Tumor-treating fields as a fourth treating modality for glioblastoma: a meta-analysis

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Abstract

Background We aim to review the available literature on patients suffering from glioblastoma treated with tumor-treating fields (TTFields) plus radio chemotherapy or conventional radio chemotherapy alone, to compare the efficacy and safety of the two methods.

Methods A systematic literature search was performed in PubMed, Cochrane library, and Scopus databases, in accordance with the PRISMA guidelines. Six studies met the inclusion criteria incorporating 1806 patients for the qualitative analysis and 1769 for the quantitative analysis.

Results This study reveals increased median overall survival (weighted mean difference (WMD) 3.29 [95% confidence interval (CI) 2.37, 4.21]; \( p < 0.00001 \)), survival at 1 year (odds ratio (OR) 1.81 [95% CI 1.41, 2.32]; \( p < 0.00001 \)) and 2 years (OR 2.33 [95% CI 1.73, 3.14]; \( p < 0.00001 \)), and median progression-free survival (WMD 2.35 [95% CI 1.76, 2.93]; \( p < 0.00001 \)) along with progression-free survival at 6 months (WMD 6.86 [95% CI 5.91, 7.81]; \( p < 0.00001 \)) for the patients treated with TTFields. Survival at 3 years was comparable between the two groups. TTFields were associated with fewer adverse events compared to chemotherapy along with similar incidence of skin irritation.

Conclusions TTFields are a safe and efficient novel treatment modality. More randomized controlled studies, with longer follow-up, are necessary to further assess the clinical outcomes of TTFields.

Keywords Glioblastoma • Tumor-treating fields • TTFields • Alternating electric fields • Meta-analysis

Introduction

Glioblastoma (GBM) is a primary malignancy of central nervous system, with an annual incidence rate of 3.2–4.6 per 100,000, that accounts for 15% of all primary brain tumors [15]. GBM is classified as a grade 4 glioma according to World Health Organization (WHO). The main treatment strategy consists of maximal surgical resection followed by radiotherapy plus concomitant daily temozolomide followed by adjunct chemotherapy with temozolomide for 6–12 months [20]. The surgical resection, as the first stage of the treating strategy, provides a pathologic diagnosis and may alleviate neurological symptoms by amelioration of mass effect. Prognosis is primarily influenced by the extent of surgical resection, age, and the Karnofsky performance status, although IDH mutation and MGMT methylation status also play roles in survival [6, 13, 25]. However, despite the current progress, the outcomes regarding median progression-free survival and overall survival remain limited (6.2–7.5 and 14.6–16.7 months, respectively) [2, 4, 20]. In fact, according to “real world” data from a population-based study [26], the median overall survival is 10.0 (4.0–10.9) months.

Tumor-treating fields (TTFields) are a novel, non-invasive treatment modality delivering low-intensity, intermediate-
frequency (200 kHz) alternating electric fields directly to the brain through arrays attached directly to the shaved scalp. The alternating electric fields interact with macromolecules and organelles of the dividing cell spindle and interrupt cell mitosis, by both p53-dependent and p53-independent pathways [18]. As the number of studies assessing the feasibility of TTFields increases, it is necessary to examine whether the results of the new treating modality are at least equivalent with those of the gold standard treatment. The purpose of this study is to summarize the existing evidence regarding the effectiveness of TTFields for glioblastoma.

Materials and methods

Search strategy and article selection

The present study was conducted in accordance with the protocol agreed by all authors and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [12]. A thorough literature search was performed in Pubmed (Medline), Cochrane Central Register of Controlled Studies (CENTRAL), and Scopus (ELSEVIER) databases (last search: April 10, 2017) using the following terms in every possible combination: “alternating electric fields,” “tumor-treating fields,” “novottf,” “ttfields,” “glioblastoma,” and “brain cancer.” Inclusion criteria were (1) original reports with ≥ 10 patients, (2) written in the English language, (3) published from 2000 to 2017, (4) conducted on human subjects, and (5) reporting outcomes of TTFields on patients with glioblastoma. Two independent reviewers (DEM, VST) performed the literature search independently. Any discrepancies between the investigators about the inclusion or exclusion of studies were discussed with the senior author (SAT) to include articles that best matched the criteria, until consensus was reached. Moreover, the reference lists of all included articles were assessed for additional potentially eligible studies.

Data extraction

For each eligible study, data were extracted relative to demographics (number of patients, mean age, sex, prior therapy) and to the primary (progression-free survival, progression-free survival at 6 months, survival at 1, 2, 3, and 5 years) and secondary endpoints (complications). Two authors (DEM, VST) performed the data extraction independently and compared the validity of the data. Any discrepancies were discussed with the senior author (SAT), until consensus was reached. Furthermore, the kappa coefficient test was applied in order to assess the level of agreement between the reviewers.

Statistical analysis

Based on the extracted data, regarding the categorical outcomes, the odds ratio (ORs) and 95% confidence interval (CI) were calculated, by means of fixed effects model (the Mantel-Haenszel statistical method). The OR < 1 denoted outcome was more frequent in the control group. Continuous outcomes were evaluated by means of weighted mean difference (WMD) with its 95% CI, using fixed effects (inverse variance statistical method) models, appropriately to calculate pooled effect estimates. In cases where WMD < 0, values in the control group were higher. Although a random effects model provides a greater scope of inference, we chose the fixed effects model because it is statistically sound for combining a very small number of studies [1]. Between-study heterogeneity was assessed through Cochran’s Q statistic and by estimating \( I^2 \) [7]. Forest plots were produced regarding the variables that were analyzed.

In cases where multiple studies analyzed the same population (i.e., series from the same hospital), only the larger study or the one with the longest follow-up (if the sample was similar) was included in the meta-analysis.

Quality and publication bias assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) [19] was used as an assessment tool to evaluate non-RCTs. The scale’s range varies from 0 to 9 stars. Since the threshold score regarding the quality of the included studies has not yet been identified, we decided that studies with a score equal to or higher than 5 were considered to have adequate methodological quality. The RCTs were assessed for their methodological quality with the tools that are used to evaluate the risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions [5]. Two reviewers (DEM, VST) rated the studies independently and final decision was reached by consensus.

The existence of publication bias was assessed by the visual inspection of funnel plots. It could not be further evaluated using Egger’s formal statistical test [3] because the number of the studies included in the analysis was not adequate (less than ten), thus compromising substantially the power of the test.

Results

Article selection and patient demographics

The flow diagram of the literature search is shown in Fig. 1 and the PRISMA checklist is provided in Supplementary Material. The level of agreement between the two reviewers was good (kappa = 0.651; 95% CI 0.391, 0.911). Among the
196 articles in Pubmed, CENTRAL, and Scopus that were retrieved, six studies were included in the qualitative synthesis [9, 10, 14, 21, 22, 24]. Five studies [9, 10, 14, 21, 22] were comparative and were included in the quantitative analysis. The study design was prospective in three studies [9, 10, 14] and randomized controlled in two studies [21, 22]. The studies included were mainly multinational [9, 10, 21, 22, 24] and were published between 2007 and 2017. The TTField sample size ranged from 10 to 466 patients. The total sample size was 1806 patients for the qualitative analysis and 1769 for the quantitative analysis. Regarding the quantitative analysis (meta-analysis), 1063 patients were treated with TTFields and 706 patients were treated with chemotherapy. Characteristics of studies comparing the outcomes between patients treated with TTFields and the control group are provided in Table 1. We performed an intention-to-treat analysis regarding survival endpoints and a per-protocol analysis regarding safety and complication endpoints. The Newcastle-Ottawa rating scale assessment for all studies is shown in Table 1 and the quality assessment of RCTs is shown in Table S1. Pooled ORs, $I^2$, and $p$ values of heterogeneity for all outcomes are summarized in Table 2.

**Efficacy endpoints**

The median OS was significantly greater in the TTField group (WMD 3.29 [95% CI 2.37, 4.21]; $p<0.00001$) (Fig. 2a). According to the subgroup analysis, the median OS was increased in patients treated with TTFields with recurrent GBM (WMD 2.55 [95% CI 1.56, 3.55]; $p<0.00001$) and newly diagnosed GBM (WMD 7.48 [95% CI 5.11, 9.86]; $p<0.00001$).

Three studies [14, 21, 22] assessed the OS at 1 year postoperatively (Fig. 2b). According to our three-arm analysis, OS at 1 year postoperatively was significantly greater in the TTField group (OR 1.81 [95% CI 1.41, 2.32]; $p<0.00001$). OS at 2 years postoperatively was also increased in patients treated with TTFields (OR 2.33 [95% CI 1.73, 3.14]; $p<0.00001$) (Fig. 2c). No significant difference was reported regarding OS at 3 years postoperatively (OR 1.62 [95% CI 0.98, 2.66]; $p=0.06$). However, this was a two-arm analysis and data from the Patient Registry Dataset (PRiDe) trial were not available, thus posing some limitations in the analysis.

In order to assess the median progression-free survival (PFS), we performed a two-arm pooled analysis (Fig. 3a). According to our findings, the median PFS was significantly increased in the group treated with TTFields compared to control group (WMD 2.35 [95% CI 1.76, 2.93]; $p<0.00001$). The median PFS6 was also significantly increased in the TTField group (WMD 6.86 [95% CI 5.91, 7.81]; $p<0.00001$) (Fig. 3b).

**Safety and tolerability endpoints**

According to our three-arm analysis, the incidence of skin reactions (OR 2.12 [95% CI 0.97, 4.64]; $p=0.06$), neurological disorders (OR 0.81 [95% CI 0.62, 1.07]; $p=0.15$), headache (OR 0.93 [95% CI 0.46, 1.89]; $p=0.85$), and psychiatric disorders (OR 0.77 [95% CI 0.32, 1.87]; $p=0.57$) was similar between patients in either TTField or control group (Fig. S1). Moreover, the incidence of vascular disorders (OR 1.07 [95% CI 0.68, 1.67]; $p=0.77$), infections (OR 0.75 [95% CI 0.45, 1.23]; $p=0.25$), and nutritional disorders (OR 0.69 [95% CI 0.35, 1.36]; $p=0.29$) was also comparable between the two groups. However, the rate of gastrointestinal disorders (OR 0.38 [95% CI 0.24, 0.59]; $p<0.0001$) was increased in the control group. It is possible that this was secondary to the increased intensity and types of chemotherapies used in the control groups.

**Publication bias**

Heterogeneity was low regarding the categorical outcomes. In contrast, heterogeneity was high regarding the continuous outcomes. The funnel plots that were produced in order to assess publication bias are shown in Figs. S2–S4. The asymmetries that were found are mainly attributed to the small number of the included studies, thus proposing that more are necessary in order to eliminate publication bias. Egger’s test was not applied.
Table 1  Characteristics of the studies that were finally included in the meta-analysis. The first author of every study along with the year of publication, the journal, the country of origin, the time period of the study, the study design, the pathology, the intervention, the number of participants, and the number of female patients, along with the mean age, the Karnofsky performance status (KPS), and the number of stars according to the Newcastle-Ottawa Quality Assessment Scale (NOS)

<table>
<thead>
<tr>
<th>Study ID, year</th>
<th>Journal</th>
<th>Country</th>
<th>Time period</th>
<th>Study design</th>
<th>Pathology</th>
<th>Intervention</th>
<th>Patients, n</th>
<th>Female, n (%)</th>
<th>Mean age (range)</th>
<th>KPS, % (range)</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirson et al. 2007 [9]</td>
<td>PNAS</td>
<td>Multinational</td>
<td>–</td>
<td>P</td>
<td>Recurrent GBM</td>
<td>TTF fields only</td>
<td>10</td>
<td>225</td>
<td>30</td>
<td>50.7</td>
<td>45</td>
</tr>
<tr>
<td>Stupp et al. 2017 [22]</td>
<td>JAMA</td>
<td>Multinational</td>
<td>7/2009–12/2014</td>
<td>RCT</td>
<td>Newly diagnosed GBM</td>
<td>Temozolomide ± TTF fields</td>
<td>466</td>
<td>229</td>
<td>32</td>
<td>31</td>
<td>56.0 (19–83)</td>
</tr>
</tbody>
</table>

The Newcastle-Ottawa Quality Assessment Scale (NOS) for assessing the quality of non-randomized studies. Every study is judged on three perspectives: the selection, the comparability, and the ascertainment of the exposure of the study groups. The highest quality studies are awarded up to 9 stars. The RCTs were assessed for their methodological quality with the tools that are used to evaluate the risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions.

R retrospective, P prospective, RCT randomized controlled study, TTF fields tumor-treating fields, KPS the Karnofsky performance status, NOS the Newcastle-Ottawa Quality Assessment Scale.
Fig. 2 Forest plot describing the differences in a median OS, b survival at 1 year, c survival at 2 years. a Median OS was significantly increased in TTF Field group. b Survival at 1 year was increased in TTFFields. c Survival at 2 years was increased in TTF Field group. M-H the Mantel-Haenszel statistical method, IV inverse variance statistical method, 95% CI 95% confidence intervals
performed due to the small number of the studies that were included.

Discussion

The use of alternating electric fields as an anti-mitotic therapy in cancer is a relatively new treatment strategy in glioblastoma management. This systematic review and meta-analysis identified six articles assessing TTFields as a novel treating modality for glioblastoma, measuring patients' outcomes, which were published between 2007 and 2017. No similar meta-analysis was identified through literature search.

The present study demonstrates that TTFields are associated with better outcomes regarding efficacy and survival. According to our analyses, patients that received the TTField modality presented increased median OS, OS after 1 and 2 years, PFS, and PFS6. There was a trend of increased OS at 3 years regarding the TTField group, but it was not statistically significant ($p = 0.06$). However, this was a two-arm analysis that did not include data from the PRiDe prospective data collection [14]. Given the relatively small numbers of 3-year survivors, it may require a larger population to reliably report that 3-year survival is enhanced with TTFields. According to subgroup analysis, patients with either newly diagnosed glioblastoma, showing increased OS and PFS regarding the patients undergoing TTField treatment. Those findings were the basis of the larger, controlled study, the EF-14 trial [22]. According to that study [22], TTFields after surgery plus chemoradiotherapy are associated with increased PFS and median OS compared to temozolomide treatment alone.

Various chemotherapy agents are used during the multimodal management of recurrent glioblastoma depending on the expertise of the physician and the history of the patient. In the included studies, in cases of primary glioblastoma, temozolomide was used, while in the studies reporting on recurrent glioblastoma, either the physician’s choice chemotherapy or bevacizumab was used, as shown in Table 1.

Gastroenterological side effects that are present during chemotherapy were significantly fewer in patients undergoing TTField treatment. Furthermore, the total analysis of neurological disorders reported similar rate between the two groups. The most common neurological disorders were headache, seizures, cognitive disorders, and convulsion. According to our subgroup analysis, no significant difference was found regarding the incidence of headache alone between the two groups. In addition, vascular and nutritional side effects were also comparable between the two groups.

Since TTField arrays are attached on the skin, the main side effects of this modality remain skin irritation and erythema, with less common erosions and ulcers. However, according to our outcomes, the incidence of skin infections was similar between the two groups. In their study, Lacouture et al. [11] describe certain preventive strategies for dermatologic adverse events regarding shaving and preparation of the scalp, use of isopropyl alcohol, and changes of transducer arrays on a regular basis. Risk factors associated with the manifestation of dermatologic complications are the simultaneous administration of anticancer treatment, the placement of the arrays over the craniotomy incisions or hardware, hyperhidrosis, or the
systemic administration of high doses of corticosteroids. The management of skin reactions includes local corticosteroids and antibiotics, when indicated, while for more severe dermatologic adverse events, TTFields interruptions of 2–7 days seem sufficiently effective [11].

This meta-analysis demonstrates the effectiveness and safety of TTFields as a novel anti-mitotic treatment for GBM. Nonetheless, it also demonstrates the need for additional studies assessing TTFields, since at present, there is available data from only two randomized trials [21, 22] (one assessing recurrent GBM and the other assessing newly diagnosed GBM). Ideally, these would be randomized controlled studies, with prospective design and longer follow-up. Based on the early promising outcomes, four trials have been launched and are actively assessing the role of TTFields for recurrent GBM (Table S2).

The limitations of this meta-analysis reflect the limitations of the studies included. Two studies (33.3%) were randomized controlled trials [21, 22], three studies (50%) were prospective [9, 10, 14], and one study (16.7%) was retrospective [24]. Moreover, the small number of the included studies poses a certain publication bias.

On the other hand, the strengths of this study are (1) the clear data extraction protocol, (2) the well-specified inclusion-exclusion criteria, (3) the search in three different databases, (4) the quality assessment of the included studies, and (5) the detailed presentation of the results of data extraction and analysis.

Conclusion

This meta-analysis identified six unique peer-reviewed studies of TTFields treating modality for GBM with patient outcomes data. These studies suggest that TTFields treatment is associated with increased median OS, OS after 1 and 2 years, median PFS, and median PFS6. Furthermore, the main adverse events were similar between the two groups. No significant differences were reported regarding the incidence of skin reactions. These results should be interpreted with caution due to the small number of randomized controlled studies. Newer studies that are currently active, with greater clarity in both primary and secondary outcomes, such as in OS, PFS, and TTFields complications are expected to further demonstrate the effectiveness and safety of TTFields for GBM.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Does not apply.

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