Clinical and Experimental Studies of TTFields on Glioblastomas

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Glioblastoma (GBM) is the most common malignant primary brain tumor. Although the standard of care, including maximal resection, concurrent radiotherapy with temozolomide (TMZ), and adjuvant TMZ, has largely improved the prognosis of these patients, the 5-year survival rate is still < 10%. Tumor-treating fields (TTFields), a noninvasive and innovative therapeutic approach, has emerged as the fourth most effective treatment option for the management of this most deadly brain cancer.

Keywords: glioblastoma ; GBM ; tumor-treating fields ; TTFields ; mechanism of action ; clinical trials

1. Introduction

Glioblastoma (GBM) is the most malignant type of primary brain tumor, with an extremely dismal 5-year postdiagnosis survival rate of <10% [1][2]. The annual age-adjusted incidence rate of GBM in the United States is 3.23 per 100,000 people [1]. Since the milestone phase 3 European Organization for Research and Treatment of Cancer (EORTC) study published in 2005 by Stupp et al. [3], maximal safe resection followed by concurrent radiotherapy with temozolomide (TMZ, 75 mg/m^2) and subsequent adjuvant TMZ (150–200 mg/m^2) has been adopted as the standard-of-care protocol worldwide for newly diagnosed GBM (ndGBM) patients. However, even with these multimodal therapies, GBM remains incurable, with a recurrence rate of 100%. Patient prognosis is bleak, with a median overall survival (OS) of 14.6 months to 16.0 months and progression-free survival (PFS) of only 4.0 months [3][4][5]. Considering the rapid development of treatment modalities and successful improvement of patient prognosis with other solid malignancies, including pancreatic adenocarcinoma and mesothelioma, GBM has, unfortunately, become the most lethal type of human cancer [6].

Tumor-treating fields (TTFields) is a noninvasive treatment modality that applies low-intensity, intermediate-frequency, alternating electric fields over the regions of the body where tumors are localized. The use of TTFields inhibits mitosis and the cell cycle, induces cancer cell autophagy, disturbs DNA repair, undermines cell migration, and thus suppresses tumor growth and invasion [7][8][9][10][11][12]. TTFields therapy also ablates the primary cilia on GBM cells that promote tumor growth and chemoresistance to TMZ and induces nuclear envelope disruption and the subsequent release of naked micronucleus clusters, which activate several types of inflammasomes to induce anticancer immunity in GBMs [13][14][15]. The Food and Drug Administration (FDA) of the United States approved the use of TTFields for the treatment of recurrent GBMs (rGBMs) in 2011 and for ndGBMs in 2015 due to the promising results that it had comparable effects with the use of the physician's best choice (PBC) for rGBMs (EF-11) and promoted improved survival relative to the standardized Stupp protocol for ndGBMs (EF-14) [4][5][16]. In recent years, the effectiveness and safety of TTFields in treating GBMs have been confirmed in various observational and randomized studies, and it has been established as the fourth treatment option in addition to surgery, radiotherapy, and chemotherapy [17]. TTFields therapy has been granted the "category 1" recommendation for the treatment of ndGBMs by the National Comprehensive Cancer Network (NCCN) guidelines, as well as the "category 2B" recommendation for the treatment of rGBMs.

2. TTFields Apparatus Applied in the Clinic

Novocure's Optune® is the most widely used electric field therapy device worldwide, consisting of an electrical field generator, two pairs of scalp-adhesive transducer arrays, a messenger bag, connection cables, portable batteries and chargers, and a power supply. Weighing just 2.7 pounds, Optune® is easily wearable and portable, enabling carrying comfort and continuous treatment almost anywhere and anytime. The second generation of the Optune® system is ergonomically improved relative to the first-generation device, with a significantly smaller size and lower weight. In the

field of GBM therapy, Optune® is designed to treat adult patients aged 22 years or older. The treatment-planning software NovoTAL, which uses computer-generated algorithms, optimizes the electric field intensity and array location based on magnetic resonance imaging from patients to enable field emanation through the scalp and skull to the tumor [18].

Optune® is currently available in many countries, including the United States, Europe, Japan, and China. More than 18,000 patients have started therapy with the device (https://www.optune.com/ accessed on: 1 June 2022). However, the unbalanced distribution of devices is still an issue, as only two-fifths of surveyed centers worldwide had TTFields available to offer to GBM patients [19]. Similar electric field therapy devices are in the process of development. For example, in Japan, the Electro-Capacitive Cancer Therapy device, developed by Dr. Warsito P. Taruno at Shizuoka University in collaboration with CTech Labs Edward Technology Company, has been approved for use by the Regenerative Medicine Act. In China, the EFE-G100 device was developed by Jiangsu Hailai Xinchuang Medical Technology Co. (Nanjing, China).

3. Initial Trials of TTFields Applied in Human GBM Patients

The first trial of TTFields treatment in human GBMs was conducted in 2002 (EF-02) as a pilot study using the NovoTTF-100A™ instrument in six patients with advanced malignant tumors, including one with melanoma, one with pleural mesothelioma, one with GBM, and three with breast cancer [20]. Unfortunately, the patient with TMZ- and carmustine-resistant GBM showed no response to TTFields treatment, possibly due to the short treatment duration of only 4 weeks. However, it is confirmed the safety profile of the use of TTFields, with a high patient compliance of > 80%, implying the potential of TTFields as a new treatment option for refractory, advanced tumors.

Kirson et al. [21] conducted the second landmark trial of TTFields (EF-07) on 10 patients with rGBMs. With prolonged used of TTFields, the median time to disease progression was 26.1 weeks, and the median OS was 62.2 weeks, which was more than double the medians observed in historical controls. A case report later showed that two patients with rGBMs were still alive in 2012 [22]. In 2009, a second group of 10 ndGBM patients was included after success in the treatment of rGBMs. Kirson et al. [23] reported that patients with ndGBMs who were treated with TTFields plus maintenance TMZ therapy after radiotherapy had a longer median OS of more than 39 months and a longer median PFS of 155 weeks than the OS of 14.7 months and PFS of 31 weeks observed in matched historical controls receiving maintenance TMZ alone. These studies set the foundation for subsequent large-scale randomized, controlled trials involving the application of TTFields in patients with rGBMs and ndGBMs.

4. Clinical Efficacy of TTFields in rGBM Patients

To date, there is no standard treatment for rGBMs. Before the introduction of TTFields, clinical trials, reoperation, chemotherapy, radiation, targeted therapy, and immunotherapy were potential treatment options. Among them, bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, is the most promising treatment choice. However, bevacizumab was shown to only provide benefits in PFS, with no significant change in patient OS [24].

The use of TTFields was approved by the FDA for rGBM treatment in 2011 and was included in the NCCN guidelines in 2013 because of its promising efficacy demonstrated in the EF-11 trial [16]. This phase 3 controlled trial demonstrated the efficacy and safety of TTFields in treating rGBMs. A total of 237 patients were included in the study, among whom 120 were randomized to be treated with TTFields alone (>18 h/d), whereas the others were treated with PBC therapy. The median OS was 6.6 months and 6.0 months (p = 0.27) in the TTFields and PBC groups, respectively, and the 6-month PFS was 21.4% and 15.1% (p = 0.13), respectively. Although rGBM patient survival was not better with the use of TTFields than with the use of PBC, this chemotherapy-free treatment had effects that appeared to be comparable to those of chemotherapy; most importantly, it induced less toxicity and improved QoL [16].

5. Clinical Efficacy of TTFields in ndGBMs

For ndGBMs, the standard of care is maximal safe surgical removal, followed by radiation plus concurrent TMZ, as well as subsequent TMZ maintenance therapy. This standard-of-care Stupp protocol prolongs the OS from the 12.1 months achieved with postoperative radiation alone to 14.6 months in ndGBM patients [3].

The use of TTFields was approved by the FDA for ndGBM in 2015 and was included in the NCCN guidelines as a category 1 recommendation in 2018 because of its high clinical efficacy. In 2009, a phase 3 controlled trial (EF-14) was launched to test the efficacy and safety of TTFields in combination with TMZ maintenance therapy for ndGBM patients. A total of 695 patients who had completed surgery and chemoradiotherapy were included. Two-thirds of the subjects were

randomized to be treated with TTFields (>18 h/d) plus adjuvant TMZ, whereas the others were given standard adjuvant TMZ maintenance therapy. An interim analysis in 2015 reported that the median PFS of the TTFields plus TMZ group and TMZ-alone group was 7.1 months and 4.0 months, respectively, and the median OS was reported to be 20.5 months and 15.6 months [5]. The final report published in 2017 demonstrated that the addition of TTFields to TMZ maintenance therapy after chemoradiotherapy increased patient OS from the 16.0 months achieved using TMZ therapy alone to 20.9 months and the PFS from 4.0 months to 6.7 months [4]. Subgroup analyses of the EF-14 trial showed that increased compliance with TTFields therapy was an independent prognostic factor for improved patient survival. For patients using TTFields > 22 h each day, the 5-year survival rate was high, reaching 29.3% [25].

6. Combination Therapy with TTFields

6.1. TTFields Combined with Chemotherapy

GBMs develop chemoresistance due to various mechanisms, including activated DNA repair, angiogenesis, hypoxic TME and acidosis, immune escape, and GBM stem cell development [26]. Moreover, the BBB, a major hurdle for the efficient delivery of chemotherapy agents, also contributes to GBM chemoresistance [27]. Identifying ways to improve chemoresistance has become an urgent issue. Prior studies on non-small-cell lung cancer demonstrated that the use of TTFields improved the treatment efficacy when combined with pemetrexed, cisplatin, paclitaxel, erlotinib, TMZ, and 5-FU [28]. Strategies to improve therapeutic outcomes in GBM patients by combining TTFields with TMZ therapy have been extensively studied. Preclinical data showed that the use of TTFields and alkylation agents led to additive or synergistic effects on GBM patients, and TMZ-resistant glioma cells responded well to TTFields treatment, highlighting the clinical potential of this combination treatment approach [29]. Kirson et al. [23] showed that the use of TTFields can increase the sensitivity of GBM cells to TMZ, making it possible to achieve similar or even improved therapeutic effects with lower dosages, thus reducing the overall toxicity. Moreover, a pilot clinical study (EF-07) reported a significantly improved therapeutic effect in those using TTFields/TMZ combined therapy than in those using maintenance TMZ alone, which further corroborated the authors' expectation [23]. The final result of the EF-14 trial in 2017 also showed that the use of the combination treatment with TTFields and TMZ resulted in significantly higher PFS and OS than the use of TMZ maintenance therapy alone [4]. Subsequently, researchers from South Korea performed a subgroup analysis of 39 patients in the EF-14 trial, showing that the median PFS was 6.2 months in the combination treatment group and 4.2 months in the group treated with TMZ alone; the median OS was 27.2 months in the combination treatment group and 15.2 months in the group treated with TMZ alone, similar to the overall results observed in the EF-14 trial [30].

In addition to the use of TMZ, the use of combination treatments with TTFields and other chemotherapeutic agents showed clinical efficacy. Preclinical studies have shown that TTFields and withaferin A synergistically inhibit the proliferation of GBM2/GBM39/U87-MG cells [31]. The NOA-09/CeTeG trial found that the combination of lomustine and TMZ was superior to TMZ monotherapy in patients with O6-methylguanine DNA methyltransferase (MGMT) promoter methylation (mMGMT) ndGBMs [32]. In 2020, Lazaridis et al. [33] reported the results of a retrospective analysis of mMGMT ndGBM patients receiving TTFields in combination with lomustine and TMZ, with a median PFS of 20 months, revealing a potential clinical benefit.

6.2. TTFields Combined with Radiotherapy

TTFields therapy synergistically enhances the efficacy of radiation in glioma cells [34]. Preclinical evidence suggests that the combination of radiation and TTFields therapy prevents GBM cells from migrating and invading and promotes cell apoptosis, DNA damage, and mitotic abnormalities [35][36]. In 2020, a study with the aim of examining the safety and efficacy of TTFields in combination with TMZ and radiotherapy was reported [37]. A total of 10 patients with ndGBM received TTFields/radiation/TMZ followed by adjuvant TMZ/TTFields, achieving a median PFS of 8.9 months from enrollment. In addition, Stein et al. [38] reported a case of thalamic GBM, IDH wild-type, showing a complete radiological response after chemoradiation with TMZ, proton boost therapy, and TMZ maintenance in combination with TTFields therapy. Recently, Miller et al. [39] evaluated the skin toxicity of scalp-sparing chemoradiation plus TTFields followed by maintenance TMZ plus TTFields in 30 patients with ndGBMs, showing good tolerance of the new protocol with no need to remove electric arrays during the radiation process, as well as a higher PFS in these patients than in the historical controls.

6.3. TTFields Combined with Targeted Therapy

The use of TTFields combined with the VEGF inhibitor bevacizumab in the treatment of GBMs has attracted considerable attention, and many phase 2 trials are being conducted. One such trial was a retrospective study of 48 patients with rGBMs. The two cohorts received TMZ, bevacizumab, irinotecan, and TTFields (TBI + T) or bevacizumab-based

chemotherapy with TTFields. The median OS and PFS for patients treated with TBI + T were 18.9 months and 10.7 months, respectively, compared with 11.8 months and 4.7 months in the bevacizumab group [40]. Another study divided patients with rGBMs into two groups: patients treated with NovoTTF-100ATM and bevacizumab and patients treated with NovoTTF-100ATM, bevacizumab, 6-thioguine, lomustine, capecitabine, and celecoxib (TCCC). The results showed that tumors were smaller in patients treated with NovoTTF-100ATM, bevacizumab, and TCCC. Although the compliance of the cohort receiving NovoTTF-100ATM, bevacizumab, and TCCC was poor, they exhibited a longer median OS (10.3 vs. 4.1 months) and a longer median PFS (8.1 vs. 2.8 months) [41]. Elzinga and Wong [42] reported that the addition of TTFields therapy led to resolution of the recurrent cystic GBM, as well as most of the surrounding cerebral edema, in a patient with an unfavorable response to bevacizumab. Ansstas and Tran [43] reported that eight patients with rGBMs who exhibited disease progression on bevacizumab underwent treatment with TTFields alone. Following TTFields therapy, the median patient OS from the last dose of bevacizumab was approximately 8 months, which was almost twice that in historical controls with bevacizumab failures.

Other targeted agents combined with TTFields therapy have also been explored. For instance, Meletath et al. [44] reported a case in which TTFields was used in combination with dabrafenib, an inhibitor of BRAFV600E, and produced a significant clinical and radiological response in patients with advanced gliomas with BRAFV600E mutations. Kim et al. [45] confirmed that sorafenib combined with the use of TTFields improved the treatment outcome of GBMs by downregulating STAT3 expression levels in vivo and in vitro. Kessler et al. [46] demonstrated that spindle assembly checkpoint inhibition augmented the effect of TTFields on U-87MG and GaMG cells.

6.4. TTFields Combined with Immunotherapy

Recently, immunotherapy has become a hot spot and forefront of research with its success in treating many solid and blood cancers. Various immunotherapies have been investigated to treat GBMs, and several clinical trials have been conducted, including those for checkpoint inhibitors, vaccines, adoptive lymphocyte transfer, and oncolytic therapy, although with few encouraging findings [47]. Although no clinical trials have been published involving the use of immunotherapy in combination with TTFields, it cannot be denied that this new method may produce some breakthroughs, considering the effect of TTFields on the immune TME [8][13][48], which is promising.

6.5. TTFields Combined with Other Treatment Modalities

The skull is one of the layers between electric arrays and the tumor bed that presents the most prominent attenuation of the electric intensity of TTFields [49]. Korshoej et al. [50] reported a trial testing the combination of skull remodeling surgery (SR surgery) with TTFields in patients with rGBMs of first relapse. SR surgery was performed by drilling five 15 mm diameter holes above the tumor resection cavity to reduce the resistance in TTFields. This phase 1 trial (NCT02893137) showed that the combination of SR surgery and TTFields treatment was safe and feasible and improved patient OS, with a median OS of 15.5 months and a median PFS of 4.6 months. On this basis, the OptimalTTF-2 phase 2 trial (NCT0422399) was launched in November 2020 and is currently ongoing. Jo et al. [51] evaluated the effects of combining the use of hyperthermia and TTFields on GBM cells, demonstrating that combined therapy induced inhibition of cell migration, higher apoptosis rates, and increased downregulation of STAT3 expression levels than the use of hyperthermia or TTFields alone.

6.6. Use of TTFields in Pediatric GBM Patients

Fewer studies have been conducted using TTFields to treat pediatric GBM patients than adult GBM patients. Green et al. [52] reported the use of TTFields and chemotherapy and/or radiotherapy in pediatric patients with high-grade gliomas, showing that all patients tolerated TTFields well. Recently, Gott et al. [53] reported that the use of TTFields in a 3-year-old patient with H3K27 M-mutated diffuse midline glioma was feasible and safe.

7. Identification of Distinct Response to TTFields Treatment

Studies were conducted to identify predictive biomarkers of the efficacy of the use of TTFields in GBM patients. A retrospective review of 149 patients with IDH wild-type rGBMs, of whom 29 were treated with TTFields, found that PTEN mutation might predict prolonged postprogression survival better in the TTFields-treated group than in the groups subjected to other treatments, whereas patients with PTEN wild-type rGBMs showed no improvements [54]. A recent genomic analysis revealed that molecular driver alterations in NF1, as well as wild-type PIK3CA and EGFR, were associated with improved response to TTFields [55]. Radiological examinations were also applied to detect treatment response to TTFields as early as 2–3 months after the start of TTFields treatment, and the findings included metabolic change of the reduction in the choline/creatine ratio in ndGBMs using physiologic and metabolic MRI [56] and a decrease

in tryptophan uptake in rGBMs based on amino acid PET scanning with alpha[C-11]-methyl-L-tryptophan [57], although more clinical studies are required for these potential applications in the future.

8. Safety/Adverse Events

The use of TTFields promotes improved clinical outcomes and exhibits no known systemic toxicity. The most predominant local adverse events (AEs) associated with the use of TTFields treatment for GBMs are dermatologic events due to the continuous contact between the arrays and the shaved scalp. TTFields-associated skin reactions include allergic or irritant dermatitis; xerosis or pruritus; mechanical lesions; hyperhidrosis; and, more rarely, skin erosion, infections, and ulcers [58][59][60]. The causes of dermatologic AEs are diverse, including a moist occluded scalp environment, chronic use of steroidal medicine and systemic anticancer drugs, and irritation of the skin at the site of the previous surgical wound by the liquid medium of the electrode array [61][62][63][64][65][66].

Because survival benefits positively correlate with the continuity of TTFields treatment [25], continuous use is highly recommended, and skin events are somewhat inevitable. Concerns regarding skin reactions should not be a barrier to continuing TTFields therapy, as most of the dermatologic AEs are mild to moderate (grade 1/2), while very few patients (only 2% in EF-14) experience severe skin involvement (≥grade 3 AE) [4][59].

Although TTFields therapy results in dermatologic AEs in a large number of patients with GBMs, dermatologic AEs are mostly reversible and manageable [16]. Prophylactic interventions, in combination with early identification and prompt topical therapies, help maintain improved skin conditions, supporting patient compliance with continuous TTFields therapy. Recommendations for preventing TTFields-associated dermatologic AEs include patient and family education, proper shaving to avoid cuts, cleaning and drying of the scalp, prevention of skin infection, scar reduction, and timely array repositioning [59][65]. An increase in scalp dose was detected when patients were treated with radiation and concurrent TTFields, and a scalp-sparing protocol could optimally mitigate skin toxicity [67].

9. Health-Related Quality of Life

It is crucial to address the effect of TTFields treatment on patient well-being, as reflected by health-related QoL (HRQoL), in addition to the prolongation of life. As reported in EF-11, there were no differences observed in global health and social functioning domains between TTFields treatment and chemotherapy groups, as assessed using the EORTC QLQ-C30 questionnaire. The scores of cognitive, emotional, and role functioning were higher, whereas physical functioning was slightly worse in the TTFields group [16]. In EF-14, no significant differences were detected between the TTFields plus maintenance TMZ group and the group treated with TMZ alone with respect to HRQoL, except that more incidences of itchy skin were observed in the TTFields group [68]. Recently, a large-scale, real-world study of HRQoL in GBM patients using TTFields revealed that a longer duration of TTFields use was strongly associated with improved HRQoL, especially in progressed patients [69]. Because patients need to continuously carry the electric device, remain alopecic, and avoid wearing wigs, TTFields-related negative impacts on patient QoL, apart from the health-related aspects, also need to be investigated [70].

10. Real-World Cost-Effectiveness

Although TTFields technology is evolving and discount options are provided, it remains an extremely high-cost treatment, with prices that are far higher than those of the conventional treatment modalities for GBMs. Studies from France showed that the incremental cost-effectiveness ratio (ICER) of TTFields is at approximately EUR 510,273 to EUR 549,909 per life year gained, which is largely outside the widely recognized willingness-to-pay thresholds [71][72], unlike the ICER of TMZ-assisted radiotherapy, at approximately USD 55,000 per life year gained [73]. However, researchers from the United States demonstrated that this value for TTFields was only USD 150,452 per life year gained, which is within the willingness-to-pay thresholds [74]. Because the existing results are conflicting, future studies concerning the cost-effectiveness of TTFields are still needed to acquire a more accurate assessment in real-world settings. Substantial price regulation by health administrations is urgent and may assist in making this promising therapy more affordable and accessible to GBM patients, especially in developing and less developed countries. It is also important to maintain incentives for innovation while managing product prices.

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