BMJ Open

Efficacy of TTFields in high-grade gliomas: a protocol for systematic review and meta-analysis

Xinlong Li ,[1,2] Juncheng Wang,[1,2] Guoqiang Yuan,[1,2] Yawen Pan[1,2]

To cite: Li X, Wang J, Yuan G, *et al*. Efficacy of TTFields in high-grade gliomas: a protocol for systematic review and meta-analysis. *BMJ Open* 2023;**13**:e073753. doi:10.1136/bmjopen-2023-073753

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-073753).

Received 15 March 2023
Accepted 15 August 2023

[1]Department of Neurosurgery, Lanzhou University Second Hospital, Lanzhou, China
[2]Laboratory of Neurology of Gansu Province, Lanzhou University Second Hospital, Lanzhou, China

Correspondence to
Yawen Pan; panyw@lzu.edu.cn

ABSTRACT

Introduction Despite their recent FDA(Food and Drug Administration) approval, tumour treatment fields (TTFields) have not seen acceptance as part of standard of care (SOC) for the treatment of high-grade gliomas (HGGs). Few studies have reported the clinical effect of simultaneous or sequential use of TTFields with the current SOC. However, whether TTFields are beneficial over the standard treatment remains to be established with a meta-analysis. Therefore, we here performed a systematic review and meta-analysis to understand the benefit of TTFields for patients with HGGs.

Methods and analysis We registered this systematic review with the PROSPERO network (registration number: CRD42023398972) and aimed to follow the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines in the study. All articles related to TTFields in glioma will be systematically searched for in the following databases since their inception until November 2023: the China National Knowledge Infrastructure, Embase, Cochrane Library, Wanfang Database, China Science Journal Database, China Biomedical Documentation Database, VIP database, Web of Science and PubMed. Article screening and data extraction will be done independently by the authors and cross-checked by two of the authors on completion. The Cochrane risk of bias assessment tool will be used for quality assessment of the included studies. Review Manager V.5.3 (Cochrane Collaboration) will be used to perform the meta-analysis.

Ethics and dissemination Ethical approval is not required because the data used will be obtained from published studies, and there will be no concerns about privacy. The results of this study will be published in a peer-reviewed journal.

PROSPERO registration number CRD42023398972.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ No relevant reports were seen (a meta-analysis comparing tumour treatment fields efficacy on a standard of care basis).
⇒ The quality of the included literature and final outcomes, even adverse events, will be evaluated.
⇒ In the case of neurological symptoms in the adverse events, each study difference may be relatively large, and we can only make data statistics based on the data they provide.
⇒ Restriction of publication language to English only is a limitation of this study.

INTRODUCTION

Even though gliomas, which are brain tumours of glial cell origin, account for a relatively small proportion (28%) of all primary brain tumours, they comprise ~80% of all malignant primary brain tumours in adults.[1] Recently reported molecular-based data suggest that some gliomas have growth patterns and molecular features of high-grade gliomas (HGGs). Gliomas with WHO grade III and grade IV are considered HGGs, and these gliomas present a malignant growth pattern and are associated with extremely poor overall survival (OS).[2] Anaplastic astrocytoma is the most common WHO grade III glioma. The OS of patients having anaplastic astrocytoma after diagnosis is typically 2–3 years. Conversely, glioblastoma multiforme (GBM) is the most common WHO grade IV glioma.[1] In adults, HGGs such as GBM typically have dismal prognoses owing to frequent recurrence and treatment resistance even after all standard of care (SOC) treatments.[3] Patients with GBM have a median survival period of ~20 months and 1-year and 5-year survival rates of 35.0% and 4.7%, respectively,[4] indicating dismal prognoses.

The SOC for HGGs is maximally safe surgical resection followed by 6-week treatment with concurrent temozolomide (TMZ) and radiation therapy and then 6-month treatment with adjuvant TMZ.[5] In addition to TMZ, one device (tumour treatment fields, TTFields) and four drugs (bevacizumab, carmustine wafer implants, intravenous carmustine and lomustine) have received FDA approval for the treatment of HGGs.[6–8] However, for newly diagnosed HGGs, only carmustine, TTFields, TMZ and wafer implants have been approved by the FDA.[9] In addition, new research therapies, which

include immunotherapies such as checkpoint suppression, oncolytic viruses and vaccine therapy,[10] have not received FDA approval.

TTFields, a novel cancer therapeutic modality, exert their effect based on the principle that alternating electric fields applied at specific frequencies have the ability to interrupt cancer cell division and cause cancer cell death.[11] In 2015, TTFields received FDA approval for use in cases with newly diagnosed GBM(ndGBM).[6] These fields are applied via a portable device and pulsed through the shaved scalp. The device is used for over 18 hours daily for at least 4 weeks. This device delivers intermediate frequency (200 kHz), low intensity (1–3 V/cm) alternating electric fields that selectively disrupt mitosis in tumour cells.[12] Skin disorders (36%), general disorders/application site conditions (31%) and nervous system disorders (27%) were the most commonly reported adverse events (AEs) among all patients, the incidence rate varied little among age groups. Treatment-related skin responses were significantly less pronounced in recurrent GMB(rGBM) (29%) than in ndGBM (28%). Other AEs associated with TTFields included electric sensation (ie, underarray tingling, 11%) and heat sensation (ie, underarray warmth, 10%), These AEs belong to general disorders.[13] In addition, headaches and seizures were also considered as adverse effects belonging to neurological symptoms. However, because of the brain tumour and the SOC treatment, these headaches and seizures may be related to the tumour and other treatments, and it was thus difficult to determine if they were related to the primary disease. Skin reactions are the most concerning and have very high incidence. They represent the most common AEs, and although there are still some other AEs, their incidence is very low. A randomised controlled trial (RCT) comparing the effects of TTFields+TMZ versus TMZ alone on the survival of GBM patients reported that the former showed significantly improved progression-free survival (PFS, 7.1 vs 4.2 months) and OS (20.5 vs 15.6 months).[12] Several subsequent experiments since then have confirmed these improvements in the PFS.[14 15]

Currently, the clinical effect of simultaneous or sequential use of TTFields with the current SOC has been reported by few studies. Using this review protocol, we aim to identify the efficacy of TTFields in HGGs when administered concurrently with the standard treatment; furthermore, we aim to determine whether the enhanced effect, if any, justifies the remarkable increase in medical expenses. Taken together, we aim to uncover and showcase medical evidence to determine if TTFields should be an integral part of the SOC for HGG.

MATERIALS AND METHODS

Study registration

We registered this review protocol with the PROSPERO network (registration number: CRD42023398972). The protocol will follow the statement guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses.[16] Given that this is not a prospective study, ethical approval will not be required.

Searching strategy

This study will use the following databases: China National Knowledge Infrastructure, Embase, Cochrane Library, Wanfang Database, China Science and Technology Journal Database, China Biomedical Literature Database, Web of Science, Allied and Complementary Medicine Database and PubMed. Literature retrieval will not be limited to a time period but is limited to English and Chinese papers. The following keywords will be used for the literature search: “Tumor treating fields,” “Tumor-treating fields,” “TTFields,” and “alternating electric fields” related to the keywords “glioblastoma,” “glioma,” “high-grade glioma,” “HGG,” “malignant glioma,” and “GBM” using the Boolean operator “AND.” The Chinese database search will be conducted using the keywords “电场,”“电场治疗” and “肿瘤治疗电场” related to the keywords “胶质母细胞瘤,” “胶质瘤,” “高级别胶质瘤,” “恶性胶质瘤,” and “IV 级 胶 质 瘤” using the Boolean operator “AND.”. The detailed searching strategy is included in online supplemental file 1.

Eligibility criteria

Studies meeting the following criteria will be included in our analyses.

1. RCTs.
2. Patients aged more than 18 years with a new and definitive diagnosis of HGGs.
3. The intervention and control groups received the SOC+TTFields and only the SOC, respectively.
4. The studies reported findings for one or more of the following aspects: clinical efficacy, AEs, the Karnofsky performance status, OS and PFS. Besides the OS, outcome measures may differ among different literatures, such as 1-year or 2-year survival. We here aim to collect this information and conduct statistical analysis according to the actual situation. If we identify multiple studies that have analysed the same population, we will include the study with the largest sample or the longest follow-up.

Studies will be excluded if their full texts cannot be accessed, they are found to have a poor quality score as per the stated criteria, or they are duplicated citations.

Data selection

First, to select eligible studies, two investigators will use EndNote V.9 software to perform a preliminary assessment of the title and abstract of all published papers as per the established criteria for study inclusion. Full texts of the studies selected in the preliminary assessment will be evaluated, and studies with inconsistent evaluation criteria or similar data and studies that did not use controls or randomisation will be excluded. Finally, the studies selected for inclusion after applying all criteria will be exchanged and cross-checked by researchers. Any disagreements between the two researchers on the

eventual inclusion of a study will be resolved by consultation with the third author.

Data extraction

Two researchers will perform data extraction and will collect data on the following parameters: disease diagnosis, age, sample size, outcomes, AEs, interventions and details about the control group and follow-up. The third author will be approached to resolve any disagreement with respect to data collection. Studies with unclear, missing, difficult-to-extract or poorly presented data will be excluded.

Risk of bias assessment

Using the Cochrane risk of bias assessment tool, two investigators will independently assess the risk of bias associated with the included studies. Each study will be primarily evaluated on the following seven parameters: incomplete outcome data, blinding of outcome assessment, selective outcome reporting, random sequence generation, allocation hiding, blinding of participants and personnel, and other biases. Finally, the level of bias for each study will be rated as 'low', 'high' or 'ambiguous'. All these parameters will be independently reviewed by two reviewers, and any discrepancies or disagreements will be resolved by a third reviewer.

Statistical analysis

We will perform all statistical analyses using the Review Manager software (V.5.3), and the threshold for statistical significance will be set at a $p<0.05$. Risk ratios or ORs with 95% CIs will be used to analyse dichotomous data. Continuous variables measured on the same scale will be analysed using weighted mean differences and expressed as a mean±SD. Heterogeneity among studies will be assessed using the I^2 test and χ^2 test statistic (Q). The Q-statistic test will be used to identify heterogeneity, and the I^2 test will be used to estimate the percentage of variation caused by the heterogeneity. A Q value of >0.05 will be considered to indicate that the outcome variable is statistically significant, and if the p value is >0.1 and I^2 value is <50%, the fixed-effects model will be selected. Conversely, if I^2 value is ≥50% and the p value is <0.1, the random-effects model will be selected.

Patient and public involvement

No patient involved.

Research time

The study is scheduled to begin in April 2023 and end in June 2024. The period may be extended as appropriate in the light of the documentation.

DISCUSSION

The purpose of this study is to propose an objective and transparent method to conduct a systematic review and meta-analysis aimed at investigating the effectiveness of TTFields based on the SOC.

Glioma, particularly HGG, is the most common type of cancer in the central nervous system, and it is currently considered incurable.[17] The prognosis of HGG patients remains unfavourable despite multiple therapies and combination treatments involving surgery, radiotherapy and molecular targeting. The median survival time for GBM patients is approximately 12–15 months.[18] Owing to the low quality of life and poor prognosis of patients with HGGs, various treatment approaches have been implemented; however, none of them have yielded satisfactory final results. Even now, various treatment methods are being experimentally studied by the researchers. The development of TTFields was done by Novocure over the past two decades. This technique has achieved good results in clinical trials and in vitro and in vivo experiments, and based on these results, the FDA approved the use of TTFields for recurrent or refractory GBM in 2011 and as adjuvant treatment for newly diagnosed GBM after the completion of the SOC surgery and chemoradiation in 2015.

To our knowledge, no meta-analysis has compared the efficacy of TTFields on an SOC basis. Therefore, the biggest asset of this study is its novelty. Previous meta-analyses on TTFields incorporated too many RCTs with different treatment regimens. Although their sample sizes are large, their comparison outcomes are relatively biased.

This study has some potential limitations. Publication bias and information bias are points of concern as we only covered papers in Chinese and English. In addition, since English papers may come from different regions, differing medical conditions in these regions can also lead to biases.

TTFields have not been added to the SOC because the technique is highly cost-intensive and causes increased inconvenience to the patients. However, we believe that it is important to study the extent of benefits it has when used alongside the SOC.

Contributors YP and GY designed the study and were the main coordinators of the study. YP was the principal investigator and guarantor. JW gave statistical support. XL wrote the article. All authors reviewed and approved the final version of the manuscript.

Funding This study has support from National Natural Science Foundation of China (Grant no. 82060455 and 81960541).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Xinlong Li http://orcid.org/0000-0001-7349-2382

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