analysis. Second, there are only two studies that reported available data on AEs, so we could not predict efficacy in AEs.

Conclusion

Although treatment with CCNU plus BEV prolonged PFS, it did not confer OS advantage over monotherapies in patients with progressive GBM. The future of antiangiogenic therapy remains unclear; it is hypothesized that combining immunotherapy with antiangiogenic treatment may have a synergistic effect and enhance the efficacy of both the treatments. The encouraging results of the addition of CCNU to BEV warrant investigation in further randomized trials.

Disclosure

The authors report no conflicts of interest in this work.

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