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Review Article

Tumor treating fields for the treatment of glioblastoma: Current understanding and future perspectives

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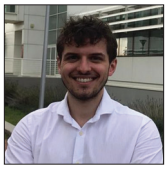

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ABSTRACT

Background: This review focuses on the recently published evidence on tumor treating fields (TTFields) administered alone or in combination with locoregional and systemic options for treating glioblastoma (GBM) in the past ten years. The aim is to critically summarize the novelty and results obtained with this innovative tool, which is becoming part of the armamentarium of neurosurgeons and neuro-oncologists.

Methods: A comprehensive search and analysis were conducted on pivotal studies published in the past ten years. Furthermore, all completed clinical trials, whose results were published on clinicaltrials.gov, were examined and included in the present review, encompassing both recurrent (r) and newly diagnosed (n) GBM. Finally, an additional examination of the ongoing clinical trials was also conducted.

Results: Recent trials have shown promising results both in patients with nGBM and rGBM/progressive (rGBM), leading to Food and Drug Administration approval in selected patients and the Congress of Neurological Surgeons to include TTFields into current guidelines on the management of GBM (P100034/S001-029). Recently, different randomized trials have demonstrated promising results of TTFields in combination with standard treatment of n- and rGBM, especially when considering progression-free and overall survival, maintaining a low rate of mild to moderate adverse events.

Conclusion: Optimal outcomes were obtained in nGBM and progressive disease. A possible future refinement of TTFields could significantly impact the treatment of rGBM and the actual standard of care for GBM, given the better safety profile and survival effects.

Keywords: Brain tumor, Clinical trial, Glioblastoma, High-grade glioma, Tumor treating fields

INTRODUCTION

High-grade gliomas represent the most frequent yet malignant type of brain tumor, with a median overall survival (OS) of only 14.6 months following current standard therapy comprising gross total surgical resection combined with adjuvant radiation therapy (RT) and systemic chemotherapy.[38] With an annual incidence of 3.5/100,000 people, glioblastoma (GBM) represents the most aggressive phenotype of diffuse high-grade astrocytomas due to

its high rates of cellular division and vascular proliferation, frequently involving the central regions of the brain's parenchyma.[1,27] The fifth edition of the World Health Organization classification of brain tumors published in 2021 integrates the previously adopted approaches to tumor diagnosis and characterization, such as histology and immunohistochemistry, and introduces advanced molecular panels as key factors in the nomenclature and grading of brain tumors.[25] Both locoregional and systemic therapies are advancing, considering the crucial importance of molecular mutations hosted by the tumor and moving toward a more personalized approach to manage such lesions.[10,50]

In the pursuit of achieving longer OS and progression-free survival (PFS) as well as higher objective response rates (ORRs) with limited neurological and systemic impairment, a pivotal role is played by advanced preoperative mapping techniques, allowing the resection of previously inaccessible tumors.[35] Moreover, advanced and minimally invasive stereotactic radiosurgery (SRS) strategies progressively establish themselves as a valuable tool in the multidisciplinary armamentarium frequently needed to manage these complex malignant entities.[23] In addition to the impressive advancements in the locoregional management of intracranial GBM, significant results have been achieved through systemic therapy with the patient- and tumor-specific treatment algorithms currently deployed or under investigation for newly diagnosed and recurrent GBM (rGBM).[24]

Notwithstanding, the recent advancements allowed by the vibrant and intense pre- and clinical pharmacological research and the numerous technological advancements geared toward more efficient management of GBM, survival, and local disease control are still unsatisfactory. Since the approval for clinical practice for rGBM and newly diagnosed GBM (nGBM) in 2011 and 2015, respectively,[11] tumor treating fields (TTFields) devices represent promising, additional management possibilities in combination with either standardized systemic agents or locoregional therapies. However, much uncertainty remains over the accessibility of this technology on a broad scale, its cost-effectiveness, and the actual benefit for GBM patients. The present review provides a critical analysis of the published literature since the approval granted by the Food and Drug Administration (FDA) for the use of TTFields in clinical settings, as well as a comprehensive examination of the literature granting such approval. In addition, completed and ongoing clinical trials on nGBM and progressive/recurrent disease are examined to predict future directions and applications of this new therapy.

PRINCIPLES AND FUNCTIONING OF TTFIELDS

Despite numerous advancements in cancer treatment and the introduction of innovative therapeutic options, the mortality rate for GBM remains dismal.[5] TTFields, consisting of low-intensity and intermediate-frequency electric fields, are one of the most recent and promising techniques to have been introduced.[5] After being historically considered biologically inefficient, Kirson *et al*.[18] revealed that low-intensity (1–3 V/cm) and intermediate-frequency (100–300 kHz) electric fields can disrupt the growth rate of various entities of solid tumors, including gliomas, both *in vitro* and *in vivo*. These effects were proportional to the increase in electric field intensity. Indeed, using a 2.25 V/cm field completely inhibited rat glioma cell proliferation after 24 h of continuous exposure.[52] Moreover, results were also consistent with frequency-dependent effects for TTFields, meaning that glioma cells reached a peak inhibitory effect at around 200 kHz.[17,52] To maximize the antineoplastic effect of TTFields, it is necessary to act in several ways: Increasing intensity, lengthening treatment duration, and highlighting the most effective combined therapies to be associated with TTFields and, in closing, the optimal frequency which the type of neoplastic cells must determine. Focusing on frequency, several studies reported how different optimal values should be applied to obtain the maximum anti-cytotoxic effect. For instance, in Kirson's publication, the investigation also involved mouse melanoma and human breast carcinoma cells and reported two different values, 100 kHz and 150 kHz, respectively.[17,52]

Therefore, a similar study by Porat *et al*.[37] assessed TTFields effects related to varying frequencies and intensities. Interestingly, as revealed by this study, the same optimal frequency of glioma cells should be applied in ovarian cancer cells, whereas, in the case of mesothelioma cells, a frequency of 150 kHz is recommended given the maximum cytotoxic effect that has been demonstrated at this frequency.[32]

In 2016, Kim *et al*.[16] investigated the apoptotic effect of TTFields in two human GBM cell lines alone or in combination with ionizing radiation (IR). Noticeably, the latter form of radiation differs from TTFields since it acts in the far field region with a higher frequency. Ultimately, they showed a quantitative difference in the apoptotic rates following 72 h of treatment with TTFields or IR alone or in combination (23.9 [17.1]% vs. 9.10 [2.09]% or 6.54 [2.98]% in the combination and single-treatment groups, respectively). Ultimately, they demonstrated that combining TTFields with IR delivers a synergistic suppression of cell migration and invasion, secondary to the inhibition of matrix metalloproteinase-9 and vimentin. Furthermore, various experiences have demonstrated how the peculiar intensity and frequency-specific activity of TTFields are also inversely proportional to the tumor cell size, prompting a tumor-specific field-generating device programming based on malignant cell type and consequently reducing unneeded adverse events.[9]

Notwithstanding the remaining uncertainties regarding the exact mechanisms of action of TTFields, an examination of preclinical studies allows us to summarize these antineoplastic effects into the following categories: (1) the interruption of the microtubule formation, achieved by impairing the assembly of a functioning mitotic spindle and a dielectrophoretic effect, with TTFields generating a non-uniform field which forces organelles and polar macromolecules to move in a certain direction, therefore separating them from their daughter cells,[9] (2) a mechanistic role in DNA damage, meaning that an enhancing effect on drugs involving DNA damage and replication stress has been shown,[31] and (3) autophagy effect stimulation in cancer cells, which has been demonstrated through electron microscope observations. The mechanisms through which autophagy is induced are still uncertain but may involve multiple pathways, such as AMPK, AKT2, and miR-29b;[31] (4) activation of both the cGAS/STING and the AIM2/caspase one inflammasome inducing membrane-damaged cell death, which has been determined in glioma stem cells.[7] However, despite the promising implications of this mechanism in drug delivery to the central nervous system, it is noteworthy that clinical studies are paramount to validate this speculation further and that preliminary experiments also examine the eventual TTFields alterations of normal cell morphology.[31] (5) Downstream antitumor immune response: cells that under TTFields manage to complete mitosis and ultimately give birth to aneuploid daughter cells, which are often characterized by endoplasmic reticulum stress and autophagosomes, eventually leading to immunogenic cell death that can trigger a systemic anti-cancer immune response, through surface exposure of Cal reticuline leading to the maturation of antigen-presenting cells. Evidence shows that this immune system response is a downstream effect that TTFields induce on dividing tumor cells.[41,53]

A schematic representation of the functioning mechanisms of TTFields is shown in Figure 1. While preserving the ability to perform daily activities without extensive restrictions, a portable, battery-operated TTFiels device allows the patients to receive low-intensity intermediate-frequency alternating electric fields during most of the day and night. TTFields exert directional forces and result in abnormal spindle formation and subsequent mitotic arrest or delay, possibly due to improper attachment of chromosomes to the spindle fibers. In dividing cells, this leads to an abnormal anaphase arrest during the mitotic cycle, subsequently inducing autophagy.

This innovative therapy showed impressive results when administered alone and demonstrated synergistic effects when coupled with commonly used systemic agents in various solid tumors, including gliomas.[9] Despite the most effective activity for this combination therapy being seen with paclitaxel in breast cancer cell lines, other agents, including cyclophosphamide, also proved efficient.[9] An *in vitro* assessment conducted on glioma cells in mice (U-118 glioma cells) to analyze the possible synergism between TTFields and chemotherapeutic agents revealed an improved efficacy of this device when combined with paclitaxel and cyclophosphamide.[19] The combined effect could be explained by the concomitant activity on two different metabolic phases, with the TTFields exerting its inhibitory effect mainly on the M-phase, whereas the cyclophosphamide acts primarily on the S-phase.[9] The efficiency underpinning this improved antineoplastic activity shows that cells escaping one therapy could be antagonized by the second one in a different phase.[9]

Moreover, preclinical studies revealed that combining TTFields with a standard-of-care drug could significantly reduce the doses of the latter, allowing the final therapy to be as effective as before, or even more, while significantly decreasing drug-related toxicities.[19,40] As a matter of fact, two additional preclinical studies of paramount importance in the clinical application of TTFields are worth mentioning.

First, Giladi *et al*.[13] demonstrated that applying TTFields before and after radiotherapy could inhibit the tumor's ability to repair its DNA. This means that TTFields could actively induce antineoplastic activity while enhancing the concomitant standard of care treatments for GBM. The authors suggest leaving the arrays attached to the patient's head while administering radiotherapy to achieve this effect.[13]

Moreover, Silginer *et al*.[42] demonstrated that TTFields stimulate autophagy and disrupt cell division and migration, reducing cancer cell viability. Furthermore, the authors not only demonstrated that TTFields present a synergistic effect with temozolomide (TMZ) but that they are also effective on TMZ-resistant glioma cells, indicating a significant possibility of using this treatment method in a clinical setting.

As demonstrated, TTFields have antiproliferative properties both *in vivo* and *in vitro*.[36,55] The first preclinical study on TTFields was published in 2004,[18] proving that alternating electric fields cause alteration of the mitotic spindle function with consequent mitotic inhibition on 11 vitro cancer cell lines which are observed within 72 h after exposure, preventing cell division.[30]

ROLE OF TTFIELDS IN NGBM

Following the results of pre-and clinical trials, the FDA approved TTFields in 2015 as a therapeutic option for nGBM in combination with the standard of care, consisting of total resective surgery, followed by adjuvant chemoradiotherapy and maintenance systemic therapy.[28] Finally, following regulatory approval, the combination of TTFields with

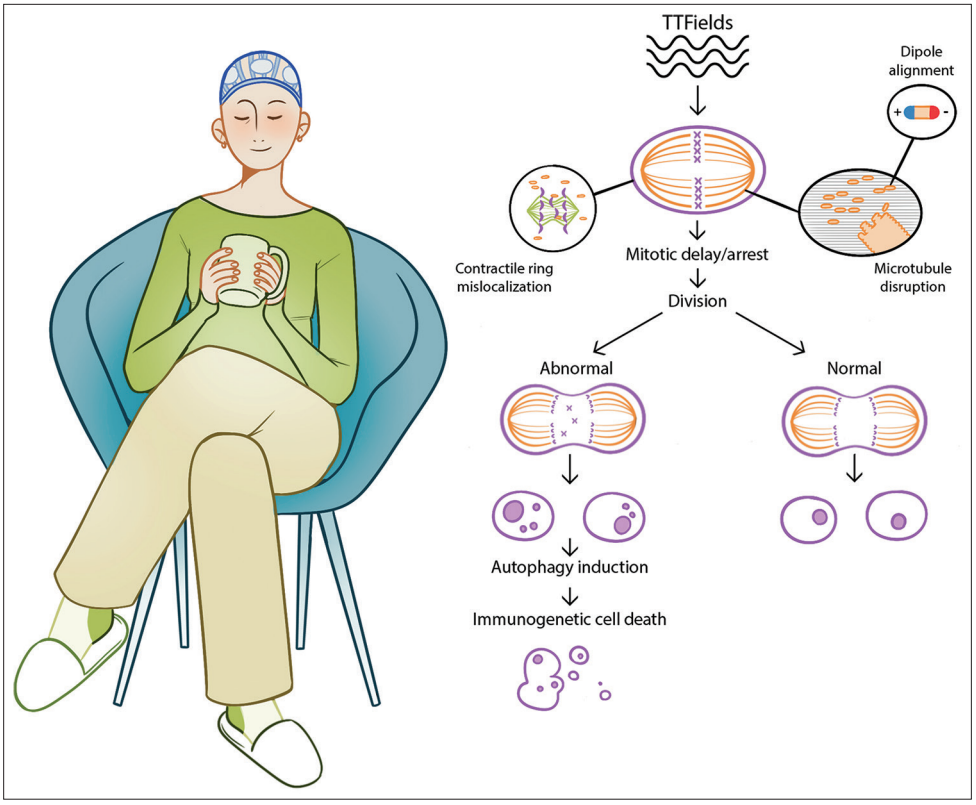

Figure 1: Schematic representation of the functioning mechanisms of tumor treating fields (TTFields). In the left part of the image, a blue mesh can be seen applied on the head of the patient performing her daily activities, without restrictions. This mesh represents the TTFields transducer array which is connected to a battery-operated field-generating device (not shown). Transducer arrays deliver low-intensity intermediate-frequency alternating electric fields and monitor the temperature of the scalp, to avoid heat-induced skin reactions. A schematic description of the physical mechanisms of TTFields is provided on the right side of the image. TTFields exert directional forces and result in abnormal spindle formation and subsequent mitotic arrest or delay, possibly due to improper attachment of chromosomes to the spindle fibers. In dividing cells, this leads to an abnormal arrest of the anaphase during the mitotic cycle, subsequently inducing autophagy and downstream immunogenic cell death.

TMZ is now recommended by the National Comprehensive Cancer Network for both nGBM (Category 1) and rGBM (Category 2B). The following sections critically describe the pre- and clinical experiences with TTFields alone and in combination with other locoregional and systemic therapies.[46]

Since then, this novel treatment option has been investigated as a sole intervention and adjuvant management of diffuse high-grade gliomas. For instance, the promising application of TTFields has been documented in several pilot studies and clinical trials.[11,45] The vibrant research panorama surrounding the applications of TTFields in neuro-oncology primarily reflects its ability to significantly prolong PFS and OS with low rates of adverse events. To further evaluate the clinical efficacy of TTFields in GBM, a pilot study was started in 2007 by Mirza and Shamim[29] and conducted for a total duration of 4 weeks with a 200 kHz TTFields frequency, an empirically identified optimal frequency for GBM. Twenty patients were enrolled, with the first ten undergoing TTFields monotherapy for rGBM after failure in controlling the disease with maintenance TMZ and the remaining 10 using it for the treatment of nGBM at least four weeks after RT and in combination with TMZ.[19] Notwithstanding the limited number of patients, primary outcomes regarding OS and PFS were superlative and clinical toxicities limited, with 18 patients (90%) presenting mild dermatitis that frequently appeared in the 2nd month of treatment. However, topical corticosteroids, along with the periodic repositioning of the electrodes, narrowed the severity of this side effect. The complete resolution was regularly observed in a time frame ranging from days to weeks after treatment.[19] Even if the first group treated for rGBM produced outstanding results, at least doubling the median OS and PFS when compared to the TMZ monotherapy group, patients with nGBM (second group) under treatment with TTFields and TMZ showed even more remarkable results, with a median OS of 39 months,

widely exceeding the median OS of their counterparts (14.7 months) who only underwent maintenance TMZ.[19] Notably, at the time of their publication (more than two years after the study start date), eight patients out of ten were still alive, and the median PFS was 155 weeks, compared to the 31 weeks of the control group.[19]

Following a further and more extensive trial (EF-11) confirming the overall comparable results in OS and clinical response between TTFields and standard-of-care therapy, the device received FDA approval in 2011 for the treatment of rGBM and in 2015 for nGBM.[5,28] As demonstrated by Kirson *et al*. in their pilot trial,[17,19] the administration of TTFields in newly diagnosed patients in combination with standard adjuvant TMZ compared to the TMZ-alone control group showed positive results in terms of median PFS (155 vs. 31 weeks) and median OS (>39 vs. 14.7 months). Similar outcomes have been reported by Stupp *et al*.[45] In their analysis, TTFields were deployed in combination with maintenance TMZ after completing standard chemoradiation, demonstrating significant differences in median PFS and OS compared to two groups where patients were randomized to receive maintenance TMZ with TTFields or TMZ alone. PFS and OS assessed in Stupp trial are also promising; indeed, the median PFS was 7.1 months (95% confidence interval [CI], 5.9–8.2 months) in the TTFields plus TMZ group and 4.0 months (95% CI, 3.3–5.2 months) in the TMZ alone group ([Hazard ratio (HR)], 0.62 [98.7% CI, 0.43–0.89]; P = 0.001); median OS in per-protocol population was 20.5 months (95% CI, 16.7–25.0 months) in the TTFields plus TMZ group and 15.6 months (95% CI, 13.3–19.1 months) in the TMZ group (HR, 0.64 [99.4% CI, 0.42–0.98]; P = 0.004). Fascinating results show how TTFields action may improve survival in nGBM patients. In Ornelas *et al*.,[34] a randomized controlled trial was selected to analyze TTFields' role. Given the addition of TTFields, median PFS was 6.7 months compared with four months with TMZ alone (HR, 0.63; 95% CI, 0.52–0.76; P < 0.001); whereas OS was 20.9 months compared with 16.0 months (HR, 0.63; 95% CI, 0.53–0.76; P < 0.001).

The compliance to the treatment is an additional feature that may interfere with TTFields effect modifying clinical outcomes; in fact, the anti-mitotic effect induced by TTFields may be limited due to insufficient use of the device. The percentage of monthly TTFields compliance collected directly from each device's internal computerized log file is the primary outcome of a randomized (2:1), open-label trial, the EF-14 phase III.[49] The investigation determines the impact of TTFields compliance on PFS and OS in nGBM patients who underwent the NovoTTFields-100A device and TMZ. Precisely, 466 patients in the TTFields + TMZ group were divided into subgroups by percent monthly compliance, while 229 were randomized to the TMZ group. Results show that an average monthly compliance >50% was related to an extension of PFS and OS when compared to the TMZ alone group, PFS (HR 0.70, 95% CI 0.47–1.05) and OS (HR 0.67, 95% CI 0.45–0.99). As demonstrated by the trial, greater compliance means greater gain in terms of PFS and OS. Indeed with levels of >90%, maximal survival benefits were reached, with a median PFS of 8.2 months for the first group compared to 4.0 months in the TMZ alone group (HR 0.538, 95% CI 0.365–0.794; P = 0.0047) and an OS of 24.9 months in the TTFields + TMZ arm compared to 16.0 months in the second arm (HR 0.522, 95% CI 0.347–0.787; P = 0.0007). An additional feature in TTFields treatment is the hypothesis that by increasing the applied dose, an improvement should be observed in the outcomes. Precisely, a simulation-based study by Ballo *et al*.[2] investigated the relationship between TTFields dose and survival in 340 patients of the 466 patients randomized to TTFields + TMZ in the abovementioned trial. The local minimum dose density (LMiDD) is essential for the investigation, which reflects compliance and power density. Identifying an optimal threshold value of average LMiDD of >0.77 mW/cm^3 and dividing the population into two groups PFS and OS evaluation was possible: OS was 25.2 versus 20.4 months (P = 0.003, HR = 0.611) and PFS was 8.5 versus 6.7 months (P = 0.02, HR = 0.699). Interestingly, the definition of TTFields dose in this study is clarified, but the trial demonstrated how higher doses are related to better survival, which is confirmed by the EF-14 trial.

Interestingly, modern research is also geared toward including molecular footprints of GBM in the patient selection process, which serves as prognostic as well as therapeutical efficacy predicting factors when administering TTFields. Most commonly investigated molecular markers include methylguanine methyltransferase (MGMT) methylation status, epidermal growth factor receptor amplification, chromosome 1p/19q codeletion, and IDH1 mutation.[28] Indeed, in Krigers *et al.* [20], trial patients treated with TTFields within six weeks after concomitant chemoradiotherapy (Stupp protocol) showed an OS significantly favorable in the case of MGMT promoter methylation. On the contrary, IDH status did not change OS (LogRank P = 0.549 IDH-mutation and IDH wild-type).

Furthermore, many researchers hold the hypothesis speculating that several subpopulations of cancer stem cells in GBM are responsible for tumor initiation and progression.[36] As elaborated in a recent study by Clark *et al*.,[8] the above hypothesis is closely linked to the effectiveness of TTFields, where a clear demonstration of cancer stem cells' sensitivity to TTFields deeply changes prognosis. In their study, a particular focus was set on assessing the effectiveness of therapy based on the molecular footprint of the tumor and whether the genomic alterations of the GBM may influence efficacy. As a matter of fact, they showed that the efficacy of

TTFields treatment is maintained in both methylated and non-methylated glioma cultured cells. Precisely, no statistical difference in efficacy was found when administering TTFields in unmethylated GBM patients treated with RT or TMZ. Nonetheless, a stronger TTFields effect was shown following RT, possibly since TTFields delay the repair of DNA damage induced by conventional photon beam radiotherapy, making cells more vulnerable.[20,29]

USE OF TTFIELDS IN THE PROGRESSIVE DISEASE

Despite recent advancements in the neuro-oncological field, the prognosis for rGBM remains dismal, hindered by the paucity of effective therapeutic options and the absence of definitive guidelines for its management.[24] Considering the low percentage of patients who tolerate a second surgery (20%) and the even lower percentages of subjects being amenable to re-irradiation, the most common therapy for recurrence remains chemotherapy.[47] The actual standard of care for treating GBM, known as the "Stupp" protocol, consists of surgery when feasible, along with the administration of TMZ chemotherapy and concurrent radiation (60 Gy in 6 weeks), followed by adjuvant chemotherapy.[33] However, both PFS at six months and response rates at recurrence remain dismal (<20% and <10%, respectively).[47] As a matter of fact, several causes may interfere with chemotherapy response; definitely, one of the leading prognostic factors is the methylation of the MGMT promoter region.[15] TMZ is an imidazotetrazine lipophilic Prodrug that can cross the blood-brain barrier and produce multiple DNA adducts due to the methyl group of methyl diazonium ions, which is transferred to DNA, causing a mismatched base pairing and, as a consequence, cytotoxicity and cell death. The enzyme encoded by MGMT promoter, O^6 – MGMT, is involved in the repair of DNA molecules whose role is to remove O6-methylguanine DNA adducts originating from the cytotoxic effect of alkylating agents, including TMZ. Hence, the methylation of the promoter makes neoplastic cells sensitive to the action of TMZ, whereas an obvious poor response can be noted in unmethylated MGMT promoter GBM.[43] Accordingly, the primary mechanism of resistance to TMZ is dependent on the MGMT activity, but symmetrically, the wide exposure to TMZ and the extreme heterogeneous and mutation prone nature of GBM are two essential points, most likely this can be caused by the increase in reparative capacity of stem cells secondary to radiation and chemotherapy.[3] Resistance is a very common circumstance in case of recurrence, which justifies the need to investigate new advanced approaches.

Consequently, an increasing number of alternative therapeutic approaches are being considered, including bevacizumab, an anti-vascular endothelial growth factor drug; alkylating agents such as carmustine or nitrosoureas; and procarbazine or TTFields.[47] The latter has been recently introduced, not only for its plausible clinical efficacy but also for its limited invasiveness and elevated safety.

A randomized phase III trial (EF11 trial) evaluated the efficacy of TTFields in rGBM compared to the actual standard of care.[54] Two hundred and thirty-seven patients were included in the clinical trial with a 1:1 randomization ratio, and, notably, the PFS and OS were shown to be equivalent to the Stupp protocol. However, no statistically significant results were found between the TTFields group and the control arm regarding the PFS at six months, the survival rate at one year, and the radiological response rate.[54] While the study's primary outcome was not reached, namely, superiority to the actual standard of care treatment, the promising survival results suggested a more detailed examination of TTFields, given that this tool is less invasive and safer than chemotherapy and radiation. In the pursuit of finding a more effective therapy, TTFields were officially approved in 2011 by the FDA for the treatment of rGBM.[22]

Following the efficacy of this innovative tool in the abovementioned trial, a Patient Registry Dataset (PRiDe) was carried out between October 2011 and November 2012 to evaluate the efficacy and safety of TTFields for rGBM in 457 adult patients, whose results were then compared to the EF-11 trial.[54] Despite similar demographic characteristics between the patient groups, some important variations should be pointed out: The patients in the EF-11 trial started TTFields therapy later compared to the PRiDe group (33.3% of patients in PRiDe started TTFields at first recurrence vs. 9% in EF-11 trial), a different percentage of patients was previously treated with bevacizumab (55.1% for PRiDe vs. 19% for EF-11), and the median duration of treatment was heterogeneous (4.1 months for PRiDe vs. 2.3 months for EF-11).[54] Given these differences, the results of the PRiDe analysis showed a median OS of 9.6 months, a 1-year survival of 44%, and a 2-year survival of 30%. However, the most promising result, consisting of a median OS of 20 months, was obtained with patients who underwent treatment with TTFields at first recurrence, presenting a 90–100 KPS, ≥75% compliance, and no previous bevacizumab treatment.

To further investigate the efficacy of this novel therapy, a case series of patients with rGBM treated with TTFields was published in 2012 by Rulseh *et al.* [39] reporting four long-term survivals. Notably, two of these were patients with rGBM, which were alive and in good health at the time of publication, seven years after completing their treatment with TTFields. Both these patients underwent TMZ and later showed asymptomatic recurrence. While the first patient showed no radiological evidence of malignant disease after TTFields treatment, the second patient had one small enhancing lesion without any clinical signs of tumor progression. Furthermore, as previously mentioned, both patients were in

good health, with a KPS of 90 and mild residual symptoms already present at the first tumor diagnosis.[39] Nonetheless, the data about the remaining patients and the molecular analysis of the long-term survivors' tumors were lacking, thwarting the possibility of drawing any valuable conclusion from it.

Another clinical trial involving 25 patients was conducted between 2013 and 2017, examining a combination of bevacizumab and TTFields for progressive disease.[12] Median PFS and OS were in line with the previous promising results (4.1 months and 10.5 months, respectively), and so were the PFS at six months (33%) and 12 months (19%). OS rates at six months (82%) and 12 months (46%) also suggested the plausible effectiveness of this combination. In conclusion, not only TTFields result to be safe and feasible, but they also demonstrated improved clinical efficacy compared to the actual standard of care for rGBM.

The enrolled prospective clinical studies are summarized in Table 1.

ONGOING CLINICAL TRIALS

In addition to the experiences that have led to the FDA approval of TTFields for rGBM and newly diagnosed disease, the following section explores ongoing clinical trials to highlight the new frontiers and future perspectives of this technology for treating high-grade brain tumors [Table 2]. A database search on clinicaltrials.gov yields four controlled trials yet in the recruiting phase, investigating new combinations of TTFields with systemic therapy and locoregional treatments, including radiosurgery and skull remodeling surgery. Following is a brief examination of the ongoing trials.

A phase II clinical trial, namely, TaRRGET (NCT04671459), has already enrolled 40 patients and aims to concomitantly administer SRS and TTFields, not only to minimize toxicities but also to increase tumor sensitivity to radiation, a consequence of the TTFields action in disrupting DNA repair and enhancing immunogenic cell death. For that purpose, SRS will be delivered seven days after starting TTFields and with a 5-day regimen, during which the TTFields will be interrupted and restarted immediately after. To accurately analyze the efficacy of this combination therapy, fluoroethyltyrosine positron emission tomography imaging will be used to define tumor volume at recurrence. While 1-year survival rate remains the primary outcome, it is noteworthy to mention that secondary outcomes also include radiation necrosis range, steroid needs until treatment failure, and failure patterns in an effort to assess possible connections between the location of failure and target volume.

Table 1: Completed clinical trials investigating the therapeutic role of TTFields in patients with newly diagnosed and rGBM.

Trial identification number	Author	Year	Patients (intervention group)	Patients (control group)	Diagnosis	Intervention 1	Intervention 2	Median PFS	Median OS	Toxicities
Pilot clinical trial	Kirson *et al*.	2009	10	N.A.	ndGBM	TTFields+ TMZ	TMZ (historic controls)	155 weeks versus 31 weeks	Not reached (>39 months) versus 14.7 months	Dermatitis, Anemia, Liver enzymes elevation
NCT00379470	Stupp *et al*.	2012	120	117	rGBM	TTFields	Physician choice	2.2 months versus 2.1 months	6.6 months versus 6 months	Dermatitis
NCT00916409	Stupp *et al*.	2015	466	229	ndGBM	TTFields+ TMZ	TMZ	7.1 months versus 4 months	20.5 months versus 15.6 months	Dermatitis, headache
NCT01894061	Fallah *et al*.	2020	25	0	rGBM	TTFields+ Bevacizumab	/	9.9 months	Not reached (>12 months)	Dermatitis, seizures, hyperglycemia

ndGBM: Newly diagnosed GBM, TMZ: Temozolomide, TTFields: Tumor treating fields, PFS: Progression-free survival, OS: Overall survival, rGBM: Recurrent GBM, N.A: Not available

Table 2: Ongoing clinical trials investigating to the therapeutic role of TTFields in patients with ndGBM and rGBM.

Trial identification number	Trial Phase	Starting Date	Estimated Enrollment	Diagnosis	Intervention
NCT03405792	Phase 2	Feb 23, 2018	31*	ndGBM	Optune®+TMZ+Pembrolizumab
NCT03223103	Phase 1	Mar 1, 2018	13*	ndGBM	MTA-based vaccine+Stupp protocol+TTFields
NCT03477110	Early Phase 1	May 4, 2018	35	ndGBM	Temozolomide, Radiation Therapy+TTFields
NCT03705351	Phase 1	Dec 2, 2019	7*	ndGBM	Optune®+Routine Treatment
NCT04221503	Phase 2	Dec 30, 2019	30*	rGBM	TTFields+Niraparib
NCT04221061	Early Phase 1	Feb 20, 2020	12	rGBM	Optune®+Niraparib
NCT04469075	Phase 2	Jul 9, 2020	58	ndGBM	TTFields+Clindamycin+Triamcinolone
NCT04492163	Phase 2	Jul 14, 2020	25	rGBM	Optune®
NCT04223999	Phase 2	Oct 1, 2020	70	rGBM	TTF+skull remodeling surgery
NCT04471844	N.A.	Dec 8, 2020	950	ndGBM	Optune®+RT+TMZ
NCT04671459	Phase 2	Dec 26, 2020	40	rGBM	TTFields and SRS
NCT04474353	Phase 1	May 21, 2021	12	ndGBM	TTFields+SRS+TMZ
NCT04397679	Phase 1	Aug 12, 2021	10	ndGBM	Partial Brain Radiation Therapy+TMZ+Chloroquine+TTFields
NCT05086497	N.A.	Jan 15, 2023	155	N.A.	Optune®+Whole Brain Spectroscopy Imaging Array Mapping

*Active, not recruiting. TTFields: Tumor treating fields, TMZ: Temozolomide, SRS: Stereotactic radiosurgery, rGBM: Recurrent glioblastoma, ndGBM: Newly diagnosed glioblastoma, RT: Radiation therapy, N.A: Not available, MTA: Mutation-derived tumor antigen

An open-label and single-arm pilot study (NCT04492163) is being conducted on 25 patients with an innovative medical device named Optune, which has already received FDA approval as well as a CE mark for the treatment of progressive and nGBM. Requirements include using the device for a minimum of 18 h a day, allowing the remaining time for hygiene and other personal necessities. The traditional version of the device consists of 4 high-intensity transducer arrays delivering 200kHz TTFields to the brain. This clinical trial aims to test new-generation arrays that reduce skin heating, enabling a larger delivery of high-intense TTFields. This pilot study's purpose is to assess whether the maintenance of high-intensity frequencies, guaranteed by the decreased skin side effects of the new device, improves the final clinical outcome of the patients enrolled. Unlike the previous clinical trial, the present focuses on examining the clinical therapeutic effects of TTFields alone, therefore, in the absence of any other therapeutic procedure, including chemotherapy and radiotherapy.

Another ongoing, phase 2/3 Danish study (NCT04223999) is actively recruiting patients with rGBM who will be randomized 1:1 to receive either skull remodeling-surgery, TTFields and best practice oncological therapy, or TTFields and best oncological therapy alone (control arm). The purpose is to test this minor and safe surgical procedure, creating small burr holes in the patient's skull over the tumor location, combined with standard TTFields at first progression. The background of this investigation is based on the local resistance caused by the skull, which would be sensibly reduced by funneling the electricity through the path of least resistance, namely, the adequately placed burr holes, approximately 15 mm in diameter. Primary outcome measures will be OS at 12 months, while median OS, PFS, and PFS at six months are expected to be calculated with an estimated follow-up time of 18 months and a total study duration of 36 months.

A pivotal, randomized, and open-label study (NCT04471844) is still in a state of recruitment with an estimated enrolled population of 950 patients until August 2026. The goal of the trial is to test the effectiveness and safety of Optune with a concomitant RT and TMZ in nGBM patients and compared it to the control arm that underwent radiochemotherapy (randomized 1:1). In both arms, TMZ concomitant with TTFields at 200 kHz to the brain is applied as maintenance therapy. OS is the primary outcome of the study, while secondary outcomes include PFS (at 6 and 12 months and up to 5 ys) and next PFS, calculated in case of second tumor progression and associated with the evaluation of pathological changes in resected GBM tumors during the study treatment. Further, secondary points are 1- and 2-year survival rates, Objective response rate (ORR) based on the Response Assessment in Neuro-Oncology (RANO) criteria, the quality of life tested with the EORTC QLQ C-30 questionnaire, the NANO scale for neurological assessment, and adverse events expressed in terms of frequency and severity. In addition, one of the aims of the trial is to understand whether the TTFields dose delivered to the tumor correlates with the OS. The dependency will be examined in both groups.

In a non-randomized trial (NCT03405792), close to being completed (February 2023) with 31 patients enrolled, pembrolizumab is combined with TMZ plus Optune; the purpose of the study is to determine whether the triple combination succeeds in increasing PFS in patients with

nGBM. Four to six weeks after completing standard treatment of GBM, monthly cycles (from 6 to 12 cycles) of adjuvant TMZ are administered with concomitant application of TTFields. After cycle 2 of adjuvant TMZ and Optune, in the first arm, pembrolizumab is added to be administered every three weeks for two years in case of no progression of disease or poor adverse events. The primary outcome is PFS, investigated in the triple combination arm and historical arm to compare the results and clarify the potential additional effects that pembrolizumab may add to the combined therapy. OS, augmentation of TTFields-initiated glioma-specific immune reaction by pembrolizumab, and toxicity and tolerability examined by the Common Terminology Criteria for Adverse Events version 4.0 are the secondary outcomes measured. All estimated outcomes are assessed up to 24 months except for OS, which is extended up to 5 years.

Finally, a non-randomized, phase 2 study actively enrolled patients with rGBM to evaluate the efficacy and safety of neratinib in combination with TTFields. Thirty patients are expected to be enrolled between December 2019 and December 2025 and will be divided into two cohorts depending on the clinical indication for surgical resection. In each cohort, neratinib and TTFields will be administered in combination. The rationale is based on pharmacodynamic pathways: neratinib is a selective inhibitor of the poly-ADP ribose polymerase, a mechanism allowing cells to repair single-strand DNA breaks, whereas TTFields have been demonstrated to induce a downregulation of the BRCA1 signaling and reduce DNA double-strand break repair capacity. A synergistic effect is, therefore, to be expected. The primary outcome of this study is disease control, defined as the achievement of either complete, partial response, or stable disease as defined by modified RANO criteria. Secondary outcomes include number of adverse events, duration of disease control, and objective radiographic response.

In conclusion, the presence of several ongoing clinical trials, broadly different from one another, suggests the applicability of TTFields in various management protocols for progressive and nGBM, further demonstrating the importance of this innovative device in promising optimal results while maintaining a sustainable safety profile.

SAFETY AND TOXICITIES

When compared to chemotherapy, TTFields showed a significantly lower rate of hematological, gastrointestinal, and infectious adverse events.[47] The most common adverse effects are dermatologic toxicities, which generally fall into four categories: ischemic, mechanical, skin infection, and dermatitis, as explained by Lacouture *et al*.[21,26] Despite the possible influence of pre-existing conditions or side effects of chemotherapy on increasing the predisposition to the abovementioned toxicities, it is still possible to limit their extension with accurate placement of the arrays, along with careful scalp preparation.[26] Furthermore, even when skin toxicities occur, mostly in the form of irritation of the patient's scalp, topical corticosteroids are completely successful in their treatment, and no additional therapy is generally required.[47,48] From a review paper by Zhu and Zhu, it was observed that heat sensations represent the most common possible side effect of TTFields, accounting for 11.3% of the analyzed sample. Although neurological disorders were also detected in the same registry analysis, their correlation with the medical device has been excluded.[54]

Confirming the previous statement, a recent phase III study[56] investigated the combination treatment with TTFields and TMZ, selecting cognitive status as a secondary endpoint. The examination was performed through questionnaires such as health-related quality of life, assessed with EORTC QLQ-C30/BN20 administered once every three months, KPS, and mini-mental state examination administered once monthly. However, no significant differences resulted between the two groups.

LIMITATIONS OF THE DEVICE

Although TTFields devices' portability and non-invasiveness, several limitations prevent this novel tool's broad acceptance and use. As highlighted by Turner *et al*.[51], in the case of local progression, the directional adjustment of fields could lead to a better response; therefore, the electrodes should be located through magnetic resonance imaging to avoid treatment failure.[34] Therefore, the best efficacy is detected in patients who are able to understand the device and learn to use it with high compliance, as the device usage time remains to date, the only patient-dependent factor that could improve the outcomes.[28] An additional difficulty was detected during a retrospective analysis of Chinese patients, where different compliance between females and males was highlighted, reflecting a distinct degree of acceptance of the TTFields device, probably due to esthetic reasons.[7] Therefore, to improve acceptance, the device should be modified, reducing the weight, volume, and skin irritation caused by the electrodes.

Notwithstanding the impact of this novel therapy on GBM treatment, some evaluations have been made and should, therefore, be reported: (1) an absence of a specific biomarker to identify the molecular subgroup most likely to benefit more from this therapy;[22] (2) the high estimated costs that a wide usage of this therapy would bring to health-care systems;[4,14] (3) lack of secondary analysis providing clinically relevant effects on quality of life;[36] and (4) possible privacy breaches linked to the difficulty of hiding the device when in public places.[6] Finally, Lassman *et al*.[22] concluded that the perceived benefit of TTFields may be higher than the actual clinical impact of the device.

CONCLUSION

Practical advantages of TTFields compared to the other specific oncological treatment include: (i) non-invasiveness of the device and relatively free scheduling of the "device-on period," allowing the patient to organize his/her routine; (ii) safe addition to the cytotoxic chemotherapy; (iii) absence of any significant negative interaction with radiotherapy whose effects are ultimately enforced by concomitant TTFields administration which delays DNA damage repair;[44] and (iv) safety and feasibility also in elderly patients. As summarized in the present review, this novel approach has demonstrated promising results when adopted in combination with standard therapy, prolonging OS and PFS. Furthermore, optimal outcomes were obtained in nGBM as well as in progressive disease. A possible future refinement of TTFields could significantly impact the treatment of rGBM, given the better safety profile and survival effects. Furthermore, the advancement of the synergistic effect between TTFields and other currently available therapies is foreseen to improve the actual standard of care for GBM.

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Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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