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Tumor treating fields: a novel treatment modality and its use in brain tumors

Andreas F. Hottinger, Patricia Pacheco, Roger Stupp

[1]*CHUV University Hospital and Lausanne University, Departments of Clinical Neurosciences and Oncology, Lausanne, Switzerland (A.F.H., P.P.); University Hospital Zurich and University of Zurich, Department of Oncology, Zurich, Switzerland (R.S.)*

Corresponding Authors: Andreas F. Hottinger, MD-PhD, Departments of Clinical Neurosciences, and Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 46, 1011 Lausanne, Switzerland (andreas.hottinger@chuv.ch); Roger Stupp, MD, Department of Oncology, University Hospital Zurich, Raemi-Street 100, 8091 Zurich, Switzerland (roger.stupp@usz.ch)

Tumor treating fields (TTFields) are low-intensity electric fields alternating at an intermediate frequency (200 kHz), which have been demonstrated to block cell division and interfere with organelle assembly. This novel treatment modality has shown promise in a variety of tumor types. It has been evaluated in randomized phase 3 trials in glioblastoma (GBM) and demonstrated to prolong progression-free survival (PFS) and overall survival (OS) when administered together with standard maintenance temozolomide (TMZ) chemotherapy in patients with newly diagnosed GBM. TTFields are continuously delivered by 4 transducer arrays consisting each of 9 insulated electrodes that are placed on the patient's shaved scalp and connected to a portable device. Here we summarize the preclinical data and mechanism of action, the available clinical data, and further outlook of this treatment modality in brain tumors and other cancer indications.

Preclinical Data and Mechanism of Action

Living cells consist of charged or polar molecules and ions and thus are responsive to electrical fields and currents. Electric activity of cells plays a key role in many essential biological processes including cell division. Cellular processes can be influenced by electric fields. The overall effect will depend upon the magnitude of the potential difference between the 2 electrodes (field intensity) and the frequency: at very low frequencies (<1 kHz) excitable cells such as neurons or myocytes will be depolarized.[1] Cardiac pacemakers or deep brain stimulators work in this range of frequency. At very high frequencies (>MHz), heat is generated in the tissues due to dielectric loss. This property is mainly used for radiofrequency ablation or diathermy treatments.[2] The alternating frequency of electrical fields at intermediate frequencies (range, 10–1000 kHz) is too fast to induce cell depolarization and induces no or only minimal heat by dielectric loss. In the past, these frequencies were considered to have no interaction with biological processes.[3] Nevertheless, a number of effects have been observed in biological tissues such as microscopic particle alignment,[4] cell rotation,[5] and transient pore formation in cell membranes.[6] At low intensities (2V/cm) and intermediate alternating frequencies (between 100–300 kHz), Kirson and Palti et al. demonstrated a specific inhibiting effect on cell division in cancer cell culture models.[7]

Tumor treating fields (TTFields) are alternating, low-intensity, intermediate frequency electric fields that aim to disrupt cell division and inhibit tumor growth. In initial experiments, exposure of a variety of tumor cell lines to TTFields was shown to exert a profound growth inhibitory effect by inducing cell cycle arrest and apoptosis, while no effect was induced on non-dividing cells.[7] These in vitro observations could also be confirmed in vivo in mice and rabbit tumor models.[8] Further studies demonstrated that the growth inhibitory effect is largely mediated by interference on the mitotic spindle apparatus. TTFields will target proteins with large dipole moments (ie, septins and the spindle microtubules, components essential in the metaphase and anaphase stages of the mitotic cycle for separation and equal distribution of chromosomes).[9,10] Furthermore, inhibition of the polymerization of microtubules interferes with proper assembly of the mitotic spindle apparatus. In telophase, during cytokinesis the hourglass shape taken by the daughter cells that are about to separate induces a nonuniform electric field that is strongly enhanced at the level of the furrow region (→ fig. 1). This results in dielectrophoretic forces that may attract charged molecules from the cytosol and compromise normal cytokinesis.[7] The antitumoral effect results from disruption of the microtubular assembly during mitosis, blocking formation of the mitotic spindle apparatus and blocking separation of the 2 daughter cells.[9] This effect also results in abnormal chromosomal segregation and reduced clonogenic potential of the cell's progeny.[10]

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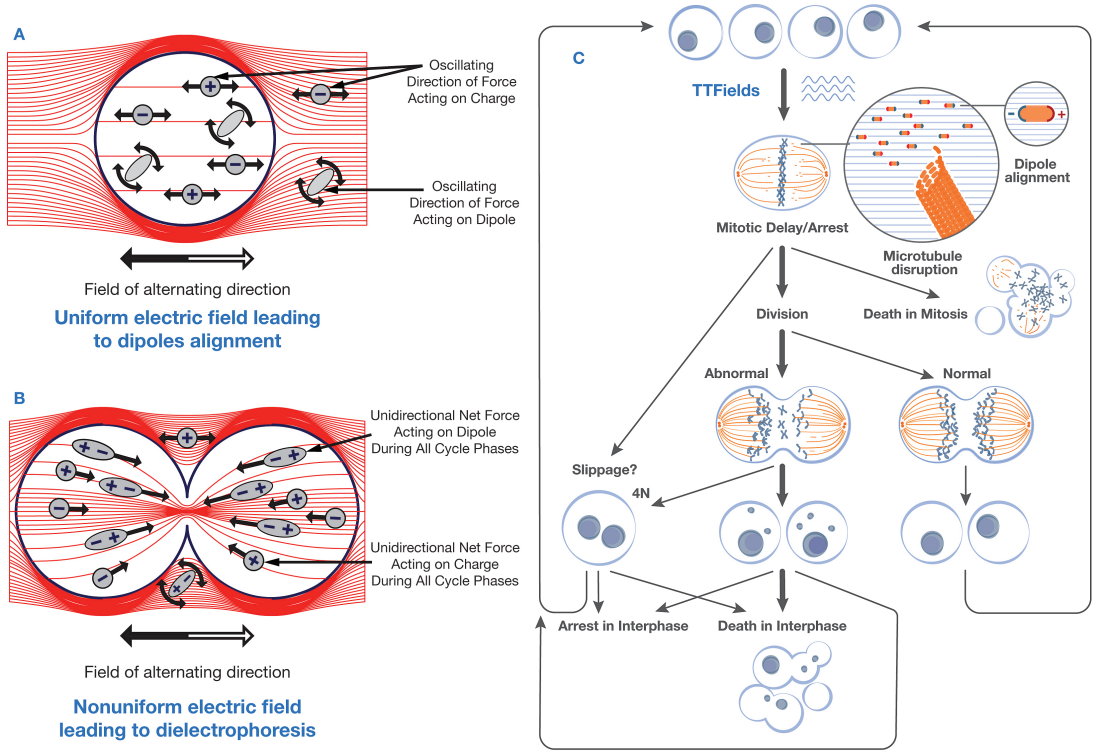

Fig. 1. Mechanisms of action of tumor treating fields in and around quiescent and dividing cells. Inside quiescent cells (1A), the field is uniform, and the oscillating electric forces result only in "vibration" of ions and dipoles (the forces associated with each half cycle are denoted with white and gray arrows). In contrast, the nonuniform field within dividing cells (1B) induces forces pushing all dipoles toward the furrow. [reprinted with permission from ref. 12] 1C: Tumor treating fields (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. Cells can die in mitotic arrest or progress to cell division leading to abnormal aneuploid progeny (highlighted by bold arrow). Abnormal daughter cells die in the subsequent interphase, undergo a permanent arrest or proliferate through additional mitosis where they will be subjected to further TTFields assault. [adapted with permission, refs. 11 and 12]

Animal models of various tumors, including glioblastoma (GBM), non–small cell lung cancer, pancreatic cancer, and malignant melanoma confirmed the inhibition of tumor growth or metastatic seeding when externally applied TTFields were delivered at the appropriate frequencies.[11] As an example, an experimental model of rats with intracranially inoculated GBM cells treated with TTFields at a frequency of 200 kHz over 6 days showed smaller tumors compared with untreated rats.[12] The inhibitory effect was significantly increased when 2 or more, rather than 1 field directions were used.[12] Importantly, synergistic antitumor activity was demonstrated when TTFields were applied in conjunction with cytotoxic chemotherapy with paclitaxel, doxorubicin, cyclophosphamide, or dacarbazine (DTIC).[13]

In summary, TTFields will block the mitotic cell cycle, in particular during metaphase, anaphase, and telophase. This will result in cell cycle arrest or delay in cell division and interfere with organelle assembly, particularly the spindle apparatus (fig. 1 C). The consequences are inadequate cell division and unequal chromosome distribution. Ultimately, cells will die in apoptosis. In order to have an optimal treatment effect, the field intensity and frequency needs to be adapted to the tumor type and cell properties (eg, cell size). The optimal frequency to maximize the antitumor effect is inversely correlated with cell size and when the incident angle of the electrical field is perpendicular to the mitotic plate.[7]

As the cell division may occur at any time, prolonged exposure to the electrical fields is required for maximal effect. For the delivery of TTFields, a portable and battery-powered device has been developed (→ fig. 2). The electric field is applied to the brain through 4 transducer arrays with 9 insulated electrodes each and continuous temperature sensing fixed to the patient's shaved scalp.

Clinical Experience:

Glioblastoma as a Proof of Concept Model

In the very first clinical application, TTFields treatment was applied to patients with cutaneous metastases of melanoma or breast cancer. Tumor shrinkage or even complete disappearance was demonstrated.[12,14] However, metastatic cancer is a systemic disease, thus most effects of application of TTFields would be expected to be seen in diseases or situations where primarily locoregional control is warranted. Primary brain tumors—and notably glioma—rarely metastasize; recurrence in the brain is the predominant cause of treatment failure and was chosen as the first disease in which the effect of TTFields could be investigated prospectively.

Fig. 2. Tumor treating fields (TTFields) device (2nd generation Optune) and its clinical use TTFields are administered by 4 transducer arrays placed on the shaved scalp and connected to a portable device generating 200 kHz electric fields within the brain. The position of the transducer arrays are determined by the localization of the tumor using a mapping software (NovoTal™). (Photo with permission from the patient)

In a computational model, the optimal frequency of TTFields for GBM was found to be in the range of 200 kHz. The field strength should be ≥ 1 V/cm. These TTFields are able to penetrate into the deep brain tissue from the surface of the scalp. The computational model also revealed inhomogeneous fields with intensification of the field strength near the ventricles as a result of the high conductivity of the cerebrospinal fluid. Necrotic areas and edematous regions also showed high conductivity of the TTFields. In contrast, areas with high cellularity showed lower conductivity.[15]

Following the demonstration of feasibility in a small pilot trial, the clinical merits of this innovative cancer treatment were evaluated in 2 pivotal randomized trials in recurrent (EF-11) and newly diagnosed (EF-14) GBM. In our summary, herein we always refer to the results of the intent-to-treat population (ITT); for details on the predefined per protocol populations, the reader is kindly directed to the respective original publications[16,17] (→ table 1).

TTFields in Recurrent Glioblastoma

The EF-11 Trial

For this trial, GBM patients with progressive or recurrent disease after initial treatment with radiotherapy and TMZ chemotherapy were eligible. Patients may have received several lines of prior chemotherapy. A total of 237 patients were then randomized 1:1 to either the novel TTFields therapy (120 patients) or to the best available treatment (117 patients) according to the local oncologist's best choice (active control, fig. 3A). The primary endpoint of the trial was OS. Patients' median age was 54 years, with a median KPS of 80% (range, 50–100%). Eighty-eight percent of patients had received 2 or more lines of prior chemotherapy including prior bevacizumab in 18% of patients. With a median survival of only 6.6 and 6.0 months in the TTFields and the control arm, respectively (hazard ratio: 0.86 [95% CI, 0.66–1.12), *P*=0.27) and a 1-year survival rate of only 20% in both groups, the trial failed to demonstrate superiority over "established" or commonly used chemotherapy

Table 1. Results of EF-14 & EF-11 trials

Trial	Treatment arm	Number of patients	Progression-free survival		Overall survival		
			Median	at 6 months	Median	at 1 year	at 2 years
EF-14: newly diagnosed [Interim data set]	TTFields & TMZ	210 (466 total)	7.1 mo*	57%	19.6 mo	75%	43% (36–50)
	Maintenance TMZ	105 (229 total)	4.0 mo*	34%	16.6 mo	69%	29% (21–39)
	Hazard ratio		0.63 (CI, 0.43–0.89)		0.74 (CI, 0.56–0.98)		
	P value		< 0.01 (stat. significant)		0.0004 (stat significant)		
EF-11: recurrent GBM	TTFields	120	2.2 mo.	21%	6.6 mo*	20%	8%
	chemotherapy¶	117	2.1 mo.	15%	6.0 mo*	20%	4%
	Hazard ratio		0.81 (CI,0.60–1.09)		0.86 (0.66–1.22)		
	P value		0.13 (not significant)		0.27 (not significant)		

Abbreviations: CI, 95% confidence interval; mo, months; TMZ, temozolomide; TTFields, Tumor Treating Fields; EF, electrical fields
¶: best physician's choice chemotherapy as active control
*: primary trial endpoint, other values are predefined secondary endpoints

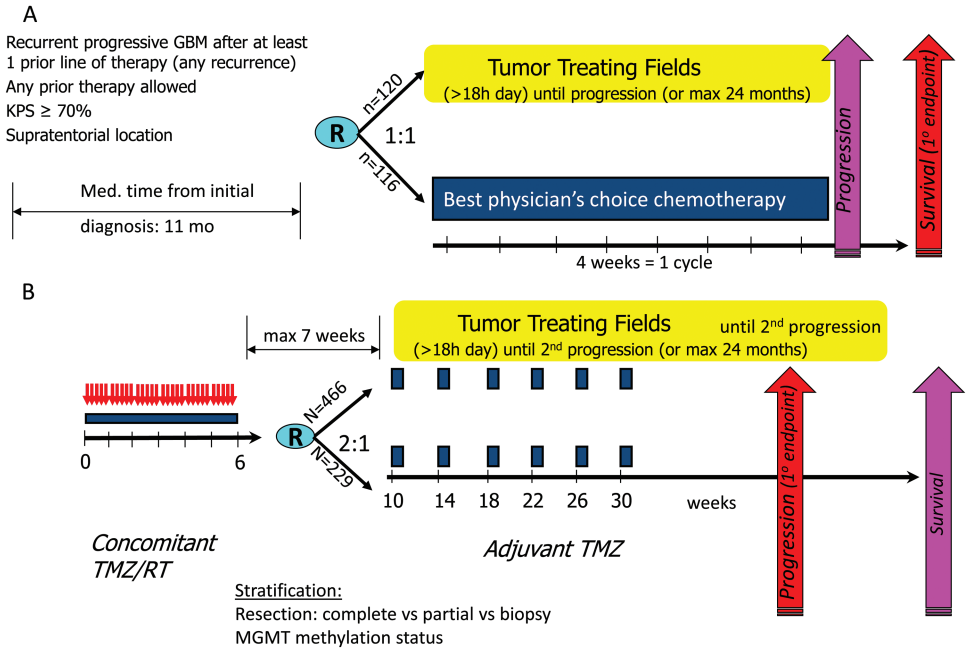

Fig. 3. Design of the pivotal trials in GBM. A: EF-11 Trial Design B: EF-14 Trial Design

regimens. The median duration of TTFields administration was only 2.3 months (95% CI, 2.1– 2.4) with tumor progression as the primary reason for discontinuation of treatment. Still it showed objective responses with TTFields alone in 14% of patients compared with 9.6% in the control arm. The study demonstrated safety and feasibility of TTFields in a large multicenter setting.

The design and conduct of the EF-11 trial had some inherent limitations: numerous prior treatment lines were allowed and led to a heterogeneous patient population. More than 40% of patients were included after the third recurrence, including many patients who had failed prior bevacizumab therapy. Thus, most patients suffered from very advanced disease and had only few available treatment options and limited life expectancy. In the absence of a commonly accepted standard treatment for recurrent GBM, the control patients were to receive the best available systemic therapy according to the current local practice. The heterogeneity of treatments prescribed to the control patients reflects this fact: about one-third of the control patients received bevacizumab alone or in combination, 25% nitrosoureas, and 11% re-exposure to TMZ. A number of patients were discontinued from TTFields therapy very early (after <1 month of therapy), presumably due to absence of a treatment response (rather than true tumor progression) based on skepticism of the investigators. It is known that TTFields take a prolonged period of time until its effects can be clinically demonstrated or that delayed responses may occur after initial radiological tumor growth; thus, some patients may have discontinued TTFields treatment prematurely.

Based on the results of the EF-11 trial, the US Food and Drug Administration (FDA) felt that these results provided reasonable

assurance that the benefits of TTFields outweigh its risks when administered as monotherapy in place of standard medical therapy and therefore approved TTFields in 2011 (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm251669.htm).

TTFields in Daily Practice: PriDE Dataset

After FDA approval, TTFields became commercially available in the United States, and Mrugala et al summarized the daily practice experience on 457 patients treated at 91 US institutions (Patient Registry Dataset; PRiDe).[18] Interestingly, patients' age and performance status were similar in this dataset and in the EF-11 trial; however, treatment with TTFields was initiated much earlier in the course of the disease. One-third of patients were treated at first recurrence (compared with 9% in the EF11 trial). Overall, median survival was 9.6 months, and the subgroup of patients who were treated at first recurrence (n=152) had a median survival of 20 months.[18]

TTFields in Newly Diagnosed GBM (EF-14 Trial)

This open label phase 3 study in patients with newly diagnosed GBM was initiated while the trial for recurrent disease was still ongoing. For practical reasons (interference of the electrodes during radiotherapy), patients had to be randomized only after completion of standard concomitant TMZ chemoradiotherapy to standard maintenance TMZ chemotherapy (for 6–12 cycles) with or without concomitant administration of TTFields (fig. 3B). The primary endpoint was PFS, and OS was a powered secondary endpoint. Eligible adult patients (KPS ≥ 70%, supratentorial tumor location) had to be progression-free after the end of chemoradiotherapy, thus excluding the patients with the worst prognosis. After stratification by extent of resection (biopsy, partial resection, gross total resection, determined on MRI 24–48 hours postsurgery) and *MGMT* status (methylated, unmethylated, unknown) patients were randomized at a ratio of 2:1 within 3–7 weeks from the last day of radiation. Patients assigned for TTFields therapy received additional instruction and technical support for the use of the device by a device specialist (technician) during the first weeks of treatment and thereafter with monthly visits. This support was limited to technical aspects of the device and assistance with the application of arrays.

A total of 695 patients from 83 centers across the world were included between July 2009 and November 2014. More than half of the patients came from the United States. The medical follow-up was similar in both treatment arms. It included monthly clinic visits for complete physical examination and blood hematology and chemistry analyses. A mini-mental status examination (MMSE), quality of life evaluation (EORTC QLQ-C30 questionnaire and the brain-specific module BN-20) were performed at baseline and every 3 months thereafter.[19,20] MRI and disease assessment using the Macdonald criteria were to be performed every 2 months. All treatment-related clinical decisions were based on local interpretation of imaging; however, a blinded central imaging and disease assessment review determined the date of progression. Patients experiencing tumor progression were offered second-line treatment according to local practices. Patients were allowed to continue TTFields treatment beyond first progression based on the prior experience of pseudoprogression and delayed responses. For the purpose of the trial, the date of first progression, as assessed by the independent review panel, was considered the primary endpoint.

The baseline patient characteristics were well balanced between the 2 groups. In both groups, 66% were male, and the median age at inclusion was 57 years (range, 20–83y), and the median KPS was 90%. Sixty-four percent of patients underwent gross total resection, and 11% had biopsy only. Central *MGMT* gene promoter methylation analysis was available for 72% of patients. *MGMT* was methylated in 39% of patients in the TTFields/TMZ group and in 41% of the control TMZ group. The median time from end of radiation therapy to randomization was 36 and 38 days in the TTFields and control groups, respectively. The median time from randomization to initiation of TTFields was 5 days. Median time from diagnosis of GBM to randomization was 3.8 months in both groups (ranges, 2.0–5.7 and 1.4–5.7 months in the treatment and control groups, respectively). Of note, 53% of patients were randomized after initiation of the first cycle of TMZ (as allowed by the protocol). Per protocol, TTFields treatment was continued up to the second progression in two-thirds of the patients; the median duration of treatment with TTFields was 9 months (range, 1–58 mo). Three-quarters of patients receiving treatment with TTFields were adherent to therapy as prescribed (ie, wearing the device ≥ 18 hours per day on average during the first 3 treatment months) (*n*=157/210).

At a prespecified interim and futility analysis to be performed once the first 315 randomized patients reached a minimum follow-up of 18 months, a significant improvement in progression-free and overall survival was seen; consequently the independent data monitoring committee recommended that the trial be terminated early for success and that patients be allowed to cross over to the TTFields arm. In the interim analysis, the ITT median PFS was increased by 3.1 months in the TTFields group with a median PFS of 7.1 months (95% CI, 5.9–8.2 mo) compared with 4.0 months (95% CI, 3.3–5.2 mo) in the control group (HR, 0.62 [98.7% CI, 0.43–0.89]; *P*=.001). As a direct consequence, patients in the control group received a median of 4 cycles of TMZ (range, 1–24), whereas patients in the TTFields group received a median of 6 cycles (range,1–26) of TMZ. Median OS from randomization (ITT) was 19.6 months (95% CI, 16.6–24.4 mo) in the TTFields plus TMZ group compared with 16.6 months (95% CI, 13.6–19.2 mo) in the TMZ control group (HR: 0.74 [95% CI, 0.56–0.98]; *P* =.03). The percentage of patients alive at 2 years following enrollment was 43% in the TTFields/TMZ group and 29% in the TMZ alone group (*P*=.006)[17] (→ fig. 4). At first progression, 67% of the patients in the TTFields/TMZ group received a second-line therapy compared with 57% of patients in the TMZ control group. The type of salvage chemotherapy offered was balanced between the 2 groups: about 40% of second-line therapies included bevacizumab and about 40% nitrosoureas.

Preliminary subgroup analyses showed that the positive effect observed on PFS and OS by the addition of TTFields was not restricted to any subgroup of patients: in particular neither age, performance status, *MGMT* methylation status nor extent of resection was predictive for a better treatment

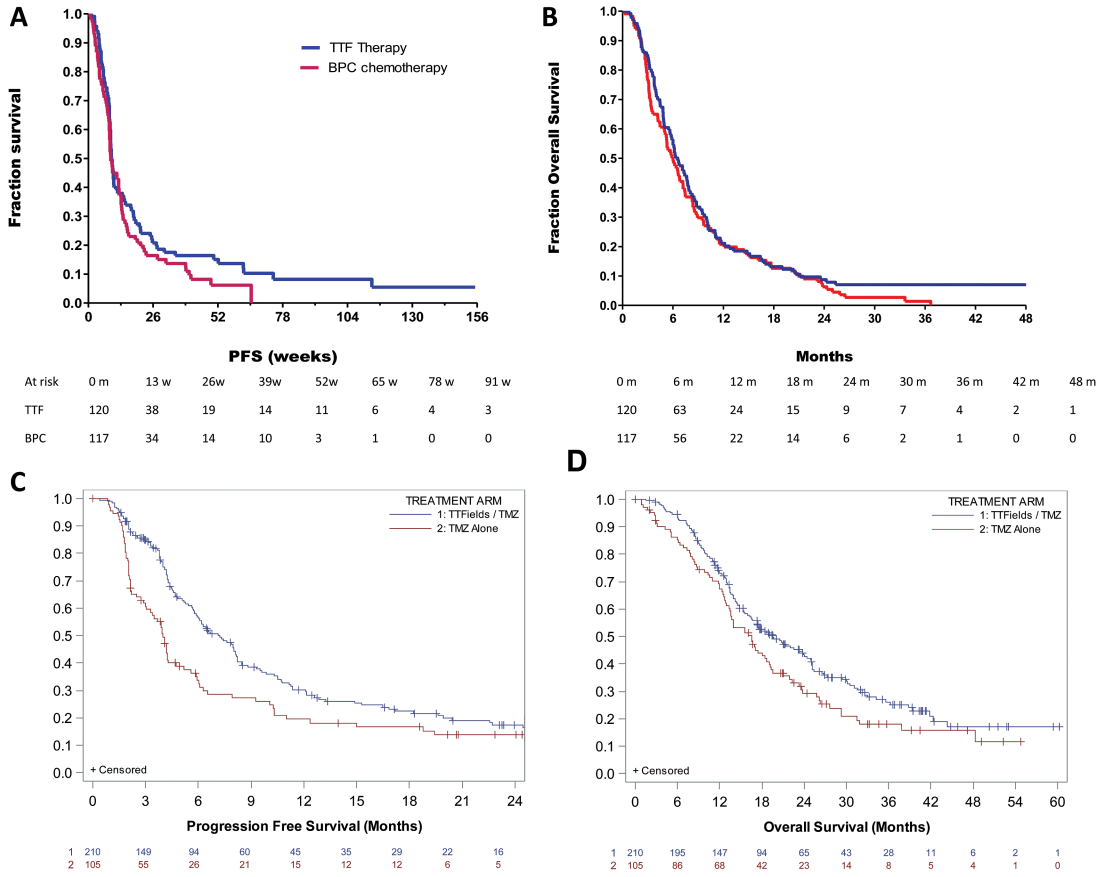

Fig. 4. Progression-free and overall survival in EF-11 (A&B) & EF-14 (C&D) trials. EF-11 trial: Progression-free survival (A) and overall survival (B) of the intent-to-treat population. Hazard ratio for overall survival: 0.86 (CI, 0.66–1.12, *P*=0.66) [Reprinted with permission from ref, 16] Progression-free survival (C) and overall survival (D) of the intent-to-treat population in the EF-14 trial (interim data set). Hazard ratio for progression 0.63 (95%CI 0.43–0.89, *P*<0.01); for survival 0.74 (CI 0.56–0.98, *P*=0.0004). [Reprinted with permission, ref. 17]

effect. However, the sample size of the interim dataset may not be large enough to identify meaningful subgroups, and detailed subgroup analyses are to be performed on the final and validated dataset. Due to the 2:1 randomization, the control arm comprised only 105 patients, which limited the ability to perform formal subgroup analyses. In the final dataset, the control group will comprise 229 patients. Before publication of the interim analysis, the overall dataset of 695 randomized patients was statistically scrutinized. It was concluded that the results are unlikely to change substantially once the whole dataset reaches a mature follow-up (see supplemental material, reference[17]). In October 2015, the FDA approved TTFields for use in newly diagnosed GBM patients.

Toxicity, Support, and Quality of Life with TTFields

Toxicity related to TTFields therapy consisted, by the nature of this treatment, mainly of local skin irritation. This is usually mild, self-limiting, easily manageable with local application of steroid-containing ointments, and may require an occasional treatment break for a few days. In the EF-11 trial, skin toxicity was reported in 16% of patients (grade 3 in only 2%). In the EF-14 trial for newly diagnosed GBM patients, where the treatment exposure was longer than that for recurrent disease, grades 1 and 2 skin reactions were reported in 43% of patients. Severe (grade 3) reactions were again seen in only 2% of patients. Examples of allergic contact dermatitis, irritant contact dermatitis, folliculitis, and erosions are shown in → fig. 5.[21]

Importantly, when compared with TMZ maintenance treatment alone, the addition of TTFields did not result in any modification of the overall incidence, severity, and distribution of side effects in patients with newly diagnosed GBM. The incidence of seizures was identical in both treatment groups (7% in the TTFields group vs 8% in the control group). Some nonspecific adverse effects including nervous system disorders such as grade 1–2 headache (21% in the experimental group vs 14% in patients with TMZ alone), mild anxiety, confusion, insomnia, and headaches were reported more frequently in the patients treated with TTFields plus TMZ and occurred mainly at the time of therapy initiation.

Given the need for continuous and long-term use of the TTFields device, the quality of life of patients has been a concern. In the EF-11 trial, there were no differences in global health and social functioning between patients treated with TTFields or chemotherapy. In fact, cognitive and emotional functioning was higher in the TTFields group than in the chemotherapy group.[16] In the EF-14 trial, preliminary quality of life

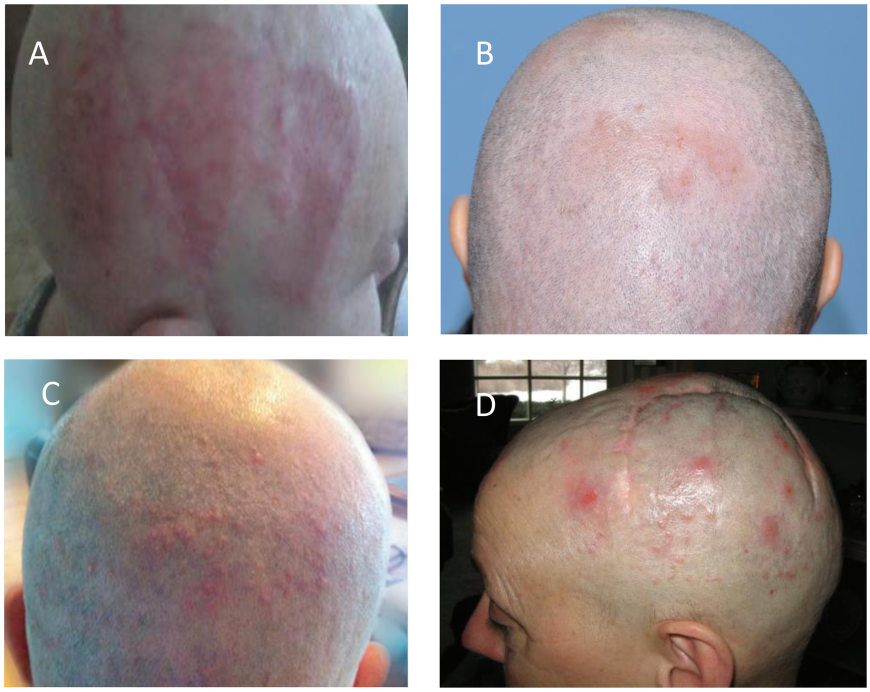

Fig. 5. Skin toxicities observed under tumor treating fields (TTFields). Some mild-moderate (grade 1–2) skin reaction is observed in up to half of patients (in EF-14 trial reported in 43%, grade 3 in 2%); however, it is usually self-limiting and resolves by removing the electrodes for a few days and applying local steroid-containing ointments. The images represent a few examples of skin reactions. (A) allergic contact dermatitis (B) irritant contact dermatitis (C) folliculitis (D), erosions [Reproduced from ref. 21].

data showed identical scores at baseline and at 12 months for patients in the treatment and control groups at the levels of cognitive, emotional, physical, and social functioning.[22] Moreover, the global health status showed an improvement at 3 and 6 months in comparison with baseline for patients treated with TTFields and TMZ, whereas patients in the control group showed a decrease in global health status over the same time period.

Discussion

More than a decade ago, in vitro and in vivo experiments in tumor cell lines and in mouse, rat, and rabbit tumor models have demonstrated antitumor activity of low-intensity, intermediate-frequency alternating electric fields. Dividing cells are arrested in metaphase and anaphase, assembly and function of the mitotic spindle are perturbed, and cells ultimately undergo apoptosis. However, in order to translate these findings into a clinically useful treatment, certain conditions must be met: (1) TTFields need to be delivered in a continuous manner to achieve the expected cytotoxic effect; (2) TTFields can only be applied to certain areas of the body, and this (3) requires the possibility to affix transducer array to the skin of the patient over the area of the tumor. As GBM is a disease that remains confined to the CNS and the scalp offers an easy application site for long-term use of transducer arrays, it appeared to be the ideal candidate to serve as a proof of concept demonstration of TTFields.

Two pivotal randomized trials have been reported to date. In recurrent disease, the trial has not demonstrated improved outcome compared best physicians' choice chemotherapy. However, TTFields when administered as part of the initial treatment in newly diagnosed patients showed a consistent prolongation of both PFS and OS (hazard ratio for death HR: 0.74 (95% CI, 0.56–0.98). Giving TTFields early in the disease course allows for prolonged exposure, and the in vitro observed synergy with TMZ may further enhance its efficacy. The median treatment duration in recurrent disease was only 2.3 months compared with 9 months in newly diagnosed GBM. Still, TTFields alone in recurrent disease have shown objective responses in 14% of patients, consistent or even numerically higher than that observed in other trials using alkylating agent chemotherapy with lomustine [23,24] or TMZ.[25] In the PriDE dataset reflecting routine clinical use of the device, patients who received TTFields at first recurrence were treated for a median of 6.2 months and had a median survival of 20 months, comparing favorably with recent trial results investigating other novel agents. However, a strong selection bias and inclusion of patients with pseudoprogression after initial TMZ chemoradiotherapy cannot be ruled out in this uncontrolled routine practice patient population.[26] The best results with this novel treatment modality have been achieved when TTFields were administered early in the disease course in combination with standard maintenance TMZ therapy,[17] similar to that shown 10 years ago when TMZ was added to standard radiotherapy.

It may be scientifically regrettable that the trial had to be open label and did not include a double-blinded control group. However, a sham device would neither be practically feasible (some heating of the electrodes is inevitable; technically

savvy patients would rapidly figure out whether there is any current flowing), nor acceptable for patients, caregivers, and ethics committees given the perceived burden of shaving the scalp and replacing transducer arrays every 3 days. Whereas some placebo effect might be expected on subjective endpoints, such as quality of life or cognitive function, it is difficult to envision an effect on objective endpoints such as OS or PFS (especially when progression was determined by blinded central radiologists).[27] Requiring a placebo or sham device would also mean a paradigm shift in conducting clinical trials with survival endpoints in oncology. Sham radiation therapy would be required for RT trials, and a placebo control would only be feasible for agents that have rare and mild toxicities.

Indeed, patients receiving TTField therapy received some additional assistance by the technical support team providing the TTFields device and arrays. However, this support was on average limited to 1 visit per month, and 1–2 extra visits or contacts at the initiation of treatment. Most patients became rapidly independent and self-proficient with the device; on average, there was a median of 1.12 visits per patient and month of treatment (range, 0.5–4 visits per month).

It is highly unlikely that this additional technical support would translate into a 3-month prolongation of median survival, which is in the range of the benefit seen with the introduction of TMZ.[26] In a contemporary randomized open-label non-placebo-controlled trial, patients in the experimental arm received twice weekly i.v. administration of cilengitide. Still, this did not translate into any benefit in outcome (hazard ratio for death: 1·02; 95% CI 0·81–1·29).[28]

It might have been possible that the control arm in EF-14 performed exceptionally poorly. We thus scrutinized the data and compared the performance of the control arms of contemporary trials. The patient characteristics of both the TTFields and control groups were comparable with other clinical trials for newly diagnosed GBM patients in respect to all known prognostic factors (distribution of age, performance status, extent of resection, *MGMT* status).

One important difference in the EF-14 trial compared with many other reports is that patients were randomized only after the end of chemoradiotherapy, and for most patients the first cycle of maintenance TMZ had already been started at time of randomization. This implies that all patients with early tumor progression during the concomitant radiation and TMZ part of the treatment were excluded from this trial. On the other hand, the 3.8 months from diagnosis to randomization will need to be added to survival times in order to have an estimate of the individual patients' effective outcome. The PFS of 4.0 months (from randomization) observed in the control group of the EF14 trial is numerically shorter (likely due to the independent imaging review and assessment of progression) but overall comparable to the observed PFS of 5.5 months observed in the RTOG 0525 trial,[29] a trial that also randomized patients only after completion of the concomitant radiochemotherapy part of treatment. Moreover, in both trials, the OS was identical at 16.6 months for the control groups. It is therefore unlikely that the benefit observed in the treatment group of the EF14 trial can be attributed to patient selection and a poor outcome of patients in the control arm.

For many experts in neuro-oncology who were not involved in the trial, the most important criticism to TTFields was the requirement for patients to wear a device and their presumed stigmatization. Having to shave the scalp is indeed a psychological barrier, although in oncology, for decades we have been using cytotoxic agents that are inducing complete hair loss of all body hair and not only the scalp. In our experience, patients and families rapidly adapt to wearing the device and are able to continue their regular activities including work and even sports. Preliminary analysis of the self-reported quality of life data from the EF14 trial showed identical scores for both groups at baseline and at 12 months for patients in the treatment and control group at the levels of cognitive, emotional, physical, and social functioning.[22] To reduce some of the burden of therapy, a second generation of the TTFields device with a reduction in size and weight by about 50% compared with the device used in the EF-11 and EF-14 devices has been developed.

Conclusions & Future Perspectives

The results of the randomized phase III EF-14 trial provide level 1 evidence that alternating electric fields are able to positively impact tumor growth and significantly extend survival in GBM. As a logical consequence, TTFields were approved by the FDA for newly diagnosed GBM in October 2015. Nevertheless, numerous questions remain and need to be addressed, both within the EF-14 trial and in future studies; Notably, it will be essential to be able to (1) identify the patients most likely to respond to TTFields therapy, (2) further elucidate the mechanism of action of TTFields, (3) elucidate the mechanisms of resistance to and failure of TTFields therapy, and (4) elucidate the pattern and predictors of response.

In GBM we will need to integrate this novel treatment approach in the current standard of care, and ultimately novel clinical trials will also need to integrate TTFields (at least in the control arm). A pragmatic alternative is to stratify patients for the use of TTFields as part of their standard of care in both the standard and experimental arms.

TTFields is a locoregional treatment, and extending its use to other tumor types and metastatic disease is most promising in clinical situations where locoregional disease control is key for quality of life. The excellent compatibility between TTFields and various chemotherapeutic agents has already been demonstrated, not only in GBM patients in the EF-14 trial but also in lung cancer patients.[30] TTFields may also be synergistic with immune therapy approaches. Senovilla et al showed that cells that cannot undergo mitotic exit show hallmarks of immunogenic cell death where the immune system induces a strong response against the dying cells.[31]

The positive results of the EF-14 demonstrate that neuro-oncology can lead the way to innovation. The results of the EF-14 trial paves the way to investigate the role of alternating electrical fields in other oncologic situations amenable to locoregional treatment such as brain metastases, ovarian carcinoma, mesothelioma, or pancreatic tumors (→ table 2). These trials are currently ongoing. For instance, in pancreatic cancer, TTfields therapy, in addition to gemcitabine resulted in a median PFS of 8.3 months (CI, 3–10.3 mo) in a phase 2 study

Table 2. Ongoing clinical trials in solid tumors

Disease, indication	Name of trial	Protocol description	# Pts	Phase	Endpoints	Sponsor	NCT#
Recurrent GBM							
Recurrent GBM	EF-26 (Japan)	Prospective, single arm, multicenter, postapproval study of TTFields in recurrent GBM patients	30	IV	Incidence & severity of treatment-related skin & CNS disorders: secondary: 1-y survival; PFS6mo	Novocure (EF-26) (Japan)	NA (Japan)
Recurrent GBM, bev-naive	Optune™+ bev & hypofractionated stereotactic RT in bev-naive GBM	TTFields + bev + SRT in recurrent GBM	27	I	Safety	U Maryland	NCT01925573
Recurrent GBM, at first relapse	Optune™ with bev & carmustine in treating patients with GBM in first relapse	TTFields+ bev + BCNU	20	II, single arm	Safety, PFS, PFS6, OS	UC Davis	NCT02348255
Recurrent bev-refractory GBM	Multicenter study of TTFields & pulsed bev	TTFields + pulsed Bev	25	II, single arm	PFS, QoL questionnaires	Univ of Florida	NCT02663271
Recurrent GBM	Phase 2 study of TTFields, enhanced by genomic analysis to identify a genetic signature for response	TTFields	30	II, pilot	Efficacy; QoL	Washington Univ School of Medicine	NCT01954576
Recurrent GBM	Optune™ with bev in GBM	TTFields + bev	40	II, open label	Safety & Efficacy	Case Comprehensive Cancer Ctr, Cleveland, OH	NCT01894061 Start- June 2013 End- April 2017
Newly diagnosed & recurrent GBM	High Resolution MRI 7 MRS to Evaluate Therapeutic Response to Novo-TTF in Newly & Recurrent GBM	TTFields	10	II	RR, using SOC MRIs	Univ of Penn	NCT02441322
Newly diagnosed GBM							
Newly Diagnosed GBM, unresectable	A Phase II Study of Optune™ in combo with BEV &TMZ in pts with newly diagnosed unresectable GBM	RT + bev, followed by TTFields in combo with bev & TMZ	46	II, single arm	Safety & efficacy	Carolinas Healthcare System	NCT02343549
Low grade gliomas							
Newly diagnosed low grade gliomas	Phase II study of Optune™ ± TMZ in pts with Low-Grade Gliomas	TTFields ± TMZ	42	II, single arm	ORR, Secondary- PFS	UCSD	NCT02507232

Table 2. *Continued*

Disease, indication	Name of trial	Protocol description	# Pts	Phase	Endpoints	Sponsor	NCT#
Meningioma							
Recurrent Atypical & Anaplastic Meningioma	Pilot Study of Optune™ for Recurrent Atypical & Anaplastic Meningioma	TTFields	21	Pilot	Safety & Efficacy	MSKCC	NCT01892397
Brain metastases							
NSCLC with 1–5 brain metastases following optimal standard local treatment	COMET	Maintenance TTFields vs supportive care-best SOC alone (after completion of standard local therapy)	60	II, randomized	Time to local/ distant progression	Novocure (EF-21) EU	NCT01755624
NSCLC with 1–10 brain metastases	METIS	Radiosurgery ± TTFields	240	III, randomized	Time to first cerebral progression	Novocure (EF-25) Global	Pending FDA IDE approval
Solid tumors							
Advanced pancreatic adenocarcinoma	PANOVA	+ gem or gem/nab-paclitaxel	40	I/II, 2-cohorts	Safety; feasibility; prelim efficacy	Novocure (EF-20) EU	NCT01971281
Recurrent ovarian carcinoma	INNOVATE	Concomitant with weekly paclitaxel	30	I/II pilot study	Safety, toxicity, feasibility & prelim efficacy	Novocure (EF-22) EU	NCT02244502
Pleural mesothelioma	STELLAR	Pemetrexed & cisplatin or carboplatin + TTFields	80	II, open label	Safety & efficacy (OS)	Novocure (EF-23) EU	NCT02397928
Front-line treatment for advanced NSCLC with squamous histology	LUNAR	combination chemotherapy ± TTFields	300	pivotal open-label randomized	Protocol in preparation	Novocure (EF-24) Global	NA

NCT#; ClinicalTrials.gov Identifier, Novocure; Novocure Ltd, manufacturer of TTFields (Optune™) device
Abbreviations: BCNU, carmustine;bev, bevacizumab (Avastin®); EU, European Union; GBM, glioblastoma; Gem, gemcitabine; MSKCC, Memorial Sloan-Kettering Cancer Center; nab-paclitaxel; albumin-bound paclitaxel (Abraxane®), NSCLC,non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; EU

on 20 patients. The partial response rate was 30% and another 30% stable disease. The median OS for all patients was promising for this disease at 14.9 months. It was not reached in patients with locally advanced disease, and 8.3 months (CI, 4.3–14.9 mo) for patients with metastatic disease with 1-year survival rates of 86% in locally advanced patients and 40% in patients with metastatic disease[32] If those trials confirm the positive effects observed in GBM patients, a truly new cancer treatment modality has been born and will find multiple useful indications alone or in combination with other established or new treatments.

Conflict of Interest Statement. The authors declare no conflict of interest relevant to this review article.

Advisory details: Roger Stupp has served as the coordinating principal investigator on Novocure-sponsored clinical trials but did not receive any personal or institutional fees from Novocure. *Management details:* Roger Stupp serves as the president of the European Organisation for Research and Treatment of Cancer (EORTC). EORTC conducts academic clinical trials in a variety of tumor types, including brain tumors. The following authors declare paid consulting conflicts as described here: Roger Stupp has served on non-remunerated advisory boards for Novocure Ltd. Andreas Hottinger has served on advisory boards, fees (when applicable) to the institution. Roger Stupp and Andreas Hottinger have received travel support for scientific presentations of the trial results at academic meetings.

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