Tumor treating fields: a new standard treatment for glioblastoma?

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Purpose of review
Tumor treating fields (TTFields), an external therapeutic device with antimitotic properties, is a Food and Drug Administration approved treatment for recurrent glioblastoma (GBM) that has been reported to be efficacious in newly diagnosed GBM as well.

Recent findings
Preclinical data show that TTFields is an antimitotic agent that additionally augments response to alkylator-based chemotherapy. In a single study, nearly 15% of recurrent GBM treated with TTFields alone display durable responses. Responses may be delayed, sometimes after an initial progression, and are highly correlated to treatment compliance and to survival. In newly diagnosed GBM, a preplanned interim analysis of the phase III randomized trial (standard of care with or without TTFields) showed a statistically significant effect of TTFields resulting in a net gain of 3 months in both progression-free and overall survival.

Summary
TTFields is a novel noninvasive therapeutic option for recurrent GBM. The role of TTFields in newly diagnosed GBM will be adjudicated pending publication of the final results of the randomized EF-14 trial. If these results are compelling, this may result in accelerated approval and potentially a new standard of care for newly diagnosed GBM.

Keywords
glioblastoma (GBM), NovoTTF System, NovoTTF-100A, tumor treating fields (TTFields)

INTRODUCTION

Glioblastoma (GBM) is the most frequent intraparenchymal primary malignant brain tumor with an estimated incidence rate of 3.5 per 100 000 persons. Standard treatment (SOC) at diagnosis consists of maximal well tolerated surgical resection followed by radiation therapy with concomitant and adjuvant temozolomide (TMZ). Median overall survival (OS) reported with this treatment is between 12 and 18 months. Relapse of disease is seen in nearly all patients, and treatment options are limited in recurrent GBM.

The NovoTTF System (Novocure Ltd., Haifa, Israel) is a Food and Drug Administration (FDA) approved treatment for recurrent GBM [1]. TTFields is a transportable device that generates low-intensity alternating (100–300 kHz) electric fields, which have antimitotic properties. Efficacy of the device is dependent upon near constant administration. Physicians must be trained and certified to prescribe TTFields.

MECHANISM OF ACTION

There is no effect of TTFields on quiescent cells whereas there is an antimitotic effect on dividing cells. During cytokinesis, TTFields produce heterogeneous intracellular fields that cause a dielectrophoretic movement of charged or polar molecules and organelles toward higher field intensity [2,3].

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KEY POINTS

- TTFields are low-intensity, intermediate-frequency alternating electric fields that selectively kill or arrest growth of rapidly dividing GBM cells by disrupting and interfering with cell division and assembly of organelles, either directly or by interrupting mitotic spindle checkpoints.
- A significant improved outcome (3 months in both PFS and OS) was reported with TTFields in newly diagnosed GBM (phase III interim analysis).
- Treatment with TTFields should not be discontinued early as in nearly half of patients experiencing an apparent progression, subsequently manifested a delayed response.
- Compliance to treatment (minimal daily exposure of 18 h) is critical as exposure is highly correlated with response and survival.
- TTFields toxicity profile is excellent as it is confined to scalp dermatologic toxicity and does not appear to affect quality of life.

These fields exert forces that move polar macromolecules and organelles toward the narrow neck, splitting the newly forming daughter cells, by a process termed dielectrophoresis [4]. The molecular and organelle movements, together with an interference with the spindle tubulin polymerization process, inhibit cell division and lead to cell death [5].

A lack of systemic toxicity was predicted on the basis of the following in-vitro data. Dividing hematopoietic cells were not affected by TTFields because of interference by surrounding muscle and bone. Furthermore, because of the relatively high frequency range and very low intensity, TTFields do not stimulate nerves and muscles. Nor do TTFields generate a significant temperature increase in underlying tissue or cause direct injury to cell membranes as seen with strong electroporation fields [5,6].

PRECLINICAL DATA

Multiple cell lines have been treated with TTFields applied continuously for 24–72 h [5,7]. An effective and specific frequency was determined to optimize tumor inhibition for each cell line. For human glioma (U-87 and U-118) cell lines, the optimal frequency was 200 kHz. In particular, cell proliferation was studied in human breast carcinoma (MDA-MB-231) and human glioma (U-118) cell lines, exposed to TTFields, paclitaxel, doxorubicin, cyclophosphamide, and dacarbazine separately and in combination [4]. Proliferation was significantly inhibited, compared with control cultures and with those treated with TTFields alone. Under time-lapse microscopy, cancer cells underwent significantly prolonged mitosis and cell death following the formation of the mitotic cleavage furrow [7]. Immunohistochemistry studies of cell cultures treated with TTFields displayed abnormal mitotic figures that could be correlated with interference of mitotic spindle formation [8].

TTFields were also able to inhibit tumor growth in several mouse, rat, and rabbit animal models, and the effects of combining chemotherapy with TTFields in an animal tumor model were also studied [5,7]. Postmortem analysis of the TTFields treated animals showed a substantial tumor size decrease compared with controls. In-vivo experiments showed statistically significant growth inhibition required at least two or three directional fields to be delivered [7]. Last, a reduction of the extent of metastatic spread was observed in a melanoma mouse and kidney cancer rabbit model [9]. Furthermore, combination treatment results in irreparable cellular damage in contrast to chemotherapy only. The efficacy of the combination of TTFields and chemotherapy was found to be additive with a trend toward synergism for all drugs and cell lines tested. The sensitivity to chemotherapy was increased one-fold to three-fold by adjuvant TTFields. On the basis of these results, TTFields may be both an antimitotic agent and a chemotherapy sensitizing agent [4].

TTFIELDS IN RECURRENT GLIOBLASTOMA

Approval for the clinical use of TTFields for recurrent GBM was based on results of a phase III nonblinded trial that randomly assigned 237 patients to TTFields or physician's choice of best chemotherapy (PBC) [10,11].

Pilot study

Before initiating the phase III trial, a pilot study was conducted in 10 recurrent GBM patients. TTFields was prescribed alone without any concomitant chemotherapy. Two perpendicular 1–2 V/cm, 200-kHz alternating electric fields were continuously delivered for 18 h/day [7,8]. Compared with historical controls, patients showed an increased median time to progression (26.1 weeks) and 6-month progression-free survival (PFS) (50%), with a median OS greater than 62 weeks [7,8]. No serious adverse event was observed and mild-to-moderate dermatitis beneath the electrodes was the only common TTFields-related side-effect.

Phase III trial

A randomized phase III trial (EF-11) was initiated in which the primary endpoint was OS [10]. The trial design was that of a superiority study wherein it was the hypothesis that TTFields would be superior to PBC treatment. A total of 237 patients (120 TTFields, and 117 PBC) were enrolled.

Patient characteristics were balanced in both arms [median Karnofsky performance status (KPS) of 80%; median age of 54 years] and most patients were enrolled at the time of second or greater recurrence. In total, 18–19% of patients had received prior bevacizumab in both treatment arms. TTFields was administered continuously with a good patients' compliance (median daily exposure: 20 h). Approximately 30% of patients received bevacizumab as the PBC treatment.

The study was negative as the 6-month PFS, median PFS, and OS were comparable (no statistical difference) in those treated with TTFields versus chemotherapy (21.4 versus 15.1%; 2.2 versus 2.1 months and 6.6 versus 6 months, respectively). In subset analysis, an objective response was achieved in 14% of TTFields-treated patients (compared with only 9.6% with chemotherapy, $P = 0.19$), with less toxicity and better quality of life (QoL). Severe adverse events occurred in 6 and 16% ($P = 0.022$) of patients treated with TTFields and PBC, respectively. Hematologic and gastrointestinal side-effects were less frequent in TTFields patients compared with chemotherapy patients (3% versus 20%). Mild (14%) to moderate (2%) scalp dermatitis related to placement of the scalp transducer arrays was the most common TTFields-related side-effect (16%). The analysis of quality of life (QoL) in the areas of global health and social functioning did not show any meaningful difference between the two arms but was available in 27% of patients only. Nevertheless, cognitive and emotional functioning noticeably favored TTFields, whereas physical functioning looked somewhat worse with the experimental treatment. Increased pain and fatigue were reported in chemotherapy-treated patients only. The authors concluded that TTFields was not inferior to PBC in the recurrent treatment of GBM; however and importantly, the study was never designed or powered to prove this hypothesis. Rather, the study can fairly conclude that TTFields is well tolerated and not associated with a treatment-related decrement in QoL.

Patient Registry Dataset

A postmarketing Patient Registry Dataset (PRiDe) of all recurrent GBM adult patients who received TTFields in a real-world, clinical practice in the United States was recently published [12▪]. Median OS in PRiDe was compared for patients stratified by average daily compliance (≥75% versus <75% use per day) and other prognostic variables. Data from 457 patients treated in 91 cancer centers were analyzed. When compared with EF-11, more patients received TTFields for first recurrence (33% versus 9%) and more patients had previous treatment with bevacizumab (55.1 versus 19%). Survival was longer in PRiDE when compared with EF-11 (median survival 9.6 versus 6.6 months, $P = 0003$); 1-year survival (44% versus 20%), 2-year survival (30% versus 9%). Further, no new or increased toxicity was found in PRiDE compared with EF-11.

Favorable prognostic factors with regards to response and survival included a higher KPS (≥ 90% versus 70–80%), compliance with treatment (≥75% versus <75%), and earlier introduction of treatment (first or second versus third or fourth recurrence). Additionally, median OS was significantly increased in patients with increased compliance (≥75% or 18 h/day) to treatment (13.5 versus 4 months, $P < 0.0001$). Not surprisingly, and as previously reported with other salvage treatments for GBM, progression on bevacizumab was associated with a shorter survival (7.2 versus 13.4 months, $P < 0.0001$) [13,14]. A challenge with the PRiDE study conclusions is the retrospective nature, dependence upon institution voluntarily providing response and survival data and importantly, the study did not control for concomitant systemic therapies or post-TTFields progression therapy.

Response patterns in recurrent glioblastoma

The pattern of tumor response to TTFields has been studied in the population of recurrent GBM patients (phase III + pilot studies) [15▪▪]. A compartmental tumor growth model was developed to study growth kinetics and radiographic response to TTFields [15▪▪]. The model suggested 4 weeks of continuous exposure to TTFields would be the minimal time in which a radiographic response could be observed. These results are consistent with clinical findings in which nearly half (44%) of all responding patients exhibit initial tumor growth, followed by a delayed response 2–7 months later (median 4 months). In the 15% of patients with a long-duration response (median duration 12.9 months), responses developed slowly (median time to response 5.2 months).

Correlation between compliance, response, and survival

In a post-hoc analysis, response to TTFields was highly correlated with OS ($r^2 = 0.92$, $P < 0.0001$),

wherein responding patients had a median OS of 24.8 months [16▪]. As mentioned above, optimal compliance defined as exposure to TTFields at least 75% of the time or at least 18 h daily use was significantly related to both improved response and survival (7.7 versus 4.5 months; $P = 0.042$) [15▪▪,16▪,17▪].

TTFIELDS IN NEWLY DIAGNOSED GLIOBLASTOMA

Pilot study

A single-arm, pilot study combining TTFields with adjuvant TMZ in 10 patients with newly diagnosed GBM was performed [4]. Median OS and PFS were determined and compared with a matched group of concurrent-treated patients ($n = 32$) who received TMZ alone as well as to a matched historical dataset. A median OS of greater than 39 months was reported compared with 14.7 months for matched non-TTFields-treated patients. The median PFS was 155 versus 31 weeks for TTFields versus controls. No device-related serious adverse events were noted. The most common device-related side-effect was dermatitis, which occurs most frequently during the second month of treatment, and was successfully managed with topical corticosteroids and electrode relocation. As expected, no added systemic toxicity was reported. These results likely reflect a highly select population as is common in most pilot studies but do emphasize the preclinical data discussed above suggesting the potential role of TTFields as a sensitizer of TMZ [4].

Phase III trial

An international randomized (2 : 1) nonblinded phase III trial (EF-14) was initiated comparing SOC with SOC plus TTFields in newly diagnosed GBM. Preliminary results of the prespecified interim analysis and of the full data set were recently presented [18▪▪,19▪▪]. Patients received adjuvant treatment with TTFields and TMZ or TMZ alone after completion of standard TMZ-based chemoradiation (CRT). To be eligible, patients must be 18 years old or older, have a histologically proven supratentorial GBM, completed CRT without clinical or radiographic disease progression, and were on stable or decreased doses of corticosteroids. Enrollment was permitted in the period between 4 and 7 weeks after CRT completion. The planned interim analysis of the intent to treat (ITT) population assessed the first 315 enrolled patients with a minimum follow-up of 18 months. PFS was the primary endpoint and OS was a secondary endpoint to be assessed only if the primary endpoint was met. Early results of the entire 700 patients with a median follow-up of 12 months were also recently reported and were an unplanned but FDA-mandated confirmatory analysis [19▪▪].

In both interim and confirmatory analyses, patient baseline characteristics were well balanced regarding age, KPS, and MGMT status (Table 1). A blinded review panel assessed the objective trial endpoints including PFS and OS independently. Results in the ITT population (full data set) showed a significantly improved PFS in TTFields-treated patients compared with those assigned to TMZ only (7.1 versus 4.2 months, hazard ratio 0.69, $P = 0.001$). Overall survival in the ITT population was also improved (19.4 versus 16.6 months, hazard ratio 0.75, $P = 0.02$). The median interval time from diagnosis to randomization was 3.8 months in both arms. The median OS from diagnosis was 23 versus 20.1 months, with a 2-year survival rate of 43% versus 29% months, in the TTFields and control arm, respectively. The median PFS and OS from time to diagnosis (8.2 and 20.1 months, respectively) reported in the control arm are comparable to other phase III GBM studies [20–23]. Preliminary results of the full dataset were consistent with the results of the interim analysis (Table 1). Further follow-up of patients will provide a better indication whether preliminary data are confirmed with respect to trial endpoints. For a clearer understanding of survival data, it would be important to know the rate of cross-over to TTFields and, whether both arms are balanced regarding treatment at relapse, particularly for use of bevacizumab. Whether the monitoring of patients assigned to TTFields influenced OS by way of early introduction of palliative care is an unknown confounder although admittedly should not have influenced the PFS results. As expected, TTFields was not associated with any systemic toxicity and the safety profile was similar in both arms of the trial, except for scalp irritation that was significantly more frequent in the TTFields arm (2% CTC Grade 3 or higher). In the interim analysis, Grade 1–2 neuropsychiatric disorders were reported more frequently in the TTFields arm (33% versus 15%). These adverse events mainly consisted of anxiety, confusion, and insomnia. There was no difference regarding Grade 3–4 neuropsychiatric adverse events (4% versus 3%) between treatment arms [18▪▪].

Issues of cost (approximately $23 000/month in the United States) and coverage by third-party payers are an issue yet to be addressed regarding use of TTFields.

Table 1. EF-14: comparative results of the interim and the confirmatory analyses

	Interim analysis [18▪▪] *n* = 315, median f-up = 18 mo		**Confirmatory analysis [19▪▪] n = 700, median f-up = 12 mo**	
	TTF + TMZ	**TMZ alone**	**TTF + TMZ**	**TMZ alone**
n	210	105	466	229
Age, median (range)	57 (20–83)	58 (21–80)	56 (19–83)	57 (19–80)
KPS (%), median (range)	90 (60–100)	90 (70–100)	90 (60–100)	90 (70–100)
Extent of resection	100%		100%	
Biopsy only	11%	10%	13%	13%
Partial/gross total resection	26%/63%	26%/64%	33%/54%	33%/54%
MGMT status assessable	60%	61%	77%	75%
Methylated/unmethylated invalid	39%/61%	41%/59%	35%/52%	39%/51%
	NA	NA	13%	11%
Median time dg – randomization	3.8 mo	3.8 mo	3.8 mo	3.8 mo
PFS – first endpoint – ITT population				
Median from randomization	7.1 mo	4.0 mo	7.1 mo	4.2 mo
95% CI	5.9–8.2	3–4.3	6–8.1	3.9–5.5
Median from dg	10.9 mo	7.9 mo	11 mo	8.2 mo
Log rank	$P = 0.0014$		$P = 0.001$	
Hazard ratio	0.63		0.69	
OS – second endpoint – ITT population				
Median from randomization	19.6 mo	16.6 mo	19.4 mo	16.6 mo
95% CI	16.5–24.1	13.5–19.1	16.5–23.8	13.7–18.5
Median from dg	22.6 mo	19.6 mo	23 mo	20.1 mo
Log rank	$P = 0.034$		$P = 0.0222$	
Hazard ratio	0.75		0.75	
2-year survival	43%	29%	43%	29%
95% CI	36–50	21–39	36–50	21–39

CI, confidence interval; dg, diagnosis; f-up, follow-up; ITT, intent to treat; mo, months; NA, not available; OS, overall survival; PFS, progression-free survival; TMZ, temozolomide; TTF, tumor treating fields.

MANAGEMENT OF LOCAL AND DERMATOLOGIC SIDE-EFFECTS

Management of dermatologic side-effects affecting the scalp is important as this may influence patients' compliance to treatment. Treatment relies on published preventive and symptomatic recommendations [24▪]. Dermatitis is the most common side-effect of TTFields and may be contact or allergic in etiology. Prevention consists of patient and caregiver education, proper scalp preparation, infection prevention, avoidance of scar and craniotomy hardware, and array relocation. Treatment is mostly based on the judicious use of topical corticosteroids and electrodes relocation [24▪].

CONCLUSION

TTFields delivers low amplitude intermediate frequency electric fields that disrupt and interfere with cell division. The upfront GBM trial EF-14 compared SOC with or without TTFields and concluded, based on an interim and confirmatory analysis, the experimental arm was superior both with respect to PFS and OS. Whether these data are sufficiently compelling to change current clinic practice is uncertain and awaits further analysis with longer follow-up.

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Conflicts of interest

The first author was a principal investigator in France and on site (Pitie-Salpetriere Hospital, France) for the two phase III trials, EF-11 and EF-14.
There are no conflicts of interest.

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Management of dermatologic complications of TTFields: prophylactic recommendations for patients and caregivers, and curative intervention. These measures are important in order to facilitate a better compliance and efficacy of TTFields.