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The interventional effect of new drugs combined with the Stupp protocol on glioblastoma: A network meta-analysis

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ABSTRACT

Objective: New therapeutic agents in combination with the standard Stupp protocol (a protocol about the temozolomide combined with radiotherapy treatment with glioblastoma was research by Stupp R in 2005) were assessed to evaluate whether they were superior to the Stupp protocol alone, to determine the optimum treatment regimen for patients with newly diagnosed glioblastoma.

Patients and methods: We implemented a search strategy to identify studies in the following databases: PubMed, Cochrane Library, EMBASE, CNKI, CBM, Wanfang, and VIP, and assessed the quality of extracted data from the trials included. Statistical software was used to perform network meta-analysis.

Results: The use of novel therapeutic agents in combination with the Stupp protocol were all shown to be superior than the Stupp protocol alone for the treatment of newly diagnosed glioblastoma, ranked as follows: cilengitide 2000 mg/5/week, bevacizumab in combination with irinotecan, nimotuzumab, bevacizumab, cilengitide 2000 mg/2/week, cytokine-induced killer cell immunotherapy, and the Stupp protocol. In terms of serious adverse effects, the intervention group showed a 29% increase in the incidence of adverse events compared with the control group (patients treated only with Stupp protocol) with a statistically significant difference (RR = 1.29; 95%CI 1.17–1.43; $P < 0.001$). The most common adverse events were thrombocytopenia, lymphopenia, neutropenia, pneumonia, nausea, and vomiting, none of which were significantly different between the groups except for neutropenia, pneumonia, and embolism.

Conclusions: All intervention drugs evaluated in our study were superior to the Stupp protocol alone when used in combination with it. However, we could not conclusively confirm whether cilengitide 2000 mg/5/week was the optimum regime, as only one trial using this protocol was included in our study.

1. Introduction

Glioblastoma (GBM), an invasive solid tumor, is the most common primary tumor of the brain [1,2]. The standard treatment is radiotherapy (RT) plus concomitant and adjuvant therapy, with six cycles of temozolomide (TMZ) following surgical removal of the maximum safe scope, which is currently the internationally accepted treatment protocol (also was the Stupp protocol). However, despite the availability of advanced treatment, patients with GBM have a poor prognosis, with average survival of only 14.6–16 months and a 5-year survival rate of less than 10%, thus representing a significant treatment challenge [3–5]. GBM tumors are characterized by increased expression of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR), neoangiogenesis, and epidermal growth factor receptor gene amplification, among other factors. Recent research has tended towards the exploration of integrated molecular targeted drugs (e.g., bevacizumab [BEV], cilengitide, vandetanib, nimotuzumab, and cellular immune drugs) with the Stupp protocol and evaluating the subsequent effectiveness and safety of these approaches [6–11]. Nevertheless, the treatment outcomes of new drugs in large, randomized controlled trials and studies to contrast the efficacy of a variety new drugs in combination with the Stupp protocol are lacking, as clinical studies frequently compare the effectiveness of the new drugs combined with the Stupp with used it alone. Therefore, this study used a network meta-analysis approach, with the principle of direct and indirect comparison [12,13], to evaluate whether treatment with new drugs in combination with the Stupp protocol is superior to the Stupp protocol alone in patients with newly diagnosed GBM.

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2. Patients and methods

2.1. Inclusion and exclusion criteria

The inclusion and exclusion criteria for this study were based on the PICO strategy (P: patient, I: intervention, C: comparison, O: outcome). The inclusion criteria were as follows: 1) patients aged 18 years and older, with newly diagnosed and histopathologically confirmed GBM multiforme, Karnofsky status ≥ 50, and World Health Organization (WHO) performance scales ≤ 2; 2) in terms of intervention, treatment criteria were new drugs in combination with the Stupp protocol on the Stupp alone. In this study, the Stupp protocol was defined as TMZ (75 mg/m^2/d, with a maximum of 49 days from the first day of RT until the last) with concomitant RT (total dose: 60 Gy, 30 × 2 Gy) and adjuvant TMZ (150–200 mg/m^2/d, 1–5 d/28 d, total of 6 cycles); 3) randomized clinical trials, with research from China having being carried out only in hospitals of Grade 3A and above, sample size of ≥30, and only the most recent publication by a given author; 4) information on the following outcome indicators in the original text or available from the study authors: average overall survival, overall survival rate, and Kaplan–Meier survival curve. For our analysis, the overall survival rate with the longest follow-up period was selected.

Patients were excluded if they had a history of serious hematology, cardiopulmonary, liver, kidney, or other systemic disease; other primary or metastatic tumors than GBM; other intracranial diseases (e.g., intracranial hemorrhage or brain abscess); pregnant or breast-feeding women; previous treatment with radiotherapy, chemotherapy, or immunotherapy; or serious chemotherapy drug allergy.

2.2. Search strategy

The following key words, full text; and MeSH terms were used to search the PubMed; Cochrane Library; EMBASE; CNKI; CBM; VIP; and Wanfang databases for publications dated on or before October 8; 2016: glioma; glioblastoma; temozolomide; bevacizumab; carmustine; nimustine; chemotherapy; drug therapy; targeted therapy; antiepileptic; anticonvulsant; radiotherapy; radiation therapy; randomized controlled trial; non-randomized controlled trial; random*; non-random*. We also searched the references of related documents; magazines; journals; and meeting abstracts; and searched the WHO International Clinical Trials Registry Platform (WHO ICTRP) to identify trials that were ongoing or complete but not yet published; as well as trials included in relevant systematic reviews or meta-analysis published 2–3 years previously.

2.3. Study selection and quality assessment

The inclusion and exclusion criteria were applied by two systematic reviewers, who independently screened the literature retrieval results and read the full articles, using the Cochrane Quality Evaluation Method to assess randomized trials included in the present study. To avoid bias, differences were discussed by the two reviewers or agreed with a third party if consensus was not met.

2.4. Data extraction

The information extracted from the all included trials included the baseline characteristics (age; surgical status: complete removal, partial removal, biopsy, et al.; Karnofsky performance status [KPS]/WHO performance scores; steroid usage) of all patients and the number of patients per treatment group; the drugs, doses, and course of treatment; and the indicators of clinical outcome (average overall survival, overall survival rate, and hazard ratio with 95% confidence interval [CI]).

2.5. Statistical analysis

For heterogeneity, X^2 and I^2 statistics were used to analyze the data identified in our study. For values of $P < 0.1$ and $I^2 > 20\%$, results were considered to have significant heterogeneity and the random effects model was used; otherwise a fixed effects model was adopted.

Consistency checks were also performed before direct and indirect evidence was merged. The final part of the network meta-analysis strategy was an extension of the traditional head-to-head meta-analysis approach, and involved the identification of the best intervention, given the effect relationship between any two interventions. Based on this principle, network meta-analysis was identified using Stata version 13.0 statistical software.

3. Results

3.1. Literature retrieval and network chart construction

A total of 3409 items were retrieved (3375 articles from the electronic databases and the remainder from manual searches). Of these, 3272 articles were excluded after reading of the titles and the abstracts, and elimination of duplicate articles. Following full-text reading, only 19 studies remained, and when inclusion and exclusion criteria were applied, 7 studies were identified for inclusion in our analysis (Supplementary Fig. 1). In the network chart shown in Fig. 1, a

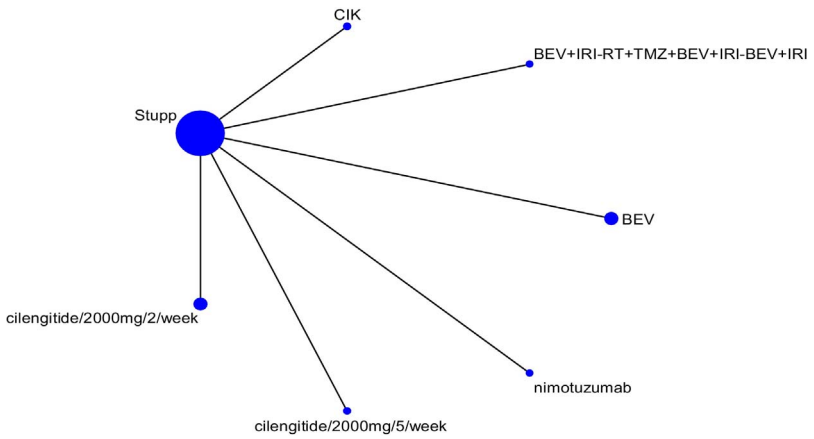

Fig. 1. Network chart.Stupp: (the Stupp protocol) TMZ (75 mg/m^2/d, with a maximum of 49 days from the first day of RT until the last) with concomitant RT (total dose: 60 Gy, 30 × 2 Gy) and adjuvant TMZ (150–200 mg/m^2/d, 1–5 d/28 d, total of 6 cycles); CIK: cytokine-induced killer cell immunotherapy added to the Stupp protocol; BEV + IRI-RT + TMZ + BEV + IRI-BEV + IRI: bevacizumab + irinotecan combined with the Stupp protocol; BEV: BEV added to the Stupp protocol; nimotuzumab: nimotuzumab added to the Stupp protocol; cilengitide/2000 mg/2/week: cilengitide/2000 mg/2/week added to the Stupp protocol; cilengitide/2000 mg/5/week: cilengitide/2000 mg/5/week added to the Stupp protocol.