The effects of alternating electric fields in glioblastoma: current evidence on therapeutic mechanisms and clinical outcomes

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Glioblastoma is both the most common and most lethal primary CNS malignancy in adults, accounting for 45.6% of all malignant CNS tumors, with a 5-year survival rate of only 5.0%, despite the utilization of multimodal therapy including resection, chemotherapy, and radiation. Currently available treatment options for glioblastoma often remain limited, offering brief periods of improved survival, but with substantial side effects. As such, improvements in current treatment strategies or, more likely, the implementation of novel strategies altogether are warranted. In this topic review, the authors provide a comprehensive review on the potential of alternating electric fields (AEFs) in the treatment of glioblastoma. Alternating electric fields—also known as tumor-treating fields (TTFs)—represent an entirely original therapeutic modality with preliminary studies suggesting comparable, and at times improved, efficacy to standard chemotherapeutic agents in the treatment of recurrent glioblastoma. A recent multicenter, Phase III, randomized clinical trial comparing NovoTTF-100A monotherapy to physician's best choice chemotherapy in patients with recurrent glioblastoma revealed that AEFs have similar efficacy to standard chemotherapeutic agents with a more favorable side-effects profile and improved quality of life. In particular, AEFs were shown to have limited systemic adverse effects, with the most common side effect being contact dermatitis on the scalp at the sites of transducer placement. This study prompted FDA approval of the NovoTTF-100A system in April 2011 as a standalone therapy for treatment of recurrent glioblastoma refractory to surgical and radiation treatment. In addition to discussing the available clinical evidence regarding the utilization of AEFs in glioblastoma, this article provides essential information regarding the supposed therapeutic mechanism as well as modes of potential tumor resistance to such novel therapy, delineating future perspectives regarding basic science research on the issue.

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KEY WORDS tumor-treating fields; alternating electric fields; glioblastoma; neurooncology; progression-free survival; overall survival

PPRIMARY and metastatic brain tumors comprise a heterogeneous group of CNS malignancies, varying in histological features,⁷ phenotypic presentation,⁵ cell origin, and tumor grade as designated by the WHO.³⁸ The incidence of primary brain malignancies has been increasing, with an estimated 23,380 diagnoses and 14,320 deaths in 2014 attributed to CNS malignancies.⁶¹ Despite technological advances in neuroimaging, which have enabled earlier detection and closer monitoring of treatment effects, these tumors continue to be associated with significant mortality and morbidity. Glioblastoma is both the

most common and most lethal primary CNS malignancy in adults, accounting for 45.6% of all malignant CNS tumors,⁴⁹ presenting a dismal 5-year survival rate of only 5.0% despite the utilization of multimodal therapy.⁶³

Management of CNS tumors involves a complex multidisciplinary team of neurosurgeons, neurooncologists, and radiation oncologists, using standard strategies consisting of resection, chemotherapy, and radiation. Specific treatment regimens are usually tailored to patients depending on age, prognostic status, tumor location, tumor type, tumor grade, and staging. Aggressive surgery with complete

ABBREVIATIONS AEF = alternating electric field; OS = overall survival; PFS = progression-free survival; PFS6 = PFS at 6 months; TTF = tumor-treating field.

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macroscopic resection for glioblastoma has been shown to improve overall patient survival;³⁶ however, complete microscopic removal of the tumor is challenging given its diffuse and infiltrative nature, with nearly all glioblastomas eventually recurring. Thus, adjuvant therapy is routinely used to improve both the progression-free survival (PFS) and overall survival (OS). Traditional adjuvant therapy following glioblastoma resection involves fractionated radiation therapy, which has been shown to improve overall survival by 3–6 months as compared with supportive care.^{34,76} For younger patients with good postoperative performance, temozolomide is often used in combination with radiotherapy and has been shown to improve survival by 2–5 months in clinical trials.^{9,25,64} Although some studies have suggested that carmustine wafers (Gliadel, Eisai) placed at the time of surgery may also improve survival in patients with recurrent high-grade gliomas, such a therapeutic modality involves a significant additional cost and its use is not widespread either in the US or Europe.⁶ Many drugs are available as alternative and salvage chemotherapy, most notably bevacizumab (Avastin, Genetech), which has been shown to slow radiological progression and improve survival in recurrent glioblastoma.^{15,33,74}

Despite their efficacy, chemotherapeutic agents are often associated with noteworthy side effects. For instance, patients receiving temozolomide have been shown to often experience hair loss, nausea, vomiting, headaches, fatigue, and anorexia.^{2,83} Additionally, temozolomide may cause lymphocytopenia leading to opportunistic infection,³² with some patients requiring prophylaxis against pneumonia by *Pneumocystis carinii* when chemotherapy is given in combination with radiation therapy. Additionally, toxicity has been reported when carmustine wafers are supplemented with other chemotherapeutic agents, but this finding has not been consistent across different studies.^{10,40,57} Finally, bevacizumab has been associated with serious hemorrhagic events,²³ hypertension,⁶⁶ impaired wound healing, colonic perforation, thromboembolism, and renal failure.^{47,81}

At present, treatment options for glioblastoma remain limited, offering only brief periods of improved survival. In a landmark clinical trial for glioblastoma treatment, Stupp et al. in 2005 noted mean PFS to be just 6.9 months, despite the combination of radiotherapy with adjuvant temozolomide following maximal surgical debulking.⁶⁴ Given the substantial side-effect profiles of chemotherapy, improvements in current available treatment strategies or, more likely, the implementation of novel strategies altogether are warranted. The field of bioelectromagnetics offers a potential avenue of innovative approaches by exploring the effects of electromagnetic fields on biological systems, including cells and tissues. The potential of electric fields in particular has already been adapted for various applications, including osteogenesis stimulation for nonhealing fractures,³ wound healing,⁸⁴ and neural cell regeneration,⁶² as well as symptomatic relief in osteoarthritis.⁶⁹ Most recently, the technology has been employed as an anti-cancer strategy.

In April of 2011, the FDA approved the NovoTTF-100A system (Novocure, Inc.) as a standalone therapy for treating recurrent glioblastoma refractory to surgical and ra-

diation treatment.⁷² Utilizing a portable, battery-operated device, alternating electric fields (AEFs) are transmitted to the tumor via disposable surface electrodes engaged indirectly on the skin using a conductive hydrogel (Fig. 1). These electrodes (Fig. 2) are placed after head mapping with a series of MR images, and the AEFs are continuously applied over an extended period, at least 4 weeks. These AEFs—also known as tumor-treating fields (TTFs)—represent a novel treatment option for high-grade gliomas that categorically differs from the traditional surgical, chemotherapeutic, and radiation approaches.

Mechanism of Action

Electric fields are forces capable of acting on charged particles, creating characteristic movements dependent on the strength of the applied field and the magnitude of the charged particle upon which they act. Cells inherently contain electrically charged molecules, including DNA¹⁶ and proteins,²¹ which are subject to forces exerted by electric fields. Thus, in the setting of AEFs, these charged molecules oscillate at a rate dependent on the frequency, intensity, and vector of the applied electric field.⁴ If this field is nonuniform, dielectric molecules can become suspended along the electric fields and separate from each other, a phenomenon known as dielectrophoresis.¹⁷

Although the precise molecular effects of AEFs still remain under investigation, the most accepted pathophysiological explanation regarding their therapeutic effects on cancer relies on the effects of the AEFs upon the molecular machinery responsible for mitosis, more specifically, the microtubules. These components of the cytoskeleton are composed of tubulin subunits, consisting of globular proteins with substantial polarity that guide chromosomal

FIG. 1. The NovoTTF-100A system, consisting of noninvasive transducers that are attached to the scalp through a hydrogel interface. These transducers are connected to a portable battery and electric field generator. Reprinted with permission from Turner SG, Gergel T, Wu H, Lacroix M, Toms SA: The effect of field strength on glioblastoma multiforme response in patients treated with the NovoTTF-100A system. *World J Surg Oncol* 12:162, 2014. DOI:10.1186/1477-7819-12-162, <http://www.wjso.com/content/12/1/162>. No modification performed in original figure. Material available under Public License: Creative Commons license 4.0 (<https://creativecommons.org/licenses/by/4.0/legalcode>).

FIG. 2. The NovoTTF-100A system transducer array apparatus, which is placed directly on the scalp. Republished with permission of W.B./Saunders Co. from “Characterization and management of dermatologic adverse events with the NovoTTF-100A System, a novel anti-mitotic electric field device for the treatment of recurrent glioblastoma,” Lacouture et al, *Semin Oncol* 41 Suppl 4:S1–S14, 2014. Permission conveyed through Copyright Clearance Center, Inc.

aggregation and segregation.⁴¹ The inherent polarity of the tubulin subunits makes them sensitive to AEFs, which, by affecting their polymerization, ultimately disrupts the formation of the mitotic spindle apparatus, prolonging the mitotic process. Such effects have already been elegantly demonstrated using microphotography.^{29,37}

In addition, following mitosis the process of cytokinesis involves a cleavage furrow undergoing ingression secondary to the action of a contractile ring, ultimately resulting in the formation of two separate cells. Interestingly, this cleavage furrow is composed of a high-density electric field region, capable of exerting significant force.^{29,85} Upon exposure to AEFs, polar molecules and organelles preferentially migrate to higher field intensities. This phenomenon ultimately results in the movement of charged molecules toward the cleavage furrow, disrupting the intracellular apparatus and ultimately leading to plasma membrane blebbing, a common phenomenon observed in physiological apoptosis.²⁹ As a result of such cellular effects, AEFs have been shown to selectively target tumor cells undergoing active mitosis and cytokinesis, while sparing nondividing cells, particularly surrounding normal neuronal and glial cells.

In addition to the above-described effects of AEFs on mitosis and cytokinesis, alternative modes of action have also been documented. AEFs have been shown to alter the alignment of negatively charged DNA molecules, thus limiting the DNA repair response in gliomas and breast cancer cell lines.¹⁹ This finding is consistent with findings from a meta-analysis assessing the effects of AEFs on a variety of cancer cell lines, which revealed alterations in genetic processes that regulate DNA replication and repair.²⁰ This particular mechanism is especially relevant when AEFs are used alongside radiation therapy, which has been shown to induce DNA damage in cancer cells by the use of focused ionizing radiation. Furthermore, it has also been demonstrated that upon exposure to AEFs,

malignant melanoma cell lines exhibit downregulation of CD34, an essential marker of increased tumor vessel density.⁸ Conversely, a prior study had reported that electric fields, in fact, promote angiogenesis.⁵⁸ Ultimately, electric fields have also been shown to alter blood circulation in vessels of variable sizes,⁶⁸ suggesting potential applications in highly vascularized solid tumors. Nuccitelli et al. reported that, in addition to decreasing tumor blood flow, application of AEFs is able to initiate pyknosis in melanoma cells, resulting in an overall 90% reduction in tumor size.⁴⁸

Lastly, AEFs have also been shown to alter membrane permeation, leading to eventual necrosis and apoptosis of cancer cells.⁶⁷ This particular finding provides a possible therapeutic mechanism that explains the observed synergistic effects of AEFs and chemotherapy observed in some patients. Ultimately, future research using novel forms of biosensors will likely provide a better understanding of how electric fields of varying intensities and frequencies may affect cancerous and noncancerous cells. For example, researchers have already been able to shed light on morphological and cell viability changes in ovarian cancer cells upon exposure to AEFs by using an impedance-based biosensor complemented with cell labeling and fluorescence microscopy.²⁴

Preclinical and Pilot Glioblastoma Studies

Beginning in 2004, a growing number of studies reporting the result of in vitro, in vivo, and pilot clinical studies have shed light on the therapeutic potential of AEFs in the treatment of a variety of cancer types (Table 1). In the first study of its type, Kirson et al. (2004) reported that AEFs were not only able to inhibit cell proliferation in a variety of cancer cell lines, but also reduce growth and initiate destruction of malignant melanoma and adenocarcinoma in murine models.²⁹ These initial in vivo experiments suggested the possibility of delivering AEFs to the

TABLE 1. Overview of clinical studies involving TTF and patients with glioblastoma

Authors & Year	Study Description	No. of Pts	Median OS (mos)			Median PFS6 (%)			Median Time to Disease Progression (wks)		
			TTF	Chemo Agent	p Value	TTF	Chemo	p Value	TTF	Chemo Agent	p Value
Kirson et al., 2007	Pilot study of TTF monotherapy for temozolomide-refractory glioblastoma	10	14.5	6.8*	NR	50%	15.3%*	NR	26.1	9.5*	NR
Kirson et al., 2009	Pilot study of TTF w/ temozolomide vs temozolomide monotherapy for newly diagnosed glioblastoma	10	>39†	14.7*	0.00018	100%†	60.0%*	NR	155†	31*	0.0002
Stupp et al., 2012	Phase III clinical trial of TTF vs physician's best choice chemo	237	6.6	6.0	0.27	21.4%	15.1%	0.13	9.4	9.0	0.16

Chemo = chemotherapy; NR = not reported by investigators; pts = patients.

* Reported historical data for comparison purposes.

† Includes adjuvant temozolomide therapy.

tumor through insulated, noninvasive electrodes. Notably, the optimal AEF frequency varied across cancer cell lines, with 200 kHz being the optimal frequency for the treatment of gliomas while frequencies around 100 kHz were the most effective against melanoma. These findings suggested the necessity of “fine-tuning” the application of AEFs to each specific tumor line. A supplementary investigation by the same authors replicated these significant findings while incorporating additional cancer cell lines and animal models, including intracranial gliomas.²⁸

These initial results prompted a single-arm pilot study that involved the application of AEFs in monotherapy in 10 patients diagnosed with recurring glioblastoma. In addition to improving the time to disease progression (median 26.1 vs 9.5 weeks, respectively) and PFS at 6 months (PFS6; 50% vs 15.3%, respectively), this study²⁸ also demonstrated a significant increase in OS when compared with historical controls (median 62.2 vs 29.3 weeks, respectively). The device was well tolerated, with the most frequent adverse effect being a moderate contact dermatitis in 9 of the 10 patients on the scalp at the site of electrode placement, which had significant relief following topical steroid administration. No hematological, gastrointestinal, neurological, or cardiac side effects were documented.

Following this study, in 2009 the same group investigated the use of adjuvant AEF application in the context of chemotherapy, exploring possible synergistic efficacy and side-effect profiles.³⁰ When combined with paclitaxel, doxorubicin, cyclophosphamide, and dacarbazine, AEFs exhibited synergistic effects on limiting the growth of human glioma and breast carcinoma cell lines in vitro. A notable dose reduction (1–3 orders of magnitude) of all types of chemotherapeutic agents was possible while maintaining similar efficacy. Comparable results were observed in rabbits implanted with tumor tissue and treated with a combination of paclitaxel and AEFs. An additional pilot clinical trial was also initiated, involving a separate cohort composed of 10 patients. This second cohort involved patients recently diagnosed with glioblastoma who were treated with a combination of AEFs and temozolomide. In comparison with matched historical controls treated solely with temozolomide, the combination therapy (AEFs and temozolomide) not only increased median PFS (155

vs 31 weeks, respectively) but also improved median OS (> 39 vs 14.7 months, respectively). Again, the only side effect associated with AEFs was contact dermatitis noted in 18 of the 20 patients, which could be alleviated with topical corticosteroids and rotation of the surface electrodes. This particular study was the first clinical study to suggest that a combination therapy of AEFs and chemotherapy may potentially improve the outcomes of patients with glioblastoma. Moreover, according to previous studies, the incorporation of AEFs might enable a dose reduction of chemotherapeutic agents while maintaining treatment efficacy. Because very little systemic toxicity has been associated with AEFs, this multimodal treatment would likely lead to improved quality of life in such a patient population.

Phase III Randomized Trial

The encouraging results from the aforementioned studies prompted a multicenter, Phase III, prospective randomized clinical trial, comparing the NovoTTF-100A monotherapy to physician's best choice chemotherapy in patients with recurrent glioblastoma.⁶⁵ The median age of the 237 selected patients was 54 years, with 120 cases assigned to AEF monotherapy and 117 assigned to chemotherapy, either as a single agent or a combination of agents. The study found that there was similar efficacy between treatment with AEFs and chemotherapy. No statistically significant difference in median OS (6.6 vs 6.0 months, $p = 0.27$), PFS6 (21.4% vs 15.1%, $p = 0.13$), radiological response rate (14% vs 9.6%, $p = 0.19$) or 1-year survival rate (20% vs 20%, $p = 0.13$) was noted between the AEF and the chemotherapy cohorts.

Although this study failed to demonstrate an improvement in survival by AEFs, adverse effects were significantly lower in the AEF group. Within the AEF cohort, contact dermatitis occurred in 16% of the patients and responded well to topical steroids. Additionally, severe adverse events occurred less frequently in the AEF-treated compared with the chemotherapy-treated patients (6% vs 16%, $p = 0.022$). Moreover, longitudinal quality of life questionnaires predominantly favored AEF therapy, including better cognitive and emotional function, less pain, and reduced fatigue.

To summarize, this landmark clinical trial revealed that AEFs have similar efficacy to standard chemotherapeutic agents in patients with recurring glioblastoma, with a more favorable side-effect profile and quality of life. As a result, AEFs received FDA approval for the monotherapy treatment of adult patients with recurrent glioblastoma.

Post-Hoc Subgroup Analyses

Following this clinical trial, numerous post-hoc studies were conducted,⁶⁵ as summarized in Table 2. These subgroup analyses suggest that in certain populations, AEF therapy may, in fact, be more efficacious when compared with conventional chemotherapy regimens. For example, it has been shown that patients with favorable prognostic characteristics (such as age less than 60 years or Karnofsky Performance Scale score greater than 80%), as well as patients with tumors refractory to bevacizumab treatment, had significantly greater OS with AEF therapy in comparison with standard chemotherapy.^{26,27,53} Moreover, when excluding patients who did not receive a complete cycle of treatment with AEFs, patients in the AEF cohort showed improved survival in comparison with physician's best choice chemotherapy.⁸⁰ A survival benefit was also noted when comparing AEF monotherapy to those patients receiving bevacizumab.⁵⁴ Interestingly, certain tumor characteristics were also associated with improved OS with AEFs, including prior low-grade glioma, refractory response to bevacizumab, and tumor size greater than 18 cm².^{26,27}

Case Reports

Several case reports have also been published, demonstrating variable individual responses to AEF therapy.

For example, continued enhancement of cystic lesions was initially observed despite AEF administration; however, a delayed inhibitory response was noted, suggesting that continued treatment with AEFs may still be reasonable despite preliminary tumor growth.^{56,73,75} AEF therapy in these cases resulted in long-term survival benefits, including anecdotal reports of patients with glioblastoma or recurrent glioblastoma treated with AEF monotherapy who did not require any further follow-up therapy for approximately 6–7 years. Other case reports have described radiological benefits for AEF therapy in combination therapy with bevacizumab despite prior bevacizumab resistance¹¹ or bevacizumab plus temozolomide resistance.⁷⁹

Compliance With AEF Therapy

Perhaps the greatest limitation to the efficacy of AEF therapy is the challenge associated with patient compliance. Unlike chemotherapy, AEF therapy involves a physical, nonchemical modality, with no associated half-life. Hence, the antitumor effects are immediately halted once the AEF therapy is stopped, explaining the need for continuous application throughout the day over extended periods. A kinetic modeling study proposed that at least 4 weeks of continuous AEF therapy is needed to achieve a substantial reversal of tumor growth.³¹ As such, the treatment with AEFs requires a substantial commitment on the part of patients. The transducers are placed directly on the scalp, requiring patients to shave their head. Correct placement of the electrodes often necessitates the assistance of another person who also needs to undergo necessary training. Compliance issues can be partially alleviated by the fact that head coverings can be worn, disguising the transducers. Future advances in the device apparatus are expected to prolong battery life and decrease the size

TABLE 2. Post-hoc subgroup analyses on data derived from the study of Stupp et al., 2012*

Authors & Year	Study Description	Sample Size			Median OS (mos)		
		TTF	Chemo Agent	Total	TTF	Chemo Agent	p Value
Ram et al., 2010	TTF monotherapy vs chemo in pts w/ favorable prognostic characteristics	NR	NR	110	8.8	6.6	<0.01
	TTF monotherapy vs chemo in pts who failed bevacizumab	23	21	44	4.4	3.1	<0.02
Ram et al., 2011	TTF monotherapy vs bevacizumab specifically	120	36	156	6.6	5.0	0.048†
Wong et al., 2011	Pts receiving <1 complete course of TTF monotherapy vs chemo	93	117	210	7.8	6.0	0.012
Kanner et al., 2013	TTF monotherapy vs chemo in pts <60 yrs of age	NR	NR	168	7.4	6.2	0.063
Kanner et al., 2014	TTF monotherapy vs chemo for bevacizumab-refractory glioblastoma	23	21	44	6.0	3.3	0.016
	TTF monotherapy vs chemo in pts w/ prior low-grade glioma	12	9	21	25.3	7.7	0.049
	TTF monotherapy vs chemo in pts w/ tumor size >18 cm ²	39	41	80	5.6	3.3	0.009
	TTF monotherapy vs chemo in pts w/ Karnofsky Performance Scale score >80	83	77	160	7.9	6.1	0.045
	TTF monotherapy vs non-bevacizumab chemo	120	81	201	6.6	6.6	0.586

* Progression-free survival at 6 months and time to disease progression not included due to limited reporting by the reported investigations.

† Based on Cox proportional hazards model.

and weight of the equipment, changes that will likely increase patients' compliance. Patients might also decide to discontinue therapy due to associated contact dermatitis commonly observed on the scalp. However, certain management techniques such as proper scalp washing and the use of topical antibiotics and steroids have already shown to effectively mitigate such adverse dermatological changes,³⁵ promoting greater adherence. Nonetheless, physicians must consider these issues when deciding to incorporate AEF therapy to their patients' treatment plan.

Overall, it has been shown that compliance problems are common, as noted in the randomized control trial conducted by Stupp et al.,⁶⁵ in which more than 20% (27 of 120) of the patients originally assigned to the AEF cohort discontinued treatment earlier than expected. Thus, only 93 of the 120 patients completed a full cycle of AEF therapy. Importantly, median OS and PFS6 were significantly longer in these 93 patients who completed the full cycle compared with those patients receiving chemotherapy.^{27,80} Interestingly, in a post-hoc analysis conducted on this randomized clinical trial, compliance in patients below 60 years of age was statistically higher compared with those above 60 (80% vs 74%, respectively; $p = 0.043$).²⁶ The importance of patient compliance cannot be overstated, as the results of the original randomized trial,⁶⁵ as well as those of a previously mentioned pilot trial,³⁰ demonstrated that the duration of AEF therapy was highly correlated with survival ($r^2 = 0.92$).⁷⁵ Further results also revealed that the patients in the trial who used the device for more than 18 hours daily also had improved survival compared with those who used the device less than 18 hours (7.7 vs 4.5 months, respectively; $p = 0.042$).²⁷

Resistance to AEF Therapy

Theoretically, long-term resistance to AEFs therapy is less likely to occur compared with standard chemotherapy, especially because no specific targeting of cell surface receptors occurs. Moreover, mitosis represents an inherent process within cancer cells necessary for proliferation. On the other hand, multiple-drug resistance in glioblastoma is a common phenomenon observed in patients treated with long-term chemotherapy.^{12,51} Additionally, the efficacy of chemotherapy agents is often limited due to the necessity that the therapeutic agent transverse the blood-brain barrier, a non-issue in AEF therapy. In accordance with such arguments, patients in the Phase III trial⁶⁵ receiving AEF therapy experienced more favorable radiological responses, with only 14% of the patients demonstrating radiological changes suggesting emergence of resistance in the recurrent tumors.

One potential mechanism of resistance of glioblastomas to AEFs involves cell size. The initial studies²⁸ demonstrated that the optimal AEF frequency was inversely related to the cell size of the particular cancer line. Turner et al.^{70,71} further substantiate this theory, having reported a patient who developed a slow-growing lesion containing a giant cell glioblastoma with multiple syncytial-type cells following AEF and temozolomide treatment. This type of resistance can be potentially overcome by reducing the frequency of the emitted electric fields, as previously dem-

onstrated in studies with ovarian cancer cells.¹⁸ This finding suggests the importance of constant imaging monitoring (and sometimes even the necessity of new biopsies) to determine whether the parameters of the treatment with AEFs need to be adjusted. Moreover, as AEF therapy has been shown to induce genetic alterations of the tumor,³⁷ it may be possible that resistance to AEFs may also occur by subsequent mutations in DNA repair mechanisms in the tumor cells.

Other research lines have attempted to increase the tumor response to AEFs by focusing on the current limitations of the applied electric fields rather than on the actual characteristics of the tumor. Specifically, Turner et al.⁷¹ suggest that a higher risk of treatment failure occurs near the margins of the tumor, where the strength of the electric field is reduced. Interestingly, recent studies have utilized MRI data to construct head models to more accurately assess the distribution of the oscillating electric fields in different areas of the brain. The obtained data suggest that the electric field strength is highest in the CSF, followed by white matter and then gray matter,^{42,78} a correlation that is directly related to relative impedance properties of such regions.⁸⁶

Contraindications to AEF Therapy

Despite its limited systemic toxicity, AEF therapy is not recommended in certain patient populations.¹⁴ No studies to date have examined the safety profile of AEF therapy in patients with implanted electrical devices, including pacemakers, defibrillators, or deep brain stimulators due to the possibility of electrical interference. Interestingly, AEF therapy was well tolerated in a patient with a glioma who had a pre-existing ventriculoperitoneal shunt with a nonprogrammable valve.⁴⁴ However, no studies up to now have evaluated the effects of AEFs in patients with programmable shunts. Additionally, any patients with a hypersensitivity to the hydrogel used for the placement of the scalp electrodes should not receive AEF therapy. Finally, as suggested above, patients unable to fully comply with the necessary continuity of AEF therapy or lacking the appropriate cognitive level or social support for successful compliance with the treatment recommendations will likely have a reduced benefit from this type of therapy.

Future Perspectives

It is expected that the use of AEFs as part of the multimodal treatment in patients with glioblastoma will continue to gain momentum following its FDA approval in 2011. Recent guidelines released by the National Comprehensive Cancer Network (2013) approve of the use of AEFs in patients with recurring or resistant tumors alongside chemotherapy options.⁴⁵ Several clinical trials examining the use of AEFs in combination therapy with temozolomide and/or bevacizumab in the context of newly diagnosed¹³ or recurrent glioblastoma have been recently approved and are already recruiting participants. Additionally, a Phase II study has been initiated in order to evaluate the efficacy of AEFs in metastatic tumors from non-small cell lung cancer following stereotactic radiosurgery in comparison with radiosurgery alone.⁷⁷ Future data as well as outcome analyses in

patients treated with AEFs are expected to become more readily available through the continued development of the Patient Registry Dataset (PRiDe), a registry of all patients with recurrent glioblastoma who receive AEF therapy in the clinical setting since its FDA approval in 2011.⁴³ Finally, future basic science investigations are warranted in order to determine the exact therapeutic mechanism of AEFs as well as to improve parameters for AEF delivery in order to achieve a more targeted application to the tumor zone.

In the future, clinical trials should also consider the therapeutic effects of AEF therapy in the context of the specific genetic composition (such as O⁶-methylguanine-DNA methyltransferase and isocitrate dehydrogenase mutations) and histological variations (such as the recently described proneural, neural, classical, and mesenchymal subtypes). This analysis may provide a better understanding of which particular subtypes of glioblastoma are more susceptible (or resistant) to AEF therapy. Eventually, these data could be used to “fine-tune” AEF frequencies to specific subtypes of tumor. Recurrent tumors will likely require a different applied frequency of AEFs, especially considering the molecular differences that have been noted between initial malignant tumors and their subsequent recurrences.⁵⁹ Additionally, the efficacy of AEFs in neurooncology has currently only been established for glioblastoma; thus, further clinical studies investigating its potential application in other CNS tumors are necessary. Interestingly, one study did report a greater than 60% radiographic decrease in size of an incidental meningioma in a patient undergoing AEF therapy for a concurrent glioblastoma.⁶⁰

Future studies must also continue to monitor the influence of AEFs on normal proliferating glial cells and permanent neuronal cell types. In previous studies AEFs have already been shown to affect neural stem cell viability and differentiation and proliferation,^{1,39} promote neuron cell body oscillation,⁵⁰ and accelerate healing through neurite growth stimulation.^{22,46} Also, studies have shown that applied electric currents may modulate neuronal activity by altering firing rate, excitation properties, and spike timing.^{52,55,82} Therefore, the long-term cognitive effects of treatment with AEFs in terms of memory and learning should also be taken into account by future safety assessment studies. However, given the especially poor prognosis of glioblastoma as well as the promising results of therapy with AEFs, such issues should not prevent further exploration of this therapeutic modality in the clinical setting.

Finally, investigation regarding how AEFs could be combined with other standard treatment modalities (such as chemotherapy and radiation) is required in order to better delineate clinical protocols for newly diagnosed and recurrent glioblastoma designed to maximize a patient's prognosis and reduce overall side effects of multimodal treatment. For instance, enhanced effectiveness in AEF therapy is expected if it is incorporated with drugs that also alter the mitotic process, such as taxols and vinblastine. This synergism has already been noted in breast cancer cells when treated with paclitaxel and AEFs.²⁹

Conclusions

Current cancer treatment protocols often incorporate multimodal therapeutic strategies including resection,

radiation, and chemotherapy, as an attempt to increase treatment efficacy without increasing toxicity. Despite this approach, the prognosis of patients with glioblastoma remains relatively poor and adverse effects associated with treatment often compromise patients' quality of life. Pre-clinical data, pilot studies, case reports, and a recent Phase III, prospective randomized clinical trial support the use of AEFs in recurrent glioblastoma as having at least similar efficacy when compared with current chemotherapeutic regimens. Additionally AEF therapy has been shown to have a benign profile in terms of systemic adverse effects, allowing its use either as a monotherapy or in combination with chemotherapeutic agents, possibly in dose-reduced regimens, ultimately improving the overall toxicity profile of such therapies while maintaining efficacy rates.

Despite initial promising results (especially in pilot in vitro and in vivo studies), the clinical data examining the efficacy of AEFs remain limited. Comparatively, current radiation and chemotherapy regimens have been substantiated by several years of clinical investigations. Nonetheless, AEF therapy represents an entirely novel strategy in the treatment of brain tumors. In the future, fine-tuning of AEFs by adjusting field intensity, frequency, and direction (as well as novel forms of AEFs with more targeted delivery) may generate new possibilities for individualized treatment and improved clinical outcomes.

As the field of neurooncology continues to progress, new developments in currently available therapies as well as the introduction of novel strategies (such as AEFs) are expected to improve the outcomes of patients harboring tumors which, at the present stage, are still associated with dismal prognoses. Although AEFs are not expected to be a magic bullet for the cure of brain cancer, they do promise to become part of the multimodal therapies in neurooncology in the near future, which are expected to improve survival while minimizing side effects of current treatment strategies and increasing patients' quality of life.

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