Review

Clinical Cancer Research

Tumor-Treating Fields: A Fourth Modality in Cancer Treatment

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Abstract

Despite major advances in therapy, cancer continues to be a leading cause of mortality. In addition, toxicities of traditional therapies pose a significant challenge to tolerability and adherence. TTFields, a noninvasive anticancer treatment modality, utilizes alternating electric fields at specific frequencies and intensities to selectively disrupt mitosis in cancerous cells. TTFields target proteins crucial to the cell cycle, leading to mitotic arrest and apoptosis. TTFields also facilitate an antitumor immune response. Clinical trials of TTFields have proven safe and efficacious in patients with glioblastoma multiforme (GBM), and are FDA approved for use in newly diagnosed and recurrent GBM. Trials in other localized solid tumors are ongoing. *Clin Cancer Res; 24(2); 266–75. ©2017 AACR.*

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Introduction

Cancer continues to be a leading cause of death in the United States, second only to heart disease among all-cause mortality (1). Despite major discoveries in cancer treatment thus far, overall cancer-related mortality rates have remained relatively stable (2). In addition, the traditional and newer modalities used to treat cancer (surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy) have associated adverse effects that negatively impact the quality of life. Hence, the search for more efficacious, more tolerable anticancer therapies continues.

Tumor-treating Fields (TTFields) are low intensity, intermediate frequency, alternating electric fields delivered through noninvasive transducer arrays placed locoregionally around the anatomic region of the tumor. TTFields selectively disrupt cell division, and preclinical research has demonstrated the antimitotic effects of TTFields in different tumor types (3–6). TTFields have been found to prolong survival in patients with glioblastoma multiforme (GBM), which led to its approval by the FDA for recurrent and newly diagnosed GBM after surgery and radiotherapy with adjuvant temozolomide (7–11). In addition, this treatment modality has been recognized by the American Society of Clinical Oncology (ASCO) as an advancement in cancer treatment due to its novel approach, effectiveness, and low toxicity profile (12). The most recent National Comprehensive Cancer Network (NCCN) guidelines recommended TTFields in newly diagnosed GBM as a category 2A treatment for patients with a good performance status (13).

This review examines the mechanism of action of TTFields, treatment delivery, findings from the pivotal phase III trials in newly diagnosed and recurrent GBM, and ongoing clinical trials of TTFields in other solid tumors, including pancreatic, ovarian, non–small cell lung cancer (NSCLC), brain metastases from NSCLC, and malignant mesothelioma.

Mechanism of Action

Biophysics of TTFields

TTFields' effects on dividing cells result from the multitude of charged macromolecules and organelles responsible for key processes in the mitotic process. Structural change or dislocation of those cellular components may alter their physiologic function, and ultimately disrupt normal mitosis. The effects of TTFields on various cellular processes can be explained by two fundamental physical principles: dipole alignment and dielectrophoresis (14–16). A dipole refers to the separation of positive and negative charges within a molecule. Under a uniform alternating electric field, any charged molecule will oscillate in an attempt to align itself appropriately parallel to the direction of the electric force vector it is exposed to (14). Key macromolecules and organelles responsible for mitosis and cytokinesis are highly polar, and their random movement, which is critical for their function, can be disrupted by the application of localized electric fields (9, 17–19).

Successful mitosis requires precise spatial and temporal alignment of polarizable or charged structures, notably tubulin and septin, at various stages of cell division (Figs. 1 and 2). In a nonuniform electric field, a force is exerted on polar molecules, leading them to migrate toward a region of high-field density in a process called dielectrophoresis (15, 16).

TTFields are nonuniformly distributed within the treated region based on multiple parameters, which include the geometry of the treated organ, the distance between transducer arrays applied to the patient's skin, and the tissue's dielectric properties (20–22). The fields do not attenuate in correlation to the distance

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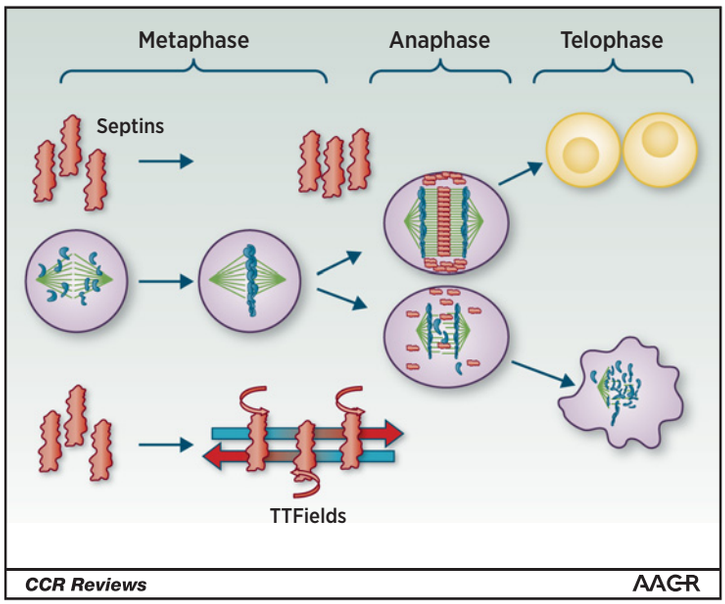

Figure 1.
Model for TTFields leading to mitotic disruption. During mitosis, the Septin 2, 6, 7 complex is recruited to the Anaphase spindle midline and the cytokinetic cleavage furrow by Anillin where it self-assembles into a fibrous lattice due to lateral interactions between parallel Septin filaments. By inducing rotational movement about the long axes of the parallel fibers, TTFields are able to inhibit the propagation of lattice formation by disrupting the ability of individual fibers to bind each other. In the absence of proper Septin function, contractile elements of the cytokinetic furrow are not restrained within the equatorial midline of the cell resulting in ectopic furrow malfunction that leads to violent membrane contractions at the onset of anaphase followed by aberrant mitotic exit. Reproduced from Gera et al. (18).

from the array, and may therefore be used for the treatment of deeply located tumors (21, 22). As electric fields do not have a half-life time, TTFields are continuously delivered during the course of treatment.

Biological effects of TTFields

Elucidation of the biological effects of TTFields is ongoing; this section describes current knowledge on the mechanism of action. Tubulin dimers are highly polar dipoles, which align along the direction of TTFields applied. TTFields have been demonstrated to disrupt the normal polymerization process of microtubules that form the mitotic spindle, by eliminating the normal randomized movement of the tubulin subunits within the cytoplasm during metaphase (4, 23, 24).This, in turn, leads to metaphase arrest, prolonged mitosis, and ultimately cell death.

The hour-glass shape of the dividing cell that escaped mitotic arrest during metaphase consequently causes a nonuniform electric field to develop, together with a high-intensity field at the narrow furrow region. The Septin complex, which is responsible for the physiologic localization of contractile proteins leading to the normal division of the cell into two daughter cells, is dislocated as a result of TTFields-exerted dielectrophoresis. This effect, which happens towards the end of telophase, can lead to violent cytoplasmic blebbing and cellular death (18, 24, 25), or to abnormal chromosomal segregation leading

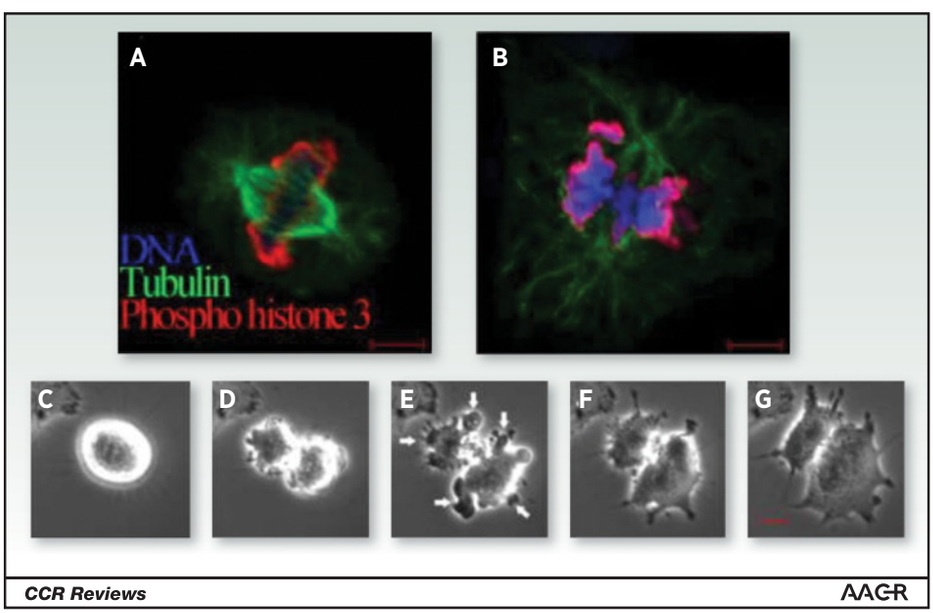

Figure 2.
TTFields affect normal spindle formation during metaphase. Control cell (**A**), TTFields-treated cell (**B**). **A** and **B** are stained with phosphohistone 3 (marker for mitotic cells). **C–G,** Time-lapse of treated cell showing membrane blebbing (arrows) during telophase. Red bar in **G** corresponds to 10 μm. 2015 IEEE. Reprinted, with permission, from Wenger, C., et al. Modeling Tumor Treating Fields (TTFields) application in single cells during metaphase and telophase. Conf Proc IEEE Eng Med Biol Soc 2015:37;6892–6895.

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to aneuploidy in daughter cells, and a subsequent decrease in clonogenic potential (5, 17, 23, 25–28). Septin has a greater dipole moment than tubulin [2711 Debyes (23) vs. 1660 Debyes (29)]. However, due to the faster dynamics of assembly/disassembly of tubulin, the effects of TTFields on microtubules might be more significant. The above effects of TTFields ultimately lead to caspase-dependent or independent apoptosis, and also increase the cellular expression of immunogenic cell death markers (18, 23, 24, 28, 30, 31). To date, no TTFields-related adverse events have been reported as a result of genetic alterations or other mitotic effects in normally dividing tissues. Further experiments would clarify these effects in greater detail, both in healthy and pathologic tissues.

TTFields have been shown to exert their antimitotic effects in numerous preclinical models of solid tumors through the same mechanisms of action (4, 5, 23, 25, 32). The maximal cytotoxic effect on each cell type is achieved by fine-tuning the frequency of TTFields applied within the intermediate range (between 100 and 300 kHz), and appears to be inversely correlated with cell size (4, 5, 24, 27). Because of the low toxicity and efficacy demonstrated in multiple clinical trials, TTFields have been tested in preclinical studies together with cytotoxic chemotherapy agents in an attempt to augment overall antitumor effects. Such chemotherapies included microtubule inhibitors, nucleoside analogues, folate antimetabolites, alkylating agents, and immune checkpoint inhibitors, all leading to an additive cytotoxic effect when combined with TTFields. Taxanes have been demonstrated to act synergistically when combined with TTFields (25, 27, 32). In addition, in preclinical models, TTFields have been shown to expose calreticulin on cell surface *in vitro*, and to significantly decrease tumor volume when combined with an anti-programmed T cell death 1 (anti-PD-1), leading to a significant increase in the infiltration of antigen-presenting cells into the tumor (33, 34). In an *in vivo* model of metastatic kidney cancer, rabbits were injected with VX-2 carcinoma cells in the kidneys and continuously treated with TTFields to their kidneys (26). A significantly lower number of lung metastases was seen in TTFields-treated rabbits than in sham controls. IHC staining for lymphocyte subsets revealed that TTFields-treated rabbits had significantly increased CD4, CD8, and CD45 T-cell counts in their lungs as compared with control. These findings suggest the potentiation of immunogenic cell death by the addition of TTFields (28, 35), which warrants further study.

TTFields Application in the Clinic: Apparatus

TTFields are delivered via noninvasive transducer arrays attached to the skin of patients (7, 8, 19). The field-generator (NovoTTF System, Novocure Ltd.) may be connected to a portable battery (total weight 1.2 kg) and is intended for continuous, home use (Fig. 3). In patients with GBM, the head must be shaved every 3–4 days, so that the transducer arrays can be placed on skin with minimal surface resistance (Fig. 4). Other tumor types are being investigated in ongoing clinical trials (see below) by utilizing different frequency/intensity field settings, and varying array sizes adjusted to torso layouts. Patients are encouraged to keep the device active for a minimum of 18 hours daily, with short treatment breaks for personal needs. Median overall survival (OS) was found to be significantly longer for patients receiving TTFields who had a compliance rate of $\geq$18 hours per day (36) compared with <18 hours per day.

As the nonuniformity of TTFields close to cytokinesis leads to dielectrophoresis and ultimately to mitotic disruption, it is essential that TTFields are aligned with the mitotic axis. Therefore, optimal TTFields delivery depends on multidirectional application of the electric fields to target cells undergoing mitosis in different spatial orientations. TTFields are delivered through two pairs of transducer arrays that sequentially deliver orthogonal or

Figure 3.
Second-generation Optune device. The complete system consists of an electric field generator (**A**), rechargeable battery pack (**B**), carrying pouch (**C**), and two pairs of disposable ceramic transducer arrays (**D**). Figure copyright Novocure, 2016.

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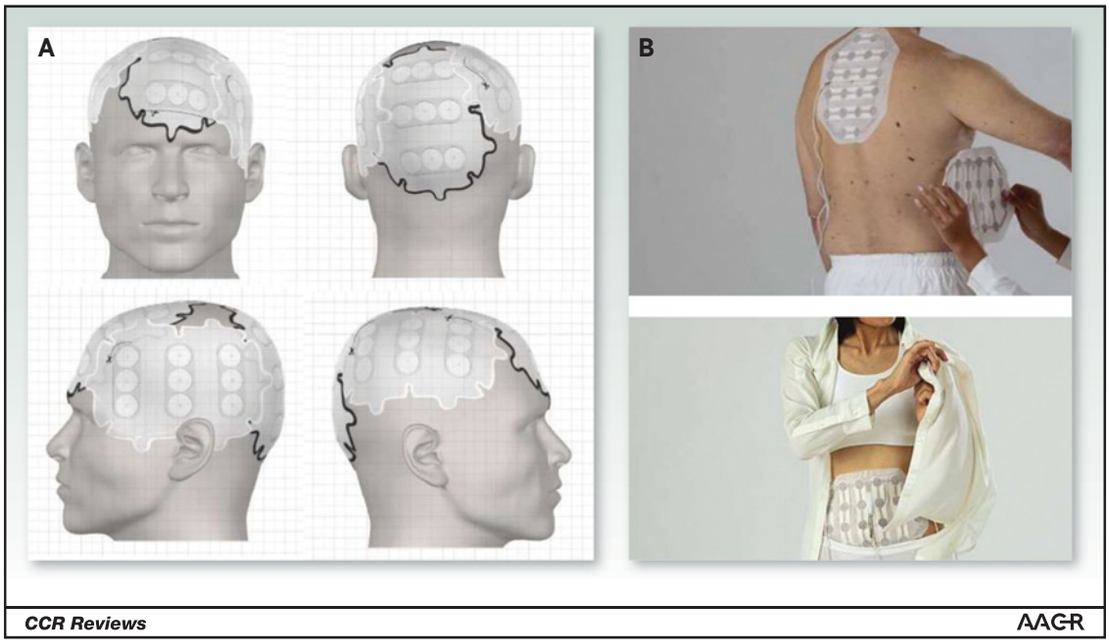

Figure 4.

A, Placement of arrays on patient's shaved scalp. An array map used as guidance for optimal placement of transducer arrays based on tumor size and location. The array map is personalized for each patient and generated using NovoTAL System software. The customization of the array layout is dependent on the patient's size and location of the tumor. **B,** Transducer arrays attached to the device, Optune, are placed on patient's body, for lung cancer (top) and ovarian cancer (bottom). Figure copyright Novocure, 2015.

perpendicular fields within the tumor, thereby maximizing TTFields delivery to all cells comprising the tumor (5, 21, 37). In GBM, patient MRI data are used to individualize the transducer array placement, maximizing field intensity at the target tissue (38). This is achieved using treatment planning software (NovoTAL, Novocure Ltd.) that allows the treating physician to use cranial morphometry and tumor location to output a personalized configuration of transducer arrays (39–41).

Specifically, simulations of TTFields delivery to the head (or other anatomic regions) are performed using realistic computerized models generated by Sim4Life V3.0 (ZMT-Zurich) electro-quasi-static solver. Several different pairs of arrays with varying amounts of transducer array disks placed at different locations are simulated. The intensity distribution and angle between the fields generated by each pair in a layout are then analyzed. In the future, electric field dose optimization may be enhanced by patient-specific models of tissue structures and boundaries.

Toxicity Profile

No high-grade systemic toxicity has been related to TTFields, as anticipated by the mechanism of action and the regional nature of the application. The most common adverse event related to TTFields is mild-to-moderate dermatitis (of either contact or allergic etiology) at the site of the transducer array placement (8, 9, 42). In recurrent- and newly diagnosed GBM patients, the frequency of this adverse event was 16% and 43% of TTFields-treated patients, respectively. The time to onset of dermatologic adverse events ranged from 2–6 weeks in recurrent GBM patients (42). Treatment strategies depend on the type of adverse event, but generally consist of topical corticosteroid creams, topical and oral antibiotics, and isolation of affected skin surfaces from adhesives or pressure (42). Multiple clinical trials conducted to date have reported no other significant TTFields-related adverse events from study patients treated for several years. Even longer-term effects of TTFields may be reported in the future. Patients have tolerated TTFields well, as demonstrated by the high average compliance observed (8, 9, 19, 43).

Clinical Trials of TTFields in GBM

GBM encompasses a heterogeneous group of highly vascularized and invasive tumors of the central nervous system (44, 45). GBM represents the most common and most lethal type of primary malignant brain tumor in adults with an age-adjusted incidence rate of 3.2 to 4.5 per 100,000 (46, 47). Median survival (treated by current standard of care – maximal resection and radiotherapy with concomitant and adjuvant temozolomide) is 16–17 months (48), and only 9.8% of patients are still alive at five years (49). Tumor recurrence is inevitable regardless of the initial treatment and there is no widely accepted standard of treatment for recurrent GBM (50). TTFields were particularly suited to a trial in patients with GBM as the tumor is locally advancing and generally does not metastasize to distant locations, enabling full coverage of the organ's volume with TTFields. In addition, the brain has minimal numbers of noncancerous dividing cells, making TTFields potentially safe for use.

The established standard of care for newly diagnosed GBM is maximum surgical resection followed by radiotherapy

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concomitant with daily temozolomide, followed by a 6-month cycle of maintenance temozolomide (51, 52). This multimodal standard was established in 2005, and since then, various unsuccessful attempts have been made to improve overall survival outcomes in this patient population by modifying temozolomide dosing or by using bevacizumab or other targeted therapies (53, 54). Checkpoint inhibitors and other immunotherapies are currently being explored as treatment for newly diagnosed GBM (51).

Recurrent GBM

Following the results of a pilot study demonstrating the safety and tolerability of TTFields in 20 newly diagnosed and recurrent GBM patients (26), 237 patients with GBM recurrence (with any number of past recurrences) were enrolled in a blinded, randomized phase III clinical trial, EF-11. Baseline characteristics were balanced between the study arms receiving either TTFields or physician's choice chemotherapy: $N = 120$ for TTFields monotherapy and $N = 117$ for physician's choice chemotherapy (7). The enrolled patients had a median age of 54 years, Karnofsky performance scale (KPS) $\geq$70%, and had been diagnosed a median of 11.8 months. The primary endpoint was OS; secondary endpoints were progression-free survival (PFS), progression free survival at 6 months (PFS6), 1-year survival, radiologic response rate (RR), quality of life (QoL), and safety. Radiologic response was guided by brain MRI and determined by blinded central radiology review according to Macdonald criteria (55). QoL was determined by a questionnaire (56) provided by the EORTC (49), with measurements performed at baseline, and repeated every 2 months.

Results showed a median survival of 6.6 versus 6.0 months (HR 0.86; $P = 0.27$); PFS 2.2 versus 2.1 months ($P = 0.16$); PFS6 21.4% versus 15.1% ($P = 0.13$); and RR 14% versus 9.6% ($P = 0.19$) in TTFields versus physician's choice chemotherapy, respectively. None of these results were found to be statistically significant. With regard to QoL and safety, TTFields resulted in a higher QoL in most domains analyzed, with the highest measurement in cognitive and emotional functioning. TTFields resulted in fewer severe adverse events with statistical significance (6% vs. 16%, $P = 0.022$). The most common side effect observed was dermatitis (16%) at the site of transducer array placement.

The study investigators concluded that while TTFields was not superior to physician's choice chemotherapy in treating recurrent GBM, it was noninferior. In addition, the QoL and safety of TTFields were superior to physician's choice chemotherapy. Following results of the EF-11 trial, TTFields was approved by the FDA for treatment of recurrent GBM indicated for histologically or radiologically confirmed GBM recurrence after receiving standard-of-care chemotherapy (10).

Newly diagnosed GBM

Following the results of the aforementioned pilot study (26), an international, randomized, phase III clinical trial, EF-14, enrolled patients with newly diagnosed GBM into one of two arms: TTFields plus adjuvant temozolomide versus adjuvant temozolomide alone (8). A total of 695 patients were enrolled in the study: $N = 466$ in the TTFields plus temozolomide arm and $N = 229$ in the temozolomide alone arm. These patients were enrolled after completion of initial radiotherapy and a concomitant initial dose of temozolomide. Median follow-up time was 12 months. Baseline patient characteristics were balanced in each arm and tumor was resected in 87% of patients.

The primary endpoint was PFS. Secondary endpoints were OS, two-year survival, QoL, cognitive function, and safety. In the TTFields plus temozolomide arm compared with temozolomide alone, results showed improved PFS (7.1 vs. 4.0 months; HR 0.62; $P = 0.001$), OS (20.5 vs. 15.6 months; HR 0.64, $P = 0.004$), and two-year survival [43%, 95% CI (36%–50%) vs. 29%, 95% CI (21%–38%), respectively (Fig. 5)]. No significant added toxicity or adverse events were noted in the TTFields plus temozolomide arm (Table 1). QoL was maintained throughout 12 months of treatment in newly diagnosed GBM patients receiving the combination of temozolomide and TTFields, and was not inferior to that of temozolomide alone (57).

On the basis of the study's interim data, specifically, the demonstration of significant PFS and OS improvement in TTFields-treated patients, the trial was terminated in November 2014 by an independent data monitoring committee (8). Subsequently thereafter, TTFields in combination with temozolomide was approved by the FDA for the treatment of newly diagnosed GBM for histologically confirmed GBM following maximal debulking surgery and completion of radiotherapy plus standard-of-care chemotherapy (11). The NCCN has recommended (Category 2A) Optune in combination with temozolomide as a postoperative adjuvant treatment option, following standard brain radiotherapy with concurrent temozolomide, for patients with newly diagnosed GBM (13).

Ongoing trials in GBM

Ongoing trials of TTFields in patients with GBM are exploring the genetic signature of response (NCT01954576) and evaluating therapeutic response by high-resolution MRI (NCT02441322). The possibility of enhancing TTFields with targeted craniotomy is also being investigated (NCT02893137). Several studies are testing TTFields in combination with bevacizumab for recurrent GBM (NCT02663271, NCT01894061, NCT02743078). Another study is incorporating stereotactic irradiation (NCT01925573). A study of patients with newly diagnosed unresectable GBM is combining TTFields with bevacizumab and temozolomide (NCT02343549).

Clinical Trials of TTFields in Other Tumor Types

TTFields in pancreatic cancer

In the preclinical setting, TTFields (150 kHz) applied *in vitro* demonstrated an antiproliferative effect on pancreatic cancer cells with decreased long-term clonogenicity, significantly increased number of abnormal mitotic figures, and decreased G_2–M cell population (27). Furthermore, in the PC1-0 hamster pancreatic cancer model, TTFields significantly reduced tumor volume with an increase in the frequency of abnormal mitotic events (58). Pancreatic tumors subcutaneously implanted in nude mice treated with TTFields plus gemcitabine showed a delay in tumor growth compared with either agent alone (4).

The safety and feasibility of TTFields in combination with chemotherapy in advanced pancreatic cancer is currently being studied in an ongoing phase II clinical trial, PANOVA (NCT01971281). This is a prospective, nonrandomized study

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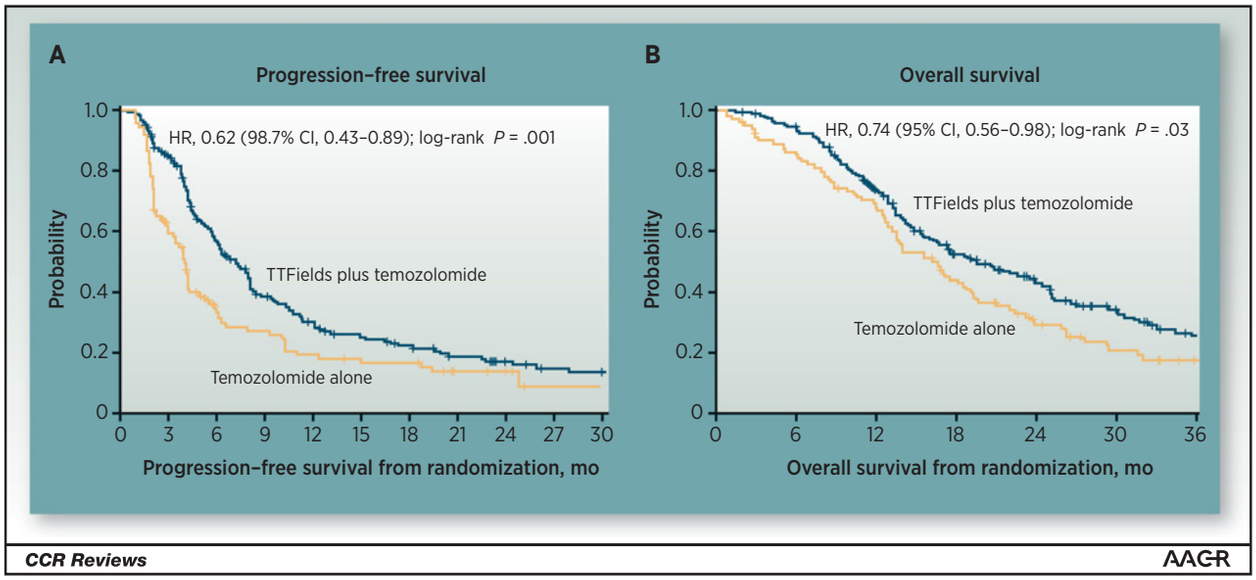

Figure 5.
Kaplan–Meier curves for patients with GBM in the EF-14 trial, treated with TTFields/temozolomide versus temozolomide alone. PFS (**A**) and OS (**B**). Reproduced with permission from JAMA 2015;314(23):2535–43. Copyright 2015 American Medical Association. All rights reserved.

designed to test the safety and efficacy of TTFields (150 kHz) concomitant with gemcitabine alone or nab-paclitaxel plus gemcitabine in patients with advanced pancreatic adenocarcinoma. The study enrollment is 40 patients.

Results from the study were recently reported (43, 59). The first cohort included 20 patients treated with a combination of TTFields and gemcitabine. Most patients (80%) had an ECOG score of 1. Twelve patients (60%) had distant metastases, while the others had locally advanced disease. Median compliance with TTFields was 78% (14 hours/day), with median duration of 5 months. Fourteen patients (70%) had serious adverse events (SAE) during the study period, of which only two were grade 3, TTFields-related skin toxicity. The other 12 patients had mild skin toxicity. No other TTFields-related SAEs were reported. The median PFS was 8.3 months (95% CI, 4.3–10.3): 10.3 months (95% CI, 2.8–NA) in patients with locally advanced disease and 5.7 months (95% CI, 3.8–14.9) in patients with metastatic disease. PFS6 was 56%. Of the evaluable tumors, 30% had partial response and another 30% had stable disease. The median OS for all patients was 14.9 months in patients with locally advanced disease, and 8.3 months (95% CI, 4.3–14.9) in patients with metastatic disease. 1-year survival rate was 55%: 86% in locally advanced and 40% in metastatic disease. The second cohort included 20 patients who were treated with TTFields in combination with gemcitabine and nab-paclitaxel. Most patients (65%) had an ECOG score of 1. Twelve patients (60%) had distant metastases. Ten patients (50%) had SAEs during the study period. Eleven patients (55%) had treatment-related skin toxicity, of which 5 had grade 3 toxicity. No TTFields-related SAEs were reported. The median PFS was 12.7 months (95% CI, 5.4–NA): 9.3 months in patients with metastatic disease and not reached in locally advanced patients. PFS6 was 65%: 50% in metastatic disease and 87.5% in locally advanced patients. Of the evaluable tumors, 40% had partial response and another 47% stable disease. The median OS was not reached, and the 1-year survival rate was 72% (62.5% in metastatic disease and 87.5% in locally advanced disease).

Results suggest greater PFS and OS for TTFields treated patients compared with previously reported historical gemcitabine- or gemcitabine and nab-paclitaxel–treated control patients, and nearly double the 1-year survival rate for patients with metastatic disease (60). On the basis of these results, a phase III trial in locally advanced patients, testing TTFields in combination with gemcitabine and nab-paclitaxel versus chemotherapy alone, is planned to be opened for enrollment soon. Applying TTFields to locally advanced patients only in the phase III trial is hypothesized to lead to a greater survival benefit and potentially higher resectability rates in unresectable, locally advanced patients, as TTFields applied to the abdomen cover the entire burden of disease in this population.

TTFields in ovarian cancer

In a preclinical setting, TTFields (200 kHz) have been shown to reduce the number of viable cells (44.6%) and clonogenic potential (23.8%) significantly in tumor cells *in vitro* compared with untreated cells *in vitro* ($P < 0.001$; ref. 61). Further reduction in viability is seen when TTFields is combined with paclitaxel, which is a plausible chemotherapy to test in combination with TTFields in view of the synergistic effect observed when the two treatments were combined in preclinical models (32). Orthotopically implanted MOUSE-L cells treated with TTFields led to significantly reduced tumors in mice (62).

The safety and preliminary efficacy of TTFields in combination with paclitaxel in patients with recurrent ovarian cancer were studied in a phase II clinical trial, INNOVATE (NCT02244502). Thirty-one recurrent, platinum-resistant, unresectable ovarian cancer patients were enrolled and treated with TTFields in combination with weekly paclitaxel (63). The

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Table 1. Patients with grade 3 to 4 adverse events in the EF-14 trial

	TTFields Plus Temozolomide ($n = 203$)	Temozolomide Alone ($n = 101$)
Hematologic disorders	25 (12)	9 (9)
Anemia	1 (<1)	2 (2)
Leukopenia or lymphopenia	11 (5)	5 (5)
Neutropenia	6 (3)	1 (1)
Thrombocytopenia	19 (9)	3 (3)
Cardiac disorders	2 (1)	3 (3)
Eye disorders	2 (1)	1 (1)
Gastrointestinal disorders	11 (5)	2 (2)
Abdominal pain	2 (1)	0
Constipation	2 (1)	0
Diarrhea	1 (>1)	2 (2)
Vomiting	3 (1)	1 (1)
General disorders	17 (8)	5 (5)
Fatigue	8 (4)	4 (4)
Infections	10 (5)	5 (5)
Injury and procedural complications	14 (7)	5 (5)
Fall	6 (3)	2 (2)
Medical device site reaction	4 (2)	0
Metabolism and nutrition disorders	7 (3)	3 (3)
Musculoskeletal disorders	8 (4)	3 (3)
Nervous system disorders	45 (22)	25 (25)
Seizure	15 (7)	8 (8)
Headache	4 (2)	2 (2)
Psychiatric disorders	9 (4)	3 (3)
Anxiety	2 (1)	0
Bradyphrenia	0	1 (1)
Confusional state	2 (1)	1 (1)
Mental status changes	4 (2)	1 (1)
Psychotic disorder	2 (1)	0
Respiratory disorders	4 (2)	1 (1)
Skin disorders	0	1 (1)
Vascular disorders	8 (4)	8 (8)
Deep vein thrombosis	1 (>1)	3 (3)
Pulmonary embolism	4 (2)	6 (6)

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primary endpoint was treatment-emergent adverse events. Secondary endpoints included PFS, OS, and RR. Most patients (77%) had serous histology. Fifty-two percent had an ECOG score of 0. All patients were platinum-resistant, and 97% of patients received prior taxane-containing regimens. Ten (32%) patients suffered from SAEs during the study. None were related to TTFields. Most patients were reported to have mild to moderate, TTFields-related skin irritation, out of whom only two patients (6.4%) had severe-grade events. The median PFS was 8.9 months (95% CI, 4.7–NA). Of the evaluable tumors, 25% had partial response and another 46.4% stable disease – a clinical benefit of 71.4%. Six patients (19.4%) had a CA 125 response, translating into a decrease of 50% or more in serum levels. The median OS was not reached. These results are encouraging due to the lack of good systemic treatment options for platinum-resistant disease. They warrant the investigation of TTFields in a phase III setting in platinum-resistant ovarian cancer.

TTFields in NSCLC

In a preclinical setting, the combination of TTFields (150 kHz) with standard chemotherapeutic agents on several NSCLC cell lines, both *in vitro* and *in vivo*, resulted in enhanced treatment efficacy across all cell lines tested. This included both squamous and nonsquamous models (5, 27).In Lewis lung carcinoma and KLN205 squamous cell carcinoma implanted mice, treatment with TTFields in combination with pemetrexed, cisplatin, or paclitaxel showed more pronounced efficacy compared with single agents (27).

A pilot clinical trial was conducted in Europe (NCT00749346) for inoperable stage IIIB and IV squamous and nonsquamous NSCLC patients ($N = 41$) who received pemetrexed (500 mg/m^2 i.v. q3w) concurrently with TTFields daily, until disease progression (64). TTFields at a frequency of 150 kHz were applied on the basis of data from preclinical models demonstrating the maximal susceptibility of NSCLC at this frequency. The results of this single-arm phase I/II trial demonstrated that combining TTFields and pemetrexed as a second-line therapy for NSCLC is safe and shows greater efficacy than pemetrexed alone compared with historic controls. In addition, there was improved disease control within the treatment field. Median PFS was 28 weeks and OS was 13.8 months, compared with 12 weeks and 8.2 months in historical controls receiving pemetrexed alone (65). There were no increases in pemetrexed-related toxicity or in TTFields-related adverse events.

The efficacy of TTFields in NSCLC is currently being investigated in a phase III trial (LUNAR, NCT02973789; ref. 66). Patients ($N = 512$) with squamous or nonsquamous NSCLC are enrolled and stratified by second-line therapy (either PD-1 inhibitor or docetaxel) and histology (squamous vs. nonsquamous). Key inclusion criteria are first disease progression (RECIST 1.1), ECOG 0–1, no prior surgery or radiotherapy, no electronic medical devices in the upper torso, and absence of brain metastasis. Docetaxel or PD-1 inhibitors (either nivolumab or pembrolizumab) are given at standard doses. TTFields are continued until progression in the thorax and/or liver. The primary endpoint is superiority in OS between patients treated with TTFields in combination with either docetaxel or PD-1 inhibitors, compared with docetaxel or PD-1 inhibitors alone. Secondary endpoints include PFS, RR, QoL, and severity and frequency of adverse events.

TTFields in brain metastasis from NSCLC

Initial safety results from a pilot study demonstrated a high safety profile in patients suffering from brain metastases from NSCLC when treated with TTFields (150 kHz; ref. 67).

The efficacy of TTFields in NSCLC with brain metastasis is currently being studied in an ongoing phase III clinical trial, METIS (NCT02831959). This is a prospective, randomized study designed to test the efficacy, safety, and neurocognitive outcomes of TTFields (150 kHz) in the treatment of NSCLC patients with 1–10 brain metastases following radiosurgery. The study is enrolling 270 patients into two arms in a 1:1 ratio: TTFields at 150 kHz plus supportive treatment versus supportive treatment alone. All patients receive an optimal systemic therapy for their basic disease. Primary outcome is time to cerebral progression based on the RANO-BM Criteria (68). Secondary outcomes include time to neurocognitive failure, OS, RR, QoL, and toxicity.

TTFields in malignant mesothelioma

In a preclinical setting, TTFields applied to mesothelioma cell lines *in vitro* showed a significant reduction in the number of cells (69%, $P < 0.001$) and in clonogenicity (78%, $P < 0.05$) compared with control cells without application of TTFields.

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Combined treatment of TTFields with paclitaxel and cisplatin shows a synergistic effect (69).

The efficacy of TTFields in combination with chemotherapy in malignant pleural mesothelioma is currently being studied in an ongoing phase II clinical trial, STELLAR (NCT02397928).This is a prospective, nonrandomized, open-label study designed to test the safety and efficacy of TTFields (150 kHz) concomitant with pemetrexed and cisplatin or carboplatin in malignant mesothelioma. The study enrolled 80 patients in a single interventional arm and patients are still undergoing follow-up. Primary outcome is OS. Secondary outcomes include PFS, RR, and toxicity. Interim results (70) from the first 42 patients included in the trial demonstrated a 12-month survival rate of 79.7% (95% CI, 57.2–91.2) and median PFS of 7.3 months (95% CI, 5.6–NA). Median survival has not been reached at that time. No device-related SAEs have been reported. Expected TTFields-related dermatitis was reported in 55% (23 patients). Only two patients had grade 3 dermatitis.

Future Directions and Other Technologies

In the future, TTFields will continue to broaden its scope of use to include new and previously unstudied solid tumors. Currently, preclinical studies investigating the utility of TTFields are underway in the following cancer types: breast, cervical, colorectal, gastric, hepatocellular, melanoma, renal, urinary transitional cell, and small-cell lung cancer (71). These preclinical studies, and the clinical trials to follow, will help determine the feasibility of utilizing TTFields more ubiquitously in cancer therapy in the future. As new cancers in different anatomic regions become considered, designing new model types and applicators with optimal functionality and user-friendliness will also pose interesting challenges. In addition, the effects of TTFields on the actively dividing noncancerous tissue in these different anatomic regions will continue to be an area of investigation.

As most GBM patients treated with TTFields ultimately succumb to tumor progression and death, continued research will need to take place in an attempt to increase the efficacy of TTFields in this and other malignancies. Possible directions may include modifications in the intensity and frequency applied and further optimization of the array layout. Another future consideration is the use of TTFields in cancers of less clearly defined boundaries or regions. For instance, as of yet, TTFields has not been studied in liquid tumors. Determining a mode for applying alternating electric fields through a patient's circulatory system, and ascertaining the efficacy and safety profile when doing so, would be a monumental contribution.

Other similar products investigating electric or electromagnetic fields have been described in the literature. One group, TheraBionic, has previously shown intrabuccal administration of low levels of amplitude-modulated electromagnetic fields (EMF) to either shrink tumor size or maintain stable disease in patients with advanced hepatocellular carcinoma (72). Tolerability studies have also been demonstrated in advanced breast cancer (73). The mechanism of action appears similarly to involve arrest of the cell cycle and the downregulation of downstream gene expression (74). However, the precise mechanisms involved in the disruption of the cancer cell cycle and potential adverse effects on noncancerous cells are still being clarified (75). Currently, FDA approval for this technology is still pending.

Conclusion

TTFields is an innovative and noninvasive therapeutic approach to cancer therapy. TTFields disrupt mitosis and selectively kill rapidly dividing cancer cells by delivering continuous (over 18 hours per day) low intensity, intermediate frequency, alternating electric fields to the tumor site.

The optimal frequency for antimitotic effect varies by cancer type, and can be adjusted for maximal anticancer effect. In addition, unlike systemic chemotherapy, the delivery of TTFields can be locally directed, minimizing the risk of systematic adverse effects. TTFields have been demonstrated to have minimal toxicity confined to the skin in multiple clinical trials. This may enable TTFields to be combined with other anticancer treatments for greater efficacy without increased toxicity. Preclinical work suggests that TTFields may act in an additive/synergistic manner with certain cytotoxic agents and potentiate immunogenic cell death when combined with immune checkpoint inhibitors. Such combination therapy involving TTFields requires further evaluation. Theoretically, maintenance TTFields therapy may also serve as a bridge between chemotherapy while the patient recovers from chemotherapy-related toxicities. Locoregional delivery and the low toxicity profile of TTFields highlights the potential to achieve tumor control and response in critical organs without the dose-limiting toxicity seen with other regional therapies. Preclinical studies have demonstrated possible potentiation of the immune system response against the tumor following the application of TTFields. Such a systemic effect will need to be further evaluated through preclinical and clinical investigations. Ongoing phase III studies in TTFields include secondary endpoints, which assess the local versus the systemic effects in patients receiving TTFields compared with control patients.

The efficacy and tolerability profile of TTFields in GBM has led to FDA approval for use in both newly diagnosed and recurrent disease. Given that the targets of TTFields are ubiquitous and essentially tumor-type nonspecific, TTFields may provide benefits for a variety of other localized cancers besides GBM. To better examine that possibility, ongoing studies are investigating TTFields in a variety of other solid tumors, including pancreatic, ovarian, NSCLC, brain metastases from NSCLC, and malignant mesothelioma.

Disclosure of Potential Conflicts of Interest

U. Weinberg and E.D. Kirson hold ownership interest (including patents) in Novocure Ltd. D. D. Von Hoff is a consultant/advisory board member for Novocure. No potential conflicts of interest were disclosed by the other authors.

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