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The efficacy of dendritic cell vaccine for newly diagnosed glioblastoma: a meta-analysis of randomized controlled studies

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Dendritic cell vaccine for the treatment of glioblastoma: a meta-analysis of randomized controlled studies

Abstract

Introduction: The efficacy of dendritic cell vaccine to treat glioblastoma remained elusive and therefore we conducted a meta-analysis to explore the influence of dendritic cell vaccine on treatment efficacy of glioblastoma.

Methods: PubMed, EMbase, Web of science, EBSCO and Cochrane library databases have been searched through October 2020, and we included randomized controlled trials (RCTs) assessing the efficacy of dendritic cell vaccine for glioblastoma.

Results: Four RCTs and 267 patients were included in the meta-analysis. Compared to control group for glioblastoma, dendritic cell vaccine demonstrated no obvious impact on on overall survival (HR=0.59; 95% CI=0.34 to 1.04; P=0.07), progression-free survival (PFS, HR=0.72; 95% CI=0.52 to 1.00; P=0.05), nervous system disorders (OR=0.61; 95% CI=0.29 to 1.29; P=0.20), or adverse events (OR=1.44; 95% CI=0.82 to 2.50; P=0.20).

Conclusions: Dendritic cell vaccine may be not effective to treat glioblastoma.

Key words: dendritic cell vaccine, glioblastoma, randomized controlled trials.

Introduction

Glioblastoma is the most common malignant primary brain tumor. Although the development of maximal safe surgical resection and radiotherapy with concurrent chemotherapy, glioblastoma is still associated with poor prognosis [1-3]. Five-year survival rate remained at 9.8% with standard of care treatment [4, 5]. The 2-year survival of glioblastoma was documented to be 26−33 % after the treatment with radiotherapy and concomitant adjuvant temozolomide [6, 7].

Molecularly defined glioblastoma subtypes were associated with the expression of certain tumor antigens [8]. Suppression of B7-H4 resulted in T-cell activation and tumor regression in glioma xenografts [9]. The status of methylated O-6-methylguanine-DNA methyltransferase (MGMT) promoter also affected the prognosis. For instance, the survival rate was 12.5% at the follow-up of 4 years in patients with unmethylated MGMT promoters, while it is 45% for methylated MGMT promoter [10, 11]. Immunotherapies may have some special ability to treat various cancers such as hematological diseases, malignant melanoma, and renal carcinoma [12-14]. Dendritic cells can enhance immune reactions due to the antigen-presenting property [15].

Several studies explored the efficacy of dendritic cell-based therapeutic vaccines for glioblastoma, and demonstrated some potential of dendritic cell vaccines in treating glioblastoma [16-18]. However, several trials showed some conflicting results regarding the efficacy of dendritic cell vaccine for glioblastoma [19-21]. This meta-analysis of RCTs aimed to evaluate the efficacy and safety of dendritic cell

vaccine to treat glioblastoma.

Materials and methods

This meta-analysis was conducted based on the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement and Cochrane Handbook for Systematic Reviews of Interventions [22, 23], and no ethical approval and patient consent were needed because all analyses were based on previous published studies.

Literature search and selection criteria

We have systematically searched several databases including PubMed, EMbase, Web of science, EBSCO and the Cochrane library from inception to October 2020 by using the following keywords: “dendritic cell vaccine” and “glioblastoma”. The reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly in order to include additional eligible studies.

The inclusion criteria were as follows: (1) study design was RCT, (2) patients were diagnosed as glioblastoma, and (3) intervention treatments were dendritic cell vaccine versus placebo.

Data extraction and outcome measures

Some baseline information (e.g. first author, year, number of patients, age, male, methylated MGMT and detail methods) was extracted from the original studies. Data were extracted independently by two investigators, and discrepancies were resolved by consensus. The primary outcomes were overall survival and progression-free survival (PFS). Secondary outcomes included nervous system disorders and adverse events.

Quality assessment in individual studies

The methodological quality of each RCT was assessed by the Jadad Scale consisting of three evaluation elements: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points) [24]. One point was allocated to each element if they were conducted and mentioned appropriately in the original article.

The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score≤2 had low quality. The study had high quality if Jadad score≥3 [25].

Statistical analysis

We assessed hazard ratio (HR) with 95% confidence interval (CI) for overall survival and PFS, odd ratio (OR) with 95% CI for nervous system disorders and adverse events. Heterogeneity was evaluated using the I^2 statistic, and $I^2 > 50\%$ indicated significant heterogeneity [26]. The random-effects model was used for all meta-analysis. We searched for potential sources of heterogeneity when encountering significant heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting one study in turn. Publication bias was not assessed due to the limited number (<10) of included studies. $P<0.05$ indicated statistically significant. All statistical analyses were performed by Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics and quality assessment

Figure 1 showed the detail flowchart of the search and selection results. Two hundred and eighty-four potentially relevant articles were identified initially. Eighty-nine duplicates and one hundred and eighty-nine papers after checking the titles/abstracts were excluded. Two studies were removed because of the study design and four RCTs were ultimately included in the meta-analysis [19-21, 27].

The baseline characteristics of four included RCTs were shown in Table 1. These studies were published between 2012 and 2019, and the total sample size was 267. Four studies reported overall survival and PFS [19-21, 27], two studies reported nervous system disorders [19, 21] and four studies reported adverse events [19-21, 27]. Jadad scores of the four included studies varied from 3 to 5, and all studies had high-quality based on the quality assessment.

Primary outcomes: overall survival and PFS

The random-effect model was used. Compared to control group for glioblastoma, dendritic cell vaccine revealed no significant influence on overall survival (HR=0.59; 95% CI=0.34 to 1.04; P=0.07) with significant heterogeneity (I^2=68%, heterogeneity

P=0.68, Figure 2) or PFS (HR=0.72; 95% CI=0.52 to 1.00; P=0.05) with no heterogeneity (I^2=0%, heterogeneity P=0.54, Figure 3).

Sensitivity analysis

There was significant heterogeneity for overall survival, but significant heterogeneity remained when performing sensitivity analysis by omitting one study in each turn.

Secondary outcomes

In comparison with control group for glioblastoma, dendritic cell vaccine showed no substantial impact on nervous system disorders (OR=0.61; 95% CI=0.29 to 1.29; P=0.20; Figure 4) or adverse events (OR=1.44; 95% CI=0.82 to 2.50; P=0.20; Figure 5).

Discussion

Dentritic cells showed a potent immune stimulatory mode of action after the stimulus of pathogen-associated microbial pattern molecules [28, 29]. Interleukin (IL)-12-secreting dentritic cells could trigger robust helper T-lymphocyte type 1 and cytotoxic T-lymphocyte dominated immune responses [30-33]. The immunostimulatory capability of dentritic cells may show some ability to treat cancers because of immunosuppressive features [32, 34, 35]. The early-stage clinical trial showed that dentritic cell vaccination may prolong the survival of patients with glioblastoma multiforme [36]. Glioblastoma stem-like cell antigens could elicit intense immune responses against gliomas [37, 38].

Previous studies evaluated the dentritic cell-based vaccinations for glioma, and revealed its possible benefits to improve survival duration, as shown by a median survival duration of more than two years [18, 21, 39-42]. However, dentritic cell-based vaccination (weekly application in 7 to 10 weeks, followed by monthly intervals) revealed no improvement in PFS at 12 months or median overall survival than control intervention [20].

Our meta-analysis suggested that dentritic cell-based vaccinations showed no significant improvement of overall survival or PFS than control intervention for glioblastoma. Dentritic cell-based vaccinations were well-tolerated. Regarding the

sensitivity analysis, there was significant heterogeneity. These inconsistence and heterogeneity may be caused by different kinds, duration and initiating time of dentritic cell-based vaccinations. In addition, patients with low B7-H4 expression may show significantly prolonged overall survival (P=0.02) after dentritic cell-based vaccinations treatment [27]. Methylated MGMT promoter may be associated with better overall survival than that of unmethylated MGMT promoter [11].

The most frequent adverse events were fatigue, convulsions, and nausea. They showed no statistical difference between two groups [19]. The incidence of nervous system disorders and total adverse events was similar between vaccine group and control group based on this meta-analysis. There were several limitations. Firstly, our analysis was based on only four RCTs, and more RCTs with large sample size should be conducted to explore this issue. Next, there was significant heterogeneity which may be caused by different kinds, duration and initiating time of dendritic cell vaccine. Finally, it was not feasible to perform the subgroup analysis based on MGMT status based on current included studies.

Conclusion

Dendritic cell vaccine may had no benefits to treat glioblastoma.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest

The authors declare no conflict of interest.

Research involving human participants and/or animals

Not applicable.

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Figure legend

Figure. 1 Flow diagram of study searching and selection process.

Figure. 2 Forest plot for the meta-analysis of overall survival.

Figure. 3 Forest plot for the meta-analysis of PFS.

Figure. 4 Forest plot for the meta-analysis of nervous system disorders.

Figure. 5 Forest plot for the meta-analysis of adverse events.

Figures

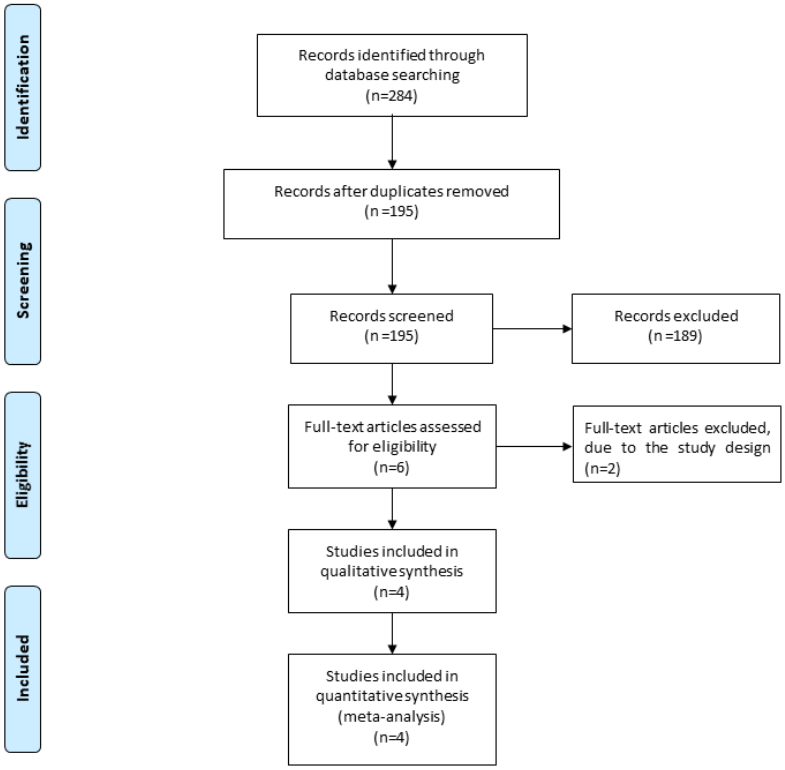

Figure. 1

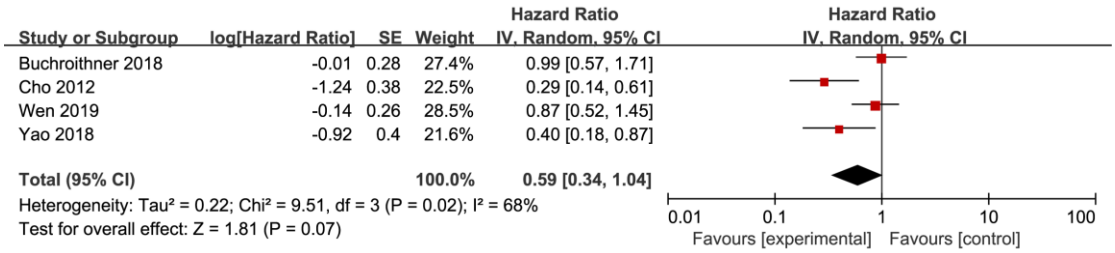

Figure. 2

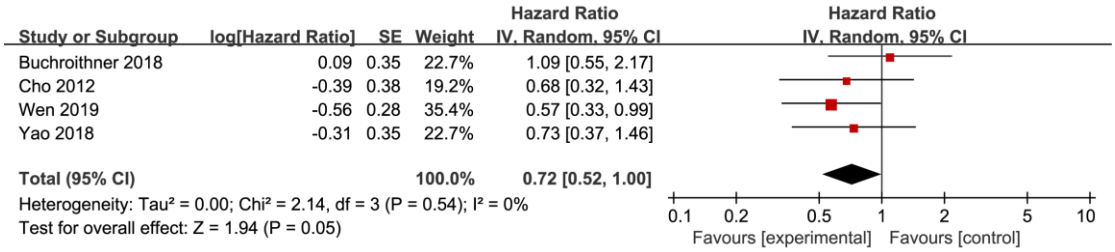

Figure. 3

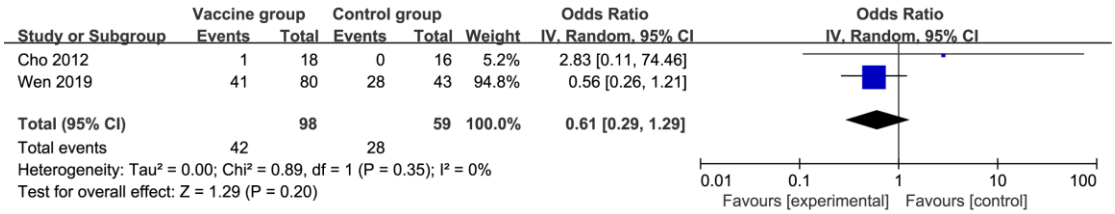

Figure. 4

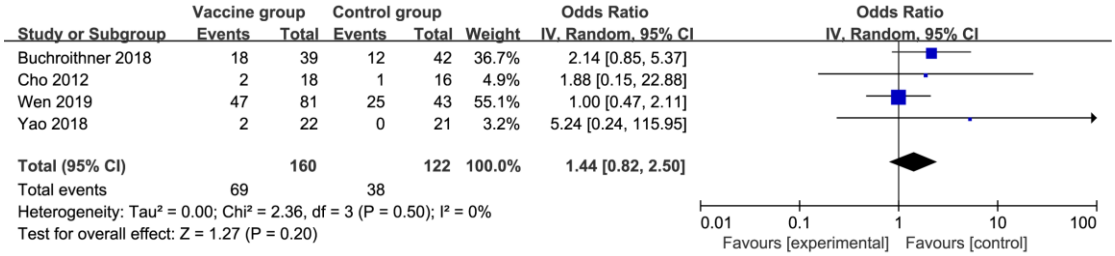

Figure. 5

Table 1 Characteristics of included studies

NO.	Author	Vaccine group					Control group					Jadad scores
		Number	Age (years)	Male (n)	Methylated MGMT (n)	Methods	Number	Age (years)	Male (n)	Methylated MGMT (n)	Methods	
1	Wen 2019	81	57.4	44	28	ICT-107 (autologous dendritic cells) weekly x 4	43	57.5	31	18	placebo	5
2	Yao 2018	22	48	13	9	dendritic cell vaccine loaded with glioblastoma stem cell-like antigens	21	50	11	12	placebo	4
3	Buchroithner 2018	34	54.6	22	7	dendritic cell vaccination weekly intranodal application in weeks seven to 10, followed by monthly intervals	24	54	29	6	placebo	4
4	Cho 2012	18	58.00 (41.00, 63.00), median (range)	8	10	autologous dendritic cell vaccine within 1 to 2 months postoperatively, with 10 inoculations given over 6 months	24	58.50 (48.50, 65.00), median (range)	8	9	placebo	3