Noninvasive Application of Alternating Electric Fields in Glioblastoma: A Fourth Cancer Treatment Modality

By Philip H. Gutin, MD, and Eric T. Wong, MD

Overview: **Tumor treating fields (TTF) therapy is a novel antimitotic, electric field–based treatment for cancer. This nonchemical, nonablative treatment is unlike any of the established cancer treatment modalities, such as surgery, radiation, and chemotherapy. Recently, it has entered clinical use after a decade of intensive translational research. TTF therapy is delivered to patients by a portable, battery-operated, medical device using noninvasive transducer arrays placed on the skin surface surrounding the treated tumor. TTF therapy is now a U.S. Food and Drug Administration (FDA)–approved treatment for patients with recurrent glioblastoma (GBM) who have exhausted surgical and radiation treatments. This article will introduce the basic science behind TTF therapy, its mechanism of action, the preclinical findings that led to its clinical testing, and the clinical safety and efficacy data available to date, as well as offer future research directions on this novel treatment modality for cancer.**

THE DEFINITION of the electric field is attributed to Michael Faraday in the 1820s and was later formulated by James Clerk Maxwell in his electromagnetic theory in 1865.[1] It is a field of electric forces that surround a source charge. When a test charge is placed within an electric field, a force acts on it. Negative charges attract positive charges, while similar signed charges repel each other. As seen in Fig. 1A, an electric field surrounding a source charge can be described using diverging lines of force. The closer the test charge is to the source charge, the closer the lines of force are to each other, which represents higher field intensity.

To understand the effects of electric fields within cells, it is important to introduce three definitions. First, electric fields can be uniform or nonuniform. A uniform electric field is represented by parallel lines of force (Fig. 1B). A nonuniform electric field is represented by converging or diverging lines of force (Fig. 1A and 1D). Second, an electric field can be a constant field or a time-varying field, resulting in electrostatic or electrodynamic phenomena, respectively. In a constant field, the source charges remain the same over time. A test charge will move in one direction within a constant electric field toward the oppositely charged source (Fig. 1B). In a time-varying or alternating electric field, the charge of the sources alternates over time (Fig. 1C). Third, the test charge can be an electric charge or an electric dipole (an element with a positive charge on one end and a negative charge on the opposite end). An electric charge will move back and forth, while a dipole will rotate within an alternating uniform electric field and align with the direction of the field. In a nonuniform converging electric field, both dipoles and charges move in the direction of the higher field intensity through a process known as dielectrophoresis (Fig. 1D).

Mechanism of Action of TTF Therapy

Over 100 years after Maxwell's original publication, Yoram Palti, MD, PhD, hypothesized that properly tuned alternating electric fields at physiological intensities (i.e., 1–3 V/cm) would disrupt the mitotic process of dividing cancer cells.[2,3] Dr. Palti hypothesized and subsequently demonstrated in vitro that at frequencies between 100 and 300 kHz, alternating electric fields disrupt the formation of the mitotic spindle during metaphase and lead to dielectrophoretic movement of charged and/or polar molecules and organelles during anaphase and telophase, disrupting normal cytokinesis and leading to apoptosis.[2,3] According to this model, the first mechanism of action is explained by the fact that the tubulin subunits are one of the most polar molecules in the cell. These tubulin subunits align in the direction of the applied electric field (Fig. 2A), interfering with the normal polymerization of the mitotic spindle, which results in formation of abnormal mitotic figures in vitro.[3] The second mechanism of action is explained by examining the change in shape of the electric field within a dividing cell from anaphase to telophase. When the cell division axis is aligned with the direction of the electric field, the field lines that enter the cell at one end converge at the cytokinetic furrow between the developing daughter cells and then diverge on the opposite side (Fig. 2B). This nonuniform electric field within the cell generates dielectrophoretic forces that act on polar and charged elements in the cell, pushing them toward the cytokinetic furrow leading to violent blebbing of the plasma membrane.[3] This finding was also validated by researchers from Beth Israel Deaconess Medical Center and may be mediated by improper placement of the contractile elements that form the cytokinetic ring on anaphase entry.[4]

Preclinical Studies of the Antitumor Effects of TTF Therapy

Between 2004 and 2010, a series of publications and conference presentations addressed the issue of the applicability range of TTF therapy to different in vitro and in vivo cancer models either alone or in combination with standard chemotherapy.[3,5-8] Tables 1 and 2 summarize the state-of-the-art preclinical research with TTF therapy. TTF therapy has been shown to effectively inhibit cancer cell growth in various cell lines in vitro (Table 1). This effect was clearly dose (field intensity) dependent in the range of 1 to 3 V/cm.[5] The optimal frequency for the inhibitory effect of TTF therapy differed between cell types and was inversely related to cell size (Table 1; e.g., glioma cell cultures at 200 kHz[3,5]). In addition, based on the directional nature of TTF

From the Department of Neurosurgery, Memorial Sloan-Kettering Cancer Center Brain Tumor Center, New York, NY; and Brain Tumor Center and Neuro-Oncology Unit, Beth Israel Deaconess Medical Center, Boston, MA.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Philip H. Gutin, MD, Department of Neurosurgery, C-703, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10065; email: gutinp@mskcc.org.

© 2012 by American Society of Clinical Oncology.

1092-9118/10/1-10

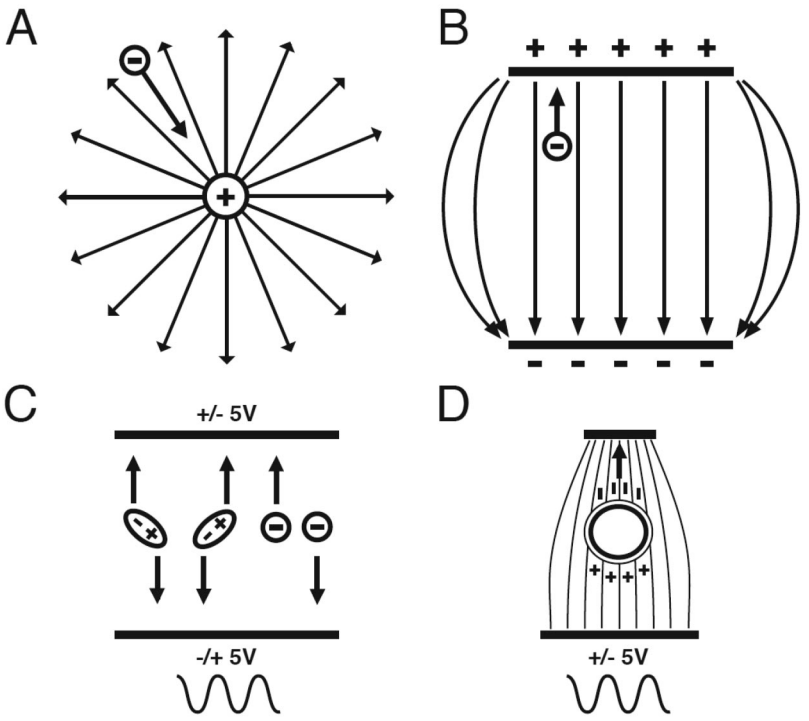

Fig. 1. Electric field theory. (A) Opposite charges attract. (B) A constant, uniform, electric field. (C) Charges and dipoles in a time-varying, uniform electric field. (D) A dipole in a time-varying, nonuniform electric field (dielectrophoresis).

therapy, its antimitotic effect in cultures was enhanced by sequentially applying more than one field direction to the treated cells.[5] The combination of TTF therapy with different chemotherapeutic agents has been shown to have at least additive if not synergistic effects.[7,9] Specifically, the combination of TTF therapy with temozolomide in glioma cell lines was shown to be additive. Interestingly, in breast cancer cells, TTF therapy showed overt synergism with taxanes (e.g., paclitaxel), probably a result of the temporal proximity of taxanes' effect in metaphase and TTF therapy's mitotic interference on cell entry into anaphase.[5]

KEY POINTS

- Tumor treating fields (TTF) therapy is an emerging, low-toxicity treatment modality for solid tumors based on the delivery of antimitotic alternating electric fields to the tumor, which interfere with cytokinesis and microtubule assembly that eventually lead to cell death.
- As a monotherapy, TTF therapy is at least as effective as currently available active chemotherapy and biologic therapies for the treatment of recurrent glioblastoma (GBM).
- The efficacy of this noninvasive treatment modality is achieved with significantly less toxicity and a better quality of life compared with chemotherapy.
- Preliminary data suggest TTF therapy acts synergistically with temozolomide and other chemotherapy in both preclinical and clinical trials.
- Future research should focus on integrating TTF therapy into the treatment of GBM in the adjuvant and maintenance settings, as well as in the treatment of other solid tumor malignancies.

TTF therapy has been tested in numerous in vivo cancer models (Table 2).[3,5,8,10] Noninvasive application of TTF therapy to animals was performed using electrically insulated transducer arrays placed on the head or torso surrounding the region of the tumor. Inhibition of tumor growth was seen in each of these models when the correct frequency of TTF therapy was applied. Specifically, 200 kHz TTF therapy applied in two sequential and perpendicular field directions lead to significant ($p < 0.01$) inhibition of a syngeneic, orthotopic F-98 glioma in rats after 7 days of treatment.[5] An additional syngeneic, orthotopic model of non-small cell lung cancer in mice showed that 150 kHz TTF therapy significantly ($p < 0.01$) inhibited tumor growth within 7 days of treatment.[8,11] Furthermore, the additive effect of TTF therapy with chemotherapy seen in vitro was recapitulated in different in vivo models.[5,8] Finally, in a metastatic tumor model using a squamous carcinoma tumor implanted in the kidney capsule of rabbits, TTF therapy applied to the abdomen blocked metastatic spread of tumor from the kidney to the lungs.[10,27]

Translating TTF Therapy into Clinical Use

Since TTF therapy is a physical antimitotic modality with no half-life, its application should be continuous. Kinetic modeling was used to predict the minimal treatment duration needed with TTF therapy.[12] Based on these data, a minimal treatment course of 4 weeks was defined and implemented in clinical studies. In vivo animal experiments and pilot clinical data subsequently verified the 4-week minimal treatment duration.[12] Such continuous delivery was made possible by the development of a portable, battery-operated, medical device that patients can use at home (NovoTTF-100A, Novocure, Haifa, Israel). Finally, extensive toxicity studies of TTF therapy were performed in healthy

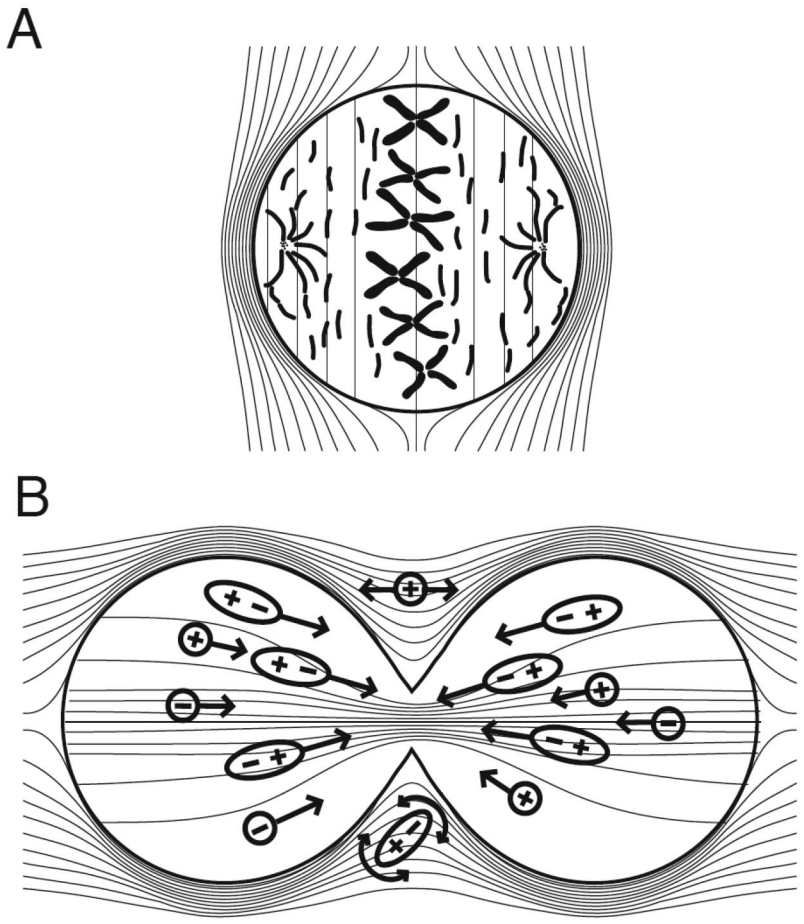

Fig. 2. Effects of tumor treating fields therapy on intracellular structures during mitosis. (A) During metaphase, tubulin dimers align with the external electric field, interfering with the formation of the mitotic spindle. (B) During cytokinesis, the nonuniform electric field formed within the dividing cell drives charged and polar macro-molecules and organelles toward the cleavage furrow.

mice, rats, and rabbits.[5,9] Clinical, laboratory, and pathologic analyses showed that TTF therapy is well tolerated and does not lead to systemic toxicity in animals. As expected by the frequency range of TTF therapy (100–300 kHz), these electric fields do not have any effect on excitable tissues (neural, muscular, or cardiac), nor do they cause significant heating.[13-15]

Clinical Testing of TTF Therapy as a Monotherapy

The NovoTTF device was first applied to patients in a small feasibility trial in Switzerland in 2003.[16] In 2004, TTF therapy was tested in a pilot clinical trial in patients with recurrent GBM (Table 3).[5] This single-center, single-arm trial included patients with favorable prognostic character-

Table 1. In Vitro Evidence Overview

Histology	Cell Line	Optimal/Effective TTF Frequency (kHz)	Additive/Synergistic with Chemotherapy	Reference
High-grade glioma	F-98; C-6; RG-2	200	Temozolomide (dacarbazine)	*Can Res*, 2004[3]
	U-118; U-87			*Proc Natl Acad Sci U S A*, 2007[5]
Breast adenocarcinoma	Normal:	120	Cyclophosphamide	*Can Res*, 2004[3]
	MDA-MB-231			
	MCF7		Doxorubicin	*Neuro Oncol*, 2011[4]
	Multiple drug resistant:	120	Paclitaxel	*BMC Cancer*, 2010[7]
	MDA-MB-231Dox			
	AA8/Emt^{R1}		Doxorubicin	
	MCF7/Mx		Paclitaxel	
Non-small cell lung cancer (adenocarcinoma)	H1299	150	Paclitaxel	*ERS*, 2010[8]
	LLC		Pemetrexed	*AACR*, 2007[6]
				Can Res, 2004[3]
Colorectal adenocarcinoma	CT-26	100*	NA	*Can Res*, 2004[3]
Malignant melanoma	B16F1 Patricia	100	NA	*Can Res*, 2004[3]
Prostate	PC-3	100*	NA	*Can Res*, 2004[3]
Cervical cancer	HeLa	200*	NA	*Neuro Oncol*, 2011[4]

Abbreviations: TTF, tumor treating fields; NA, not available (was not reported by the authors).
* Effect seen at this frequency; additional frequencies were not tested.

Table 2. In Vivo Evidence Overview

Tumor Type	Anatomic Location	Animal Model	Frequency (kHz)	Effect of TTF	References
GBM	Right hemisphere	Rat	200	Tumor growth inhibition with 2 and 3 field directions	*Proc Natl Acad Sci U S A*, 2007[5]
Non-small cell lung cancer	Lung parenchyma	Mouse	150	1. Tumor growth inhibition with 2 field directions 2. Additive tumor inhibition with pemetrexed	*ERS*, 2010[8]
Malignant melanoma	Intradermal	Mouse	100	Tumor growth inhibition with 1 and 2 field directions	*Can Res*, 2004[3] *Proc Natl Acad Sci U S A*, 2007[5]
Malignant melanoma	Intravenous	Mouse	100	Inhibition of metastatic seeding in the lungs	*Clin Exp Metastasis*, 2009[10]
VX-2 (anaplastic)	Kidney capsule	Rabbit	150–200	1. Tumor growth inhibition seen with 2 field directions 2. Increase in median survival 3. Inhibition of metastatic seeding in the lungs 4. Additive tumor inhibition with paclitaxel	*Clin Exp Metastasis*, 2009[10] *AACR*, 2009[27] *Neuro Oncol*, 2010[12]

Abbreviation: GBM, glioblastoma.

istics. Treatment with the device was well tolerated, and no treatment-related serious adverse events were reported. Most patients developed grade 1 to 2 contact dermatitis beneath the transducer arrays on the scalp. Efficacy endpoints were very encouraging with a 20% objective response rate, progression-free survival (PFS) at 6 months of 50%, median time to progression (TTP) of 26 weeks, and median overall survival (OS) of 62.2 weeks (14.4 months). Compared to the historic results of salvage chemotherapy, these results showed clear activity of TTF therapy when used as a monotherapy in recurrent GBM.[17]

Based on the results of this pilot trial, a pivotal phase III, multicenter, randomized (1:1) clinical study was initiated in patients with recurrent GBM (Table 3). The randomized study, which recruited 237 patients between 2006 and 2009, compared the efficacy and safety of monotherapy with the NovoTTF device to that of the best available active chemotherapy according to physician's choice. Thirty-six patients received bevacizumab, 36 received nitrosureas, 12 received temozolomide, and 33 received other agents. This was the largest randomized study in recurrent GBM to be completed to date. The results of the study were presented at the 2010 ASCO Annual Meeting and were updated at the 2011 Society for Neuro-Oncology (SNO) Annual Meeting.[18,19] Baseline characteristics of patients were balanced between the two treatment groups. In both groups, patients had poor prognostic predictors compared with previous clinical trials of recurrent GBM (90% of patients were at their second or subsequent recurrence; 20% had failed bevacizumab before entering the trial; and the average tumor diameter was above 5 cm). In the conservative intent-to-treat (ITT) analysis, the study showed that patients with recurrent GBM treated with NovoTTF alone had comparable OS to that of patients who received chemotherapy and/or bevacizumab (6.6 months vs. 6.0 months, respectively; $p = 0.26$; hazard ratio [HR] = 0.86; Table 3). Although NovoTTF did not show superiority over active chemotherapies, it was clear that it was at least as effective as these treatments. Secondary endpoints in the trial were supportive: blinded radiology review showed that PFS at 6 months was 21.4% in the NovoTTF group compared with 15.2% in the chemotherapy group ($p = 0.24$). There were more radiological responses seen in the NovoTTF group compared with the chemotherapy group (12% vs. 6%, respectively; $p = 0.07$), including

Table 3. Clinical Evidence Overview

Indication (Analysis Group)	Trial Phase (# of Subjects) Analysis	Overall Survival (Months) TTF	Overall Survival (Months) Chemo	Hazard Ratio (p)	Progression-Free Survival (PFS) at 6 Months or Median PFS (Weeks) TTF	Progression-Free Survival (PFS) at 6 Months or Median PFS (Weeks) Chemo	P value	References
Recurrent GBM (at first relapse)	Phase I-II (n = 10) *ITT Analysis*	14.5 m	6.0 m*	Non-randomized	50%	15%*	NA	*Proc Natl Acad Sci U S A*, 2007[5]
Recurrent GBM (at second and fourth relapse)	Phase III (n = 237) *ITT analysis*	6.6 m	6.0 m	HR = 0.86 (p = 0.26)	21.4%	15.2%	p = 0.24	*J Clin Oncol*, 2010[18] *Neuro Oncol*, 2011[19]
Recurrent GBM (treated patients only)	Phase III (n = 210) *PP Analysis*	7.8 m	6.0 m	HR = 0.67 (p = 0.012)	26.2%	15.2%	p = 0.03	*J Clin Oncol*, 2010[18] *Neuro Oncol*, 2011[19]
Recurrent GBM (KPS ≥ 80, age < 61)	Phase III (n = 110) *Subgroup analysis*	8.8 m	6.6 m	HR = NA (p < 0.01)	25.6%	7.7%	NA	*Neuro Oncol*, 2010[19]
Recurrent GBM (after bevacizumab failure)	Phase III (n = 43) *Subgroup analysis*	4.4 m	3.1 m	(p = 0.02)	NA	NA	NA	*Neuro Oncol*, 2010[20]
Recurrent GBM (TTF versus bevacizumab)	Phase III (n = 156) *Subgroup analysis*	6.6 m	5.0 m	HR = 0.65 (p = 0.048)	21%	21%	p > 0.05	*Neuro Oncol*, 2011[21]
Newly diagnosed GBM (together with temozolomide)	I-II (n = 10) *ITT Analysis*	39+ m	14.7 m*	(p = 0.002)	90% 155 w	50%* 26 w	NA	*BMC Med Phys*, 2009[9]
Relapsed advanced NSCLC (together with pemetrexed)	I-II (n = 42) *ITT Analysis*	13.8 m	8.2 m*	NA	28 w	12 w*		*ESMO*, 2010[25] *ERS*, 2010[8] *Expert Opin Investig Drugs*, 2010[11]

Abbreviations: GBM, glioblastoma; ITT, intention to treat; NA, not available (was not reported by the authors); HR, hazard ratio; PP, per protocol; KPS, Karnofsky performance status; TTF, tumor treating fields; NSCLC, non-small cell lung cancer.

* Single-arm trials with literature control.

three sustained complete responses in the NovoTTF group compared with none in the chemotherapy group. These results were accompanied by significantly ($p < 0.05$) less treatment-related adverse events with NovoTTF compared with chemotherapy. Patients in the NovoTTF group reported a higher quality of life compared with patients treated with chemotherapy. This analysis was based on the European Organisation for Research and Treatment of Cancer QLQ-C30 and mirrored the lack of chemotherapy-related toxicities in the NovoTTF group. Interestingly, patients in the NovoTTF group reported better cognitive and emotional functioning and much less pain than patients in the chemotherapy group, although these domains of the questionnaires are not related to known side effects of chemotherapy.

To date, several exploratory analyses of the study data have been performed. The first analysis compared patients who received the same "amount" of therapy in both groups. This prospectively defined per-protocol analysis excluded patients from both groups who received less than one predefined treatment course. The analysis demonstrated superior survival in the NovoTTF group compared with the chemotherapy group (7.8 months vs. 6.0 months; $p = 0.012$, HR = 0.67).[18,19] The rationale behind this analysis is that TTF is a physical modality with no half-life, so that the moment the therapy is stopped, its antimitotic effect stops as well. In contrast, chemotherapies have measurable plasma and tissue half-life, which results in continued efficacy and toxicity long after a dose has been given. Therefore, to achieve pharmacokinetic balance in the "amount" of treatment in both groups, this analysis used a simplified criterion that one course of chemotherapy (e.g., 1 day of carmustine or 5 days of temozolomide) is equivalent to four weeks of continuous TTF therapy.

Two more analyses of the study data were presented at the 2010 and 2011 SNO Annual Meetings.[20,21] The first study analyzed known clinical prognostic factors of age and Karnofsky performance status (KPS). This analysis demonstrated that in patients age 60 and younger with a KPS greater than 70, treatment with NovoTTF resulted in superior OS compared with chemotherapy (8.8 months vs. 6.6 months; $p < 0.01$). This survival advantage could be attributed to better compliance with TTF therapy in this group of patients. In support of this finding, a statistically significant correlation was seen in the NovoTTF group between treatment compliance (as measured by the device computerized log file) and OS ($p = 0.0475$).

The second analysis is a post hoc, exploratory analysis of the treatment of 120 patients with NovoTTF compared with 36 patients with bevacizumab. Although without a prespecified analysis in the trial, patients in the study treated with NovoTTF lived significantly longer than those treated with bevacizumab (6.6 months vs. 5.0 months, respectively; $p = 0.048$, HR = 0.65).[21] This analysis included all ITT patients who received either bevacizumab or NovoTTF. Patient characteristics were almost identical and, in fact, favored the bevacizumab group prognostically. Clearly, this analysis cannot be taken as final evidence of superiority of NovoTTF over bevacizumab; however, it should be treated as hypothesis-generating data for future clinical studies. Finally, in the 43 patients who entered the study after bevacizumab therapy failure (approximately 20% of patients in both groups), OS was significantly longer with TTF therapy than with chemotherapy (4.4 months vs. 3.1 months, respectively; $p = 0.02$). The data for the chemotherapy-treated group is in line with previous publications, which showed that following bevacizumab failure, the survival of patients with recurrent GBM is limited.[22]

Based on the results of this pivotal phase III study, the FDA approved the NovoTTF-100A device on April 8, 2011, through the premarket approval (PMA) regulatory pathway. The PMA pathway is reserved for class III (high-risk) medical devices and requires preclinical, clinical, and manufacturing evidence, including review of both efficacy and safety data by a panel of independent experts. The FDA concluded that the study results showed NovoTTF to be comparable in efficacy to active chemotherapy, without many of the side effects associated with chemotherapies and with a better quality of life.[23]

Clinical Trials Evaluating TTF Therapy in Combination with Chemotherapy

Two studies of combined TTF therapy and chemotherapy have been published to date. The first was a single-arm, single-center trial performed in 2006 in patients with newly diagnosed GBM.[9] Patients received the Stupp protocol with TTF therapy added to maintenance temozolomide.[24] This trial showed promising PFS and OS data (PFS > 14 months; OS > 39 months; Table 3) and served as the basis for an ongoing, multicenter, pivotal phase III, randomized clinical study comparing TTF therapy and temozolomide with temozolomide alone in the maintenance stage of the Stupp protocol.

The second study tested TTF therapy together with pemetrexed in 42 patients with pretreated, advanced non-small cell lung cancer.[8,11,25] Efficacy and safety with this combined treatment paradigm were promising. Time to local disease progression in the lungs and liver (where TTF was applied) was 28 weeks, and OS was 13.8 months. In contrast, TTP and OS for pemetrexed alone were previously reported to be 12 weeks and 8.3 months, respectively.[26]

TTF therapy is still in its early days. However, it has an established mechanism of action, and a growing body of preclinical evidence has shown its wide applicability in solid tumor malignancies either alone or in combination with standard chemotherapies. Objective antitumor activity and an unprecedented safety profile of this treatment modality have been seen in patients with recurrent GBM. Although TTF monotherapy has been shown to be at least as effective as the best available chemotherapies today for recurrent GBM, in-depth analysis of the phase III study data identified at least two subgroups where TTF therapy was superior to chemotherapy and could be offered to patients as an alternative to chemotherapy: younger patients with a better functional status and patients in whom bevacizumab treatment has failed in the past.

Conclusion

The approval of TTF therapy for recurrent GBM ushers in a fourth modality of cancer treatment. More importantly, TTF treatment has a superior safety profile, and its minor side effects do not appear to overlap with those of cytotoxic chemotherapies, targeted agents, or antiangiogenesis drugs. Therefore, the rational combination of TTF therapy with specific pharmacologic agents may enhance tumor cell death

because of potential additive or synergistic effects. First, as demonstrated in preclinical and clinical models, chemotherapy administered together with TTF therapy may result in additive or synergistic tumor control without increasing systemic toxicities. Second, TTF treatment could be combined with targeted agents that block survival signaling within the tumor cell. This block may be sufficiently strong to enhance the cytotoxic effect of TTF therapy or vice versa. Third, the combination of TTF and antiangiogenesis agents may be another promising path that combines different antitumor treatments to improve tumor control. Lastly, the proper scheduling of TTF therapy with other agents is unknown. Additional research may shed light on the optimal scheduling that may achieve a synergistic effect on tumor growth leading to long-term tumor control and enhanced patient survival.

Authors' Disclosures of Potential Conflicts of Interest

Author	Employment or Leadership Positions	Consultant or Advisory Role	Stock Ownership	Honoraria	Research Funding	Expert Testimony	Other Remuneration
Philip H. Gutin					Novocure		Novocure
Eric T. Wong					Novocure		

REFERENCES

1. Maxwell JC. A Dynamical Theory of the Electromagnetic Field. *Royal Society Transactions.* CLV:1865.
2. Palti Y, Schneiderman R, Gurvich Z, et al. Cell proliferation arrest and tumor cell destruction by low intensity, frequency tuned electric fields. *2004 AACR Meeting Abstracts.* (abstr 1000).
3. Kirson ED, Gurvich Z, Schneiderman R, et al. Disruption of cancer cell replication by alternating electric fields. *Cancer Res.* 2004;64:3288-3295.
4. Lee SX, Wong ET, Swanson KD. Mitosis Interference of Cancer Cells During Anaphase By Electric Field from NovoTTF-100A. *Neuro Oncol*. 2011;13:iii10-iii25 (suppl 3; abstr CB-17).
5. Kirson ED, Dbaly V, Tovarys F, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci U S A.* 2007;104:10152-10157.
6. Schneiderman R, Shmueli E, Kirson E, et al. Synergism between chemotherapy and alternating electric fields in the inhibition of cancer cell proliferation in-vitro. *2007 AACR Meeting Abstracts.* (abstr 2276).
7. Schneiderman RS, Shmueli E, Kirson ED, et al. TTFields alone and in combination with chemotherapeutic agents effectively reduce the viability of MDR cell sub-lines that over-express ABC transporters. *BMC Cancer.* 2010; 10:229.
8. Weinberg U, Fresard I, Kueng M, et al. An Open Label Pilot Study of Tumor Treating Fields (TTFields) in Combination with Pemetrexed for Advanced Non-small Cell Lung Cancer (NSCLC). *2010 ERS Annual Congress.* (abstr 363).
9. Kirson ED, Schneiderman RS, Dbaly V, et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). *BMC Med Phys.* 2009;9:1.
10. Kirson ED, Giladi M, Gurvich Z, et al. Alternating electric fields (TTFields) inhibit metastatic spread of solid tumors to the lungs. *Clin Exp Metastasis.* 2009;26:633-640.
11. Pless M, Weinberg U. Tumor treating fields: Concept, evidence and future. *Expert Opin Investig Drugs.* 2010;20:1099-1106.
12. Kirson ED, Wasserman Y, Izhaki A, et al. Modeling tumor growth kinetics and its implications for TTFields treatment planning. *Neuro Oncol*. 2010;12:iv36-iv57 (suppl 4; abstr NO-54).
13. Palti Y. Stimulation of muscles and nerves by means of externally applied electrodes. *Bull Res Counc Isr Sect E Exp Med.* 1962;10:54-56.
14. Shizgal P, Mathews G. Electrical stimulation of the rat diencephalon: Differential effects of interrupted stimulation on on- and off-responding. *Brain Res.* 1977;129:319-333.
15. Yearwood TL, Hershey B, Bradley K, et al. Pulse width programming in spinal cord stimulation: A clinical study. *Pain Physician.* 2010;13:321-335.
16. Salzberg M, Kirson E, Palti Y, et al. A pilot study with very low-intensity, intermediate-frequency electric fields in patients with locally advanced and/or metastatic solid tumors. *Onkologie.* 2008;31:362-365.
17. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol.* 1999;17:2572-2578.
18. Stupp R, Kanner A, Engelhard H, et al. A prospective, randomized, open-label, phase III clinical trial of NovoTTF-100A versus best standard of care chemotherapy in patients with recurrent glioblastoma. *J Clin Oncol.* 2010;28:18s (suppl; abstr LBA2007).
19. Wong ET, Ram Z, Gutin PH, et al. Updated survival data of the phase III clinical trial of NovoTTF-100A versus best standard chemotherapy for recurrent glioblastoma. *Neuro Oncol.* 2011;13:iii85-iii91 (suppl 3; abstr OT-09).
20. Ram Z, Gutin PH, Stupp R. Subgroup and quality of life analyses of the phase III clinical trial of NovoTTF-100A versus best standard chemotherapy for recurrent glioblastoma. *Neuro Oncol.* 2010;12:iv36-iv57 (suppl 4; abstr NO-55).
21. Ram Z, Gutin PH, Wong ET. Comparing the effect of NovoTTF to Bevacizumab in Recurrent GBM: A Post-Hoc Sub-Analysis of the Phase III Trial Data. *Neuro Oncol.* 2011;13:iii41-iii68 (suppl 3; abstr NO-50).
22. Iwamoto FM, Abrey LE, Beal K, et al. Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma. *Neurology.* 2009;73: 1200-1206.
23. FDA: NovoTTF-100A Information for Use, 2011. http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034c.pdf. Accessed February 23, 2012.
24. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352:987-996.
25. Pless M, Betticher DC, Buess M, et al. A phase II study of tumor treating fields (TTFields) in combination with pemetrexed for advanced non small cell lung cancer (NSCLC). *Ann Oncol.* 2010:viii122-viii161.
26. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol.* 2004;22:1589-1597.
27. Kirson E, Gurvich Z, Izhaki A, et al. Alternating electric fields (TTFields) inhibit metastatic spread of solid tumors to the lungs in-vivo. *2009 AACR Meeting Abstracts.* (abstr 151).