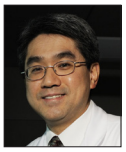
Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology November 2015

Technological Advances in the Treatment of Cancer: Combining Modalities to Optimize Outcomes

Moderator



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Abstract: The anticancer treatment modality tumor treating fields (TTFields; Optune, Novocure) use the lower frequency range of the electromagnetic spectrum to destroy tumor cells during mitosis. This treatment has been evaluated in several trials of patients with glioblastoma. In these patients, TTFields are delivered through 4 transducer arrays applied to the scalp. In a phase 3 clinical trial of patients with recurrent glioblastoma, TTFields were as effective as chemotherapy, and were associated with fewer and milder systemic toxicities. Data from a phase 3 trial in newly diagnosed glioblastoma suggested that the addition of TTFields to postoperative radiation therapy and chemotherapy represents an important advance in the management of newly diagnosed glioblastoma. Ongoing clinical trials are investigating the efficacy and safety of TTFields in other tumor types, including pancreatic cancer, mesothelioma, ovarian cancer, and non–small cell lung cancer. Other recent advances in the management of cancer have been seen with immunomodulatory therapy, including immune checkpoint inhibitors. Further study will be necessary to evaluate whether TTFields will enhance or impair other established and newly emerging therapies.

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Target Audience

This activity has been designed to meet the educational needs of oncologists, hematologists, and oncology nurses involved in the management of cancer patients.

Statement of Need/Program Overview

The anticancer treatment modality tumor treating fields (TTFields) use the lower frequency range of the electromagnetic spectrum to destroy tumor cells during mitosis. The initial approval of TTFields, in 2011, was as monotherapy for adult patients with recurrent glioblastoma multiforme who had received chemotherapy. In October 2015, this indication was expanded to include patients with newly diagnosed glioblastoma who have undergone maximal debulking surgery and completed radiation therapy with concomitant standard-of-care chemotherapy. Clinical trial data have shown that TTFields are at least as effective as chemotherapy in recurrent glioblastoma and improve outcome when added to adjuvant temozolomide in newly diagnosed glioblastoma. The most common adverse event, skin irritation, is mostly mild and manageable. Ongoing clinical trials are investigating the efficacy and safety of TTFields in other tumor types, including pancreatic cancer, mesothelioma, ovarian cancer, and non–small cell lung cancer. Other recent advances in the management of cancer have been seen with immunomodulatory therapy, including immune checkpoint inhibitors. There is ongoing research of PD-1 inhibitors. Viral oncolytic gene therapies are another area of investigation.

Educational Objectives

After completing this activity, the participant should be better able to:

- Explain the need for additional anticancer treatment modalities beyond the existing strategies of surgery, chemotherapy, and radiation therapy
- Describe the proposed mechanisms of action for novel anticancer treatment modalities, such as tumor treating fields
- Evaluate efficacy and safety data from clinical studies of novel anticancer treatment modalities
- Identify patients who would be appropriate candidates for clinical trials of novel anticancer treatment modalities
- Combine new treatment modalities, such as tumor treating fields and immunotherapy, with existing strategies, such as surgery, chemotherapy, and radiation therapy

Accreditation Statement

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Eric T. Wong, MD—Sponsored research agreement for investigating the basic biologic effects of TTFields on tumor cells: Novocure

Steven A. Toms, MD—Strategic advisory board: Medtronic and Novocure

Manmeet S. Ahluwalia, MD—Research/grant support: BMS, Novocure, Spectrum Pharmaceuticals, Boehringer Ingelheim, Novartis, and Tracon Pharmaceuticals. Consultant: Caris Life Sciences, Monteris Medical, and Incyte

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Tumor Treating Fields and Other Technological Advances in the Treatment of Cancer

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Traditionally, there have been 3 basic modalities for the treatment of cancer: surgery, radiation therapy, and chemotherapy. Unfortunately, these modalities have been associated with disappointing efficacy and substantial toxicity.[1-7]

Surgery in cancer is limited in its applications because of potential damage to surrounding tissues. Typically, in surgical oncology, the aim is to extirpate the tumor and ensure that no infiltrating cells are left behind, while minimizing damage to normal tissue. With the primary brain cancer glioblastoma, it is not possible to excise wide margins beyond the apparent tumor border because of the potential damage to critical neural structures that could cause neurologic deficits. For patients with glioblastoma, maximal resection of the tumor and sparing of normal tissue provides the best outcome and is an important component of overall prognosis.[8]

With most cancers, survival is improved when surgical resection is achieved with clean surgical margins and when no positive lymph nodes have drained the tumor field. When this outcome is not possible, it is necessary to consider additional therapies, such as radiation and chemotherapy. Since glioblastoma cells infiltrate widely beyond the apparent tumor border, use of adjuvant therapy is the standard of care.

Surgery can be considered a local treatment for cancer. Radiation therapy is considered a more broad or regional treatment. Radiation therapy provides the ability to access cells that might have spread beyond the surgical resection margins and to treat a tumor that is unresectable owing to potential damage to surrounding vital tissues. Radiation therapy typically targets rapidly dividing cells and is adjunctive in many solid tumors.

Traditional chemotherapy agents acted on rapidly dividing cells, with little differentiation between cancerous vs noncancerous cells. Targeted therapies, which block the growth and spread of cancer by interfering with specific molecules, were introduced into clinical care approximately 15 years ago, with the approval of the tyrosine kinase inhibitor imatinib for patients with chronic myeloid leukemia.[9] Research into targeted therapies is ongoing. In 2015, gefitinib, which targets the epidermal growth factor receptor (EGFR) gene mutation, was approved for patients with metastatic non–small cell lung cancer (NSCLC) who have this mutation.[10] The anaplastic lymphoma kinase (ALK) inhibitor alectinib is currently undergoing priority review by the US Food and Drug Administration (FDA) for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC.

Like radiation, chemotherapy targets rapidly dividing cells and can be associated with significant toxicity. There are many rapidly dividing cells in the body, particularly in the intestinal tract and bone marrow. In the intestinal tract, gut epithelium is constantly shed and renewed by precursor cells. These rapidly dividing cells may be easily damaged by abdominal radiotherapy or chemotherapy, which can lead to malabsorption, nausea, and diarrhea. Similarly, hematopoiesis in the bone marrow can be inhibited by radiotherapy and chemotherapy. Leukopenia is a common adverse event, leading to impaired immune responses and potential life-threatening infections. Alkylating agents, such as temozolomide, are more commonly associated with anemia, which can cause fatigue and thrombocytopenia leading to bruising or more severe bleeding disorders.

Surgery, radiation, and chemotherapy have been in use for many decades. The failure of these therapies to achieve adequate results with minimal toxicity has led to the investigation of other modalities, such as tumor treating fields (TTFields; Optune, Novocure), immunomodulatory therapies, and viral-mediated gene therapies.

TTFields

Approximately 10 years ago, Israeli scientists postulated that low-intensity, intermediate-frequency (100-300 kHz), alternating electric fields, delivered by means of insulated transducer arrays, could be engineered to interfere with cell division and might offer a way of treating cancer.[11] This technology, known as TTFields, is now approved by the

Figure 1. Components of the Optune (tumor treating fields) system.

FDA for the treatment of patients with glioblastoma. The initial approval of TTFields, in 2011, was as monotherapy for adult patients (ages 22 years and older) with recurrent glioblastoma multiforme who had received chemotherapy and shown signs of progressive disease. On October 5, 2015, this indication was expanded to include patients with newly diagnosed glioblastoma who have undergone surgical biopsy or resection and have completed radiation therapy with concomitant temozolomide.[12]

Mechanisms of Action

TTFields disrupt the rapid cell division exhibited by cancer cells. In patients with glioblastoma, 2 sets of alternating electrical fields are applied to the brain through 4 transducer arrays placed on the shaved scalp. At the frequency used in glioblastoma, approximately 200 kHz, TTFields do not stimulate nerves or muscles, nor do they affect rapidly proliferating cells in the rest of the body.

TTFields seem to impact dividing cells at several stages of mitosis. After DNA has replicated to double the number of chromosomes, highly charged proteins, such as tubulin, help attach the chromosomes to the mitotic spindle, aiding in the orderly segregation of the chromosome pairs in the daughter cells. TTFields interfere with the electrostatic charges involved in binding these proteins to the chromosome, preventing equal division of the genetic materials. Furthermore, the charge is funneled around the cell toward the cleavage furrows, impairing division of subcellular organelles and obstructing proper fission of the cell membranes into the 2 daughter cells. This process appears to enact evolutionarily conserved cell suicide programs that lead to cellular death via apoptosis. The optimal frequency for this effect varies with the size of the cell.

Early Clinical Trials

In an early study of 10 patients with recurrent glioblastoma, TTFields were shown to be safe.[13] Patients underwent treatment for a total of 280 weeks, and there were no reports of treatment-related serious adverse events or significant changes in serum chemistry or blood count. This finding led to a large clinical study, EF-11, which included approximately 230 patients and compared TTFields as monotherapy in recurrent glioblastoma vs the clinician's choice of therapy, which included treatments such as bevacizumab, lomustine, carmustine, and erlotinib.[14] The results of this study were reported in 2011 and led to FDA approval of the device for recurrent glioblastoma when used as monotherapy. Dr Wong will provide further discussion of the EF-11 trial in the next article.

The TTFields Device

The device for the treatment of glioblastoma delivers TTFields at 200 kHz via 4 transducer arrays applied to a shaved scalp (Figure 1). The transducer arrays have 9 ceramic disks with a hydrogel coating. The TTFields are transmitted from an electrical field generator powered by a battery pack or electrical outlet. This alternating current rises into cables, then through the transducer arrays, and into the patient's scalp through the ceramic discs. Patients are instructed to change these transducer arrays every 2 to 3 days and to shave their head as the hair grows. The most common adverse event observed with TTFields is local skin irritation under the transducer arrays.[15-17] The transducer arrays may cause some warmth or a slight tingle on the scalp when they are applied. In rare instances, a patient may react to the hydrogel or develop skin irritation or sores where the transducer arrays have been applied. In clinical trials, these adverse events have been largely mild to moderate and are manageable, typically with topical corticosteroids.[15-17]

The TTFields system, including the battery pack, weighs 6 pounds. It can be transported in a specially designed backpack. The manufacturers advise patients to wear the device for at least 75% of the time (or at least 18 hours a day). TTFields therapy is effective only when the arrays are worn and the device is powered on. As mentioned, TTFields appear to work when a cell is dividing, and a cancer cell may sit quiescent without dividing for several days before the mitotic event (which lasts 2 to 3 hours). If the device is not worn when a cell divides, the opportunity for the TTFields to cause an apoptotic death during that cell division is lost.

Not surprisingly, clinical trials have shown that patients who wear the device at least 75% of the time have a better outcome than those who wear it less frequently.[14,15] Given the mechanism of action, it is possible that patients who wear the device more than 75% of the time may have better outcomes, although published data are not yet available for confirmation.

Use With Other Regimens

The current standard of care for glioblastoma patients is known as the Stupp protocol, which consists of radio-

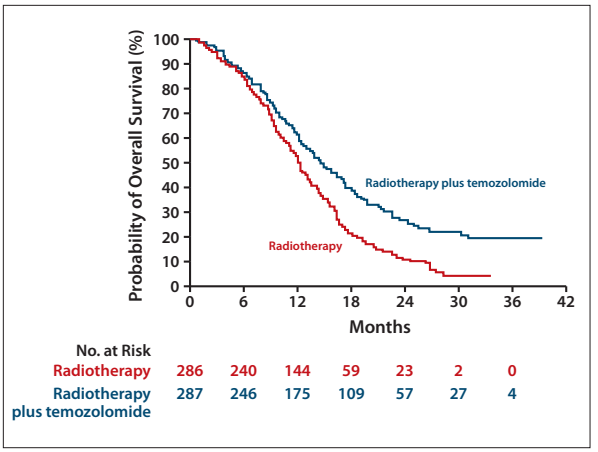

Figure 2. Overall survival among patients with newly diagnosed glioblastoma treated with radiotherapy alone or standard radiotherapy plus concomitant daily temozolomide followed by adjuvant temozolomide. Adapted from Stupp R et al. *N Engl J Med*. 2005;352(10):987-996.[16]

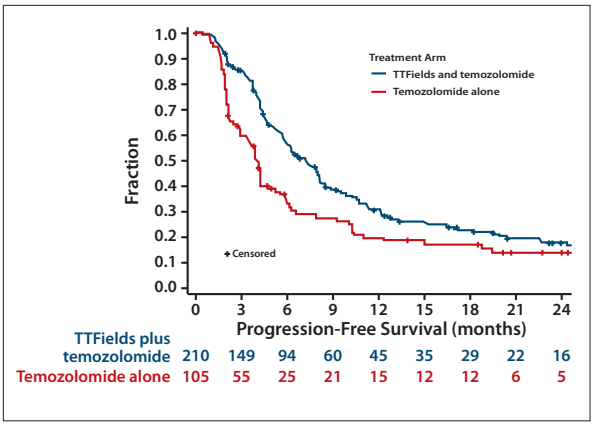

Figure 3. Progression-free survival in the phase 3 E-14 trial, which evaluated the addition of tumor treating fields to maintenance temozolomide among patients with newly diagnosed glioblastoma. TTFields, tumor treating fields. Adapted from Stupp R et al. Tumor treating fields (TTFields): a novel treatment modality added to standard chemo- and radiotherapy in newly diagnosed glioblastoma—first report of the full dataset of the EF14 randomized phase III trial [ASCO abstract 2000]. *J Clin Oncol*. 2015;33(suppl).[15]

therapy plus continuous daily temozolomide (75 mg/m^2 of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), followed by at least 6 cycles of adjuvant temozolomide (150-200 mg/m^2 for 5 days during each 28-day cycle; Figure 2).[16]

The prospective, multicenter, phase 3 EF-14 trial was designed to determine whether TTFields would be useful in treating patients earlier in their disease state.[15] The trial randomly assigned patients with newly diagnosed glioblastoma who had completed concomitant chemoradiotherapy to receive either adjuvant temozolomide chemotherapy alone or temozolomide with TTFields. The randomization schema was 2:1 in favor of TTFields. The trial ultimately enrolled 695 patients who had completed standard therapy with temozolomide plus radiotherapy and who had no evidence of disease progression during the 7 weeks prior to study enrollment. Patients in the TTFields therapy arm were instructed to wear the device for more than 18 hours per day for a maximum of 24 months. Patients who progressed on treatment continued to receive TTFields therapy until the time of second progression. The study was designed with a primary endpoint of progression-free survival and secondary endpoints including overall survival and safety.

The E-14 trial is the first study in glioblastoma halted early based on positive results in an interim analysis. Data from the interim analysis of the first 315 enrollees with a minimum of 18 months of follow-up data were presented at the 2014 Society for Neuro-Oncology meeting and the 2015 American Society of Clinical Oncology (ASCO) meeting.[15,17] The analysis showed that the addition of TTFields to maintenance temozolomide resulted in a significant improvement in median progression-free survival compared with maintenance temozolomide alone in the intent-to-treat group (7.1 vs 4.2 months; hazard ratio, 0.69; *P*=.0010; Figure 3). This benefit in progression-free survival was observed across all patient subgroups, including age, sex, region, *MGMT* promoter methylation status, Karnofsky performance status, and prior resection.

There was improved overall survival among patients treated with TTFields therapy plus maintenance temozolomide vs maintenance temozolomide alone in the as-treated cohorts (19.4 vs 16.6 months; hazard ratio, 0.75; 95% CI, 0.60-0.96; *P*=.0222). Treatment with TTFields therapy reduced the risk of death by 25%. The 2-year survival rate was higher in patients receiving TTFields therapy plus maintenance temozolomide compared with maintenance temozolomide alone (48% vs 32%; *P*=.0058).

As has been observed in other clinical trials of TTFields therapy,[14] the adverse events most frequently associated with TTFields treatment were grade 1 or 2 skin reactions, such as dermatitis and wound complications at the treatment site (45%), requiring that the transducer arrays be repositioned. All other treatment-related adverse events were mild and primarily related to temozolomide. There was no increase in neurologic side effects (such as seizures) with the addition of TTFields therapy.

The presenter of the interim analysis, Dr Roger Stupp, commented that the addition of TTFields to adjuvant temozolomide likely represents a new standard of care for glioblastoma treatment.[15,17] This approach was associated with a marked improvement in length of life without a decline in quality of life. In previous studies, the addition of temozolomide to radiation therapy increased overall

survival by approximately 3 months.[18] The increase of 4 to 5 months seen with the addition of TTFields represents the biggest single improvement in survival that I have seen in any study of glioblastoma patients.

My institution had approximately 20 patients enrolled in the E-14 trial. Our patients appeared to have a better outcome than the group reported in the interim analysis. We found that our patients became psychologically dependent on the TTFields device, and they viewed it as a tangible way to treat their own disease. They were responsible for wearing the device, taking it with them throughout the day, and recharging the batteries. They also had to change their transducer arrays every few days. In contrast, patients must passively receive most other cancer therapies, such as radiation and chemotherapy. The use of TTFields appeared to be empowering for patients. We had a support group for patients, where they would share tips on how to use and wear the device. Patients began to compete with each other to see who could wear the device the most. In our group of patients, quality of life seemed to be very good and reflected the results seen in the study analysis. We had patients who continued with their daily activities, such as teaching and hiking.

We did not observe many toxicities. There were no reports of burns or increased risk of seizures. Occasionally, patients developed minor skin irritation. Among patients who had undergone multiple surgeries, and who had a metal plate holding the skull in place, the transducer arrays sometimes caused a slight buzzing sensation or more heat than average. Patients with very thin scalps sometimes experienced more skin irritation, but most of these reactions could be easily alleviated by repositioning the transducer array or applying corticosteroid cream. The TTFields device should not be used in patients with an implanted electrical device, such as a vagal nerve stimulator, a deep brain stimulator, a pacemaker, or a spinal cord stimulator.

In the EF-11 trial, TTFields therapy appeared to be as effective as chemotherapy, with fewer toxicities, among patients receiving second-line treatment for glioblastoma.[14] All patients had already undergone radiotherapy (with or without concomitant and/or adjuvant temozolomide). The adverse events in the TTFields arm consisted mostly of scalp irritation and dermatitis, whereas many of the chemotherapies were associated with multiple other toxicities.

Data from a retrospective review presented at the 2015 ASCO meeting appeared to show a clinical benefit when stereotactic radiosurgery was added to TTFields in patients with recurrent malignant gliomas.[19] Among the 12 patients who received treatment with TTFields plus stereotactic radiosurgery, overall survival was 12 months compared with 4 months among the 28 patients treated with TTFields without stereotactic radiosurgery (P=.0036).

Emerging Approaches

Immunotherapy continues to emerge as a potential modality for cancer treatment.[20,21] Vaccines and immunomodulatory therapies, such as programmed death 1 (PD-1) inhibitors, have shown impressive results in melanoma.[22,23] In 2010, the vaccine sipuleucel-T was approved by the FDA for treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer.[24] The pivotal phase 3 trial of sipuleucel-T showed improvement in overall survival.[25] There are several therapeutic cancer vaccines in development directed against tumor-associated antigens.[26,27]

It is not yet known whether TTFields will be additive or synergistic with other therapies, although preclinical trials suggest that this modality may have synergistic effects.[28,29] It is exciting to have this new, effective therapy for glioblastoma. When I began treating these patients 25 years ago, survival was approximately 9 to 12 months. The Stupp protocol increased survival to approximately 14 months.[16] Now, with TTFields, survival has exceeded 20 months.[15,17] I am treating several patients with TTFields who have survived 4.5 to 5 years, which I have not seen previously in my clinical practice.

It will be important to evaluate how TTFields will work with older treatments and emerging therapies. TTField therapy appears to be tolerated after radiation. It is not yet known whether it can be used during radiation. There are questions concerning whether TTFields can be used with immunomodulatory therapy, which includes immune checkpoint inhibitors. It will be necessary to determine if TTFields will impair immune cell migration and function. Other therapies that may exploit immune mechanisms, such as oncologic viruses, will need to be evaluated with TTFields as well.

Conclusion

It appears that TTFields may be a fourth cancer treatment modality, complementing the traditional modalities of surgery, radiation, and chemotherapy. TTFields have been shown to prolong survival and maintain quality of life in patients with newly diagnosed glioblastoma treated with radiotherapy and temozolomide. This therapy marks an important advance in the treatment of glioblastoma.

Disclosure

Dr Toms is a member of the strategic advisory boards of Medtronic and Novocure.

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Clinical Use of Tumor Treating Fields and Other New Technologies in Cancer

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As discussed in the previous article by Dr Toms, TTFields are thought to exert dielectrophoretic forces on cellular components, thereby altering their normal functions. Basic science research published by Gera and colleagues proposed that alternating electric TTFields lead to the destruction of tumor cells through 2 major mechanisms during mitosis.[1] Mitosis is particularly susceptible to disruption, and the series of well-choreographed steps of this process must be completed without mistake to ensure that the daughter cells are identical to the parent cell. TTFields disrupt mitosis during the metaphase to anaphase transition (Figure 4). Importantly, although catastrophic errors that occur earlier in the mitotic cycle can be corrected at mitotic checkpoints, errors that occur during the later metaphase to anaphase transition typically result in aberrant mitotic exit and cell death.

TTFields inhibit cytokinesis, the process at the end of mitosis in which a cell with 2 nuclei separates into 2 individual cells. These actions are traced to the ability of TTFields to perturb the localization of septin, a large protein that is responsible for demarcating the area where the cell will separate. Septin has a very large dipole moment, making it especially susceptible to disruption from alternating electric fields. When septin dislodges from its normal position and scatters throughout the cell membranes, it causes multiple blebs on the cell membrane. This blebbing in turn causes microtubule disruption and asymmetric segregation of the chromosomes during mitosis, the second mechanism by which TTFields act. Chromosomal disruption eventually leads to cell death, by way of both apoptotic and immunologic means.

Phase 3 Data in Glioblastoma

The clinical efficacy of TTFields was established in a phase 3 clinical trial, EF-11, that investigated the efficacy and safety of this modality in patients with recurrent glioblastoma.[2] Glioblastomas are the most common form of primary brain cancer in adults, and account for more than half of all gliomas. Glioblastoma is a highly lethal cancer, with a particularly poor prognosis. One-third of patients are alive after 1 year.[3] Despite aggressive first-line radiation and chemotherapy, patients with glioblastoma almost invariably experience disease progression within 1 year. Once the disease relapses, treatment options are limited, and there is no established standard of care.

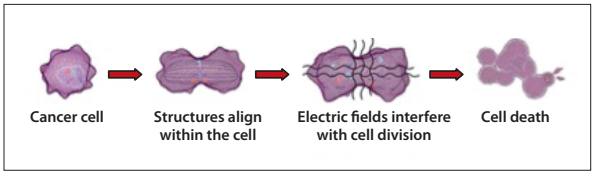

Figure 4. Tumor treating fields disrupt mitosis during the metaphase to anaphase transition.

The phase 3 EF-11 trial enrolled 237 patients with radiologically confirmed disease progression between September 2006 and May 2009.[2] The primary endpoint was overall survival. Key secondary endpoints included 6-month progression-free survival, 1-year overall survival, radiologic response rate, quality of life, and safety. Patients were randomized in a 1:1 ratio to receive either TTFields monotherapy or active chemotherapy. The type of chemotherapy was selected by the physician and could consist of a single agent or combination chemotherapy. Treatments included bevacizumab (31%), irinotecan (31%), nitrosoureas (25%), carboplatin (13%), temozolomide (11%), and other agents (5%). The baseline characteristics of patients were well-balanced between the treatment arms. The median patient age was 54 years. The population was heavily pretreated. More than 80% of patients had failed 2 or more prior lines of chemotherapy, and 20% had failed bevacizumab therapy. Approximately one-quarter of patients had undergone tumor debulking surgery before enrollment.

After a median follow-up of 39 months, median survival was 6.6 months in the TTFields arm compared with 6.0 months in the chemotherapy arm, a difference that was not significant (P=.27; Figure 5). The 1-year survival rate was 20% in each arm. Treatment with TTFields was

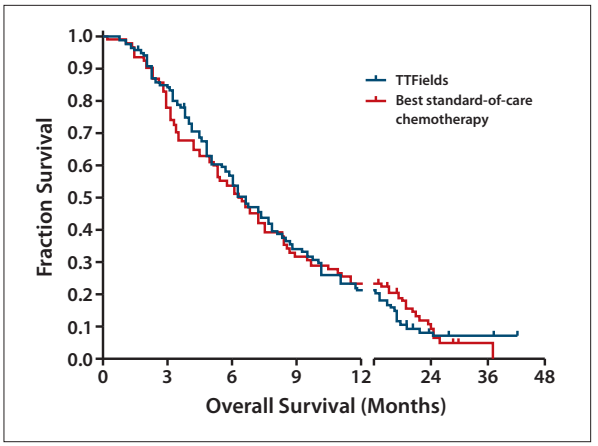

Figure 5. Overall survival in the EF-11 trial, which compared TTFields monotherapy vs chemotherapy among patients with recurrent glioblastoma. TTFields, tumor treating fields. Adapted from Stupp R et al. *Eur J Cancer*. 2012;48(14):2192-2202.[2]

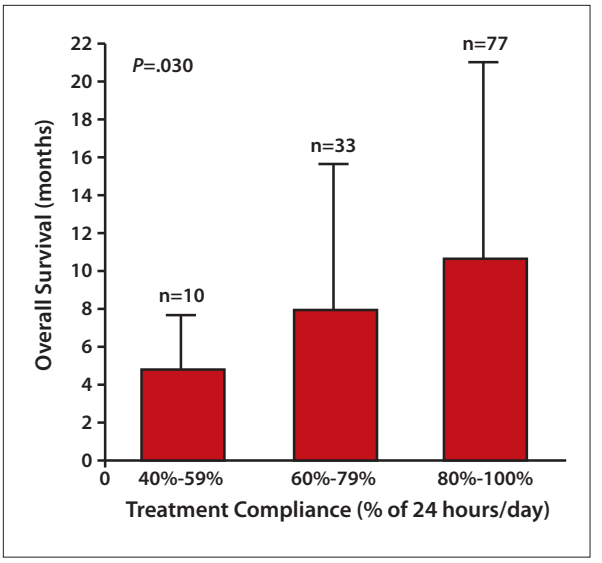

Figure 6. A post hoc analyses of the EF-11 trial showed that overall survival correlated with treatment compliance among patients in the tumor treating field arm. Adapted from Kanner AA et al. *Semin Oncol*. 2014;41(suppl 6):S25-S34.[5]

associated with a hazard ratio for death of 0.86 (95% CI, 0.66-1.12), but this improvement did not reach statistical significance (*P*=.27). Median progression-free survival showed a slight, nonsignificant benefit with TTFields vs chemotherapy (2.2 vs 2.1 months; hazard ratio, 0.81; 95% CI, 0.60-1.09; *P*=.16). The 6-month progression-free survival was 21.4% for patients in the TTFields arm and 15.1% in the chemotherapy arm (*P*=.13). The radiologic response rate was also slightly higher in the TTFields arm compared with the chemotherapy arm, but this difference did not reach statistical significance (14.0% vs 9.6%; *P*=.19). Overall, the authors concluded that TTFields failed to show superiority over chemotherapy, but was noninferior nonetheless. Therefore, in these heavily pretreated patients, the efficacy of TTFields therapy was at least equivalent to that of chemotherapy.

TTFields therapy was associated with minimal adverse events. In the TTFields arm, 16% of patients developed grade 1 or 2 contact dermatitis on the scalp beneath the transducer arrays. The contact dermatitis was well managed with topical corticosteroids. It did not require substantial treatment breaks, and resolved completely after treatment ended. Importantly, the systemic side effects typically associated with chemotherapy were infrequent among patients in the TTFields group. Among patients in the chemotherapy cohort, there was a significantly higher rate of gastrointestinal, hematologic, and infectious events. Severe adverse events were significantly more common in the chemotherapy cohort than the TTFields cohort (16% vs 6%; *P*=.022).[4] Quality-of-life measures, including global health and social functioning, showed no meaningful difference between the 2 treatment arms. Measures of cognitive and emotional function favored TTFields therapy.

A post hoc analysis evaluated a modified intent-to-treat population of "as-treated" patients—those patients from the TTFields arm who received at least 1 predefined treatment course (28 days), and patients from the chemotherapy arm who received at least 1 course of chemotherapy.[5] In this analysis, the median overall survival was significantly higher in the TTFields arm vs the chemotherapy arm (7.7 vs 5.9 months; hazard ratio 0.69; 95% CI, 0.52-0.91; *P*=.0093). Additional post hoc analysis demonstrated that the median overall survival was significantly higher with TTFields therapy vs chemotherapy among patients with certain baseline characteristics, such as low-grade glioma, tumor size at least 18 cm^2, Karnofsky performance status of 80 or higher, and previous failure to respond to bevacizumab therapy.

Importantly, this post hoc analysis also found that the median overall survival in the TTFields arm was affected by patient compliance (Figure 6). Compliance was defined as wearing the TTFields device for at least 18 hours a day. Those patients in compliance for at least 75% of days per month had a median overall survival of 7.7 months vs 4.5 months among patients who did not reach this level (*P*=.042). Kaplan-Meier analysis showed a significant trend for improved median overall survival as compliance increased (*P*=.039).

The phase 3 E-14 trial was halted after an interim analysis showed that patients treated with TTFields together with temozolomide demonstrated significant increases in overall survival and progression-free survival compared with those receiving temozolomide alone.[6,7] As Dr Toms discussed in the previous article, patients treated

with TTFields achieved a median overall survival of 19.4 months vs 16.6 months in the control arm (*P*=.0222). Median progression-free survival was 7.1 months for the TTFields group compared with 4.2 months for the control group (*P*=.0010).

NCCN Guidelines

TTFields therapy has been incorporated into the guidelines from the National Comprehensive Cancer Network (NCCN) since 2012. It was first given a category 2B recommendation, signifying consensus that the intervention was appropriate based upon a lower level of evidence. In 2014, this recommendation was changed to category 3, indicating disagreement regarding whether the intervention was appropriate. In 2015, however, the recommendation was changed back to category 2B.[3] This shifting recommendation serves as a reminder that the NCCN guidelines are a consensus recommendation formed by an expert panel based on the best available data. The fluctuation likely represents the changing opinions of the expert members within the NCCN committee.

Use by Oncology Specialists

Many kinds of oncologists can and do prescribe TTFields therapy, including medical oncologists, neuro-oncologists, radiation oncologists, and neurosurgeons. Currently, there are approximately 220 centers within the United States that are certified to use the device. Certification is provided through the manufacturer and mandated by the FDA.

Placement of the TTFields Device

Before treatment with TTFields begins, patients must undergo magnetic resonance imaging (MRI) to achieve the best visualization of the glioblastoma tumor. The measurement of the patient's head, as well as the size and location of the tumor within the head (based on the MRI images), are then imported into a computerized program called the NovoTAL System (Figure 7). This step is similar to radiation planning. The NovoTAL System is a software program that generates a transducer array layout map that doctors follow when placing the device onto the patient. The NovoTAL transducer array layout greatly optimizes TTFields therapy by personalizing the treatment and maximizing the electric field intensity to the tumor site.

A recent study evaluated device placement with the NovoTAL System vs mapping performed by the manufacturer's in-house clinical team (considered the gold standard).[8] The study included 14 physicians (7 neuro-oncologists, 4 medical oncologists, and 3 neurosurgeons), who evaluated 5 blinded MRI cases of glioblastoma. The

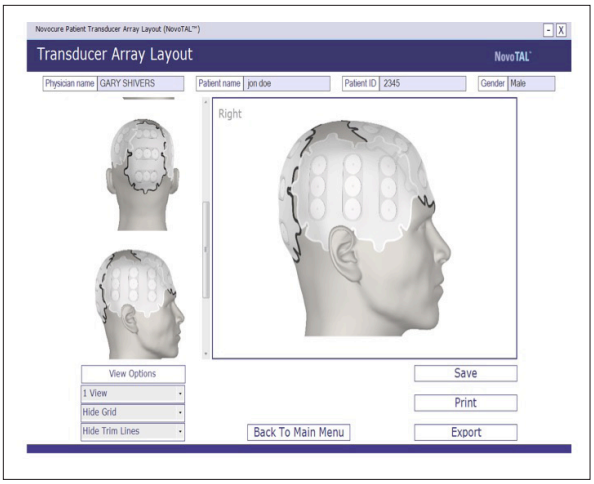

Figure 7. The NovoTAL System is a software program that generates a layout map for the tumor treating fields transducer arrays.

physicians measured head size and tumor location, and inputted these values into the NovoTAL system. The concordance correlation coefficient for each physician using the NovoTAL system vs the manufacturer's in-house clinical team on 20 MRI measurements was 0.96, indicating very high agreement between the groups. The correlation coefficients for intrarater and interrater reliability were 0.83 and 0.80, respectively, indicating that physician performance was reproducible with the NovoTAL system.

Patient Selection

Patient selection is critical for the efficacy of TTFields therapy. The patients who derive the most benefit from TTFields are those who are motivated to do so. The device, generator, and battery pack together weigh approximately 6 pounds, and patients must be able to wear the transducer arrays and carry the other components with them during their daily activities. Patients must be willing to shave their head for proper placement of the transducer arrays. Importantly, the device should be worn for at least 18 hours per day. Unlike systemic treatments, TTFields therapy works only when the device is being worn. In the event that a patient cannot wear the device for 18 hours on a particular day, he or she can wear the device for more hours the next day. It is reasonable to advise patients to wear the device as much as possible every day. The device captures the amount of time on therapy to provide the compliance rate. This rate is reported back to the physician in a monthly report.

In my own clinical experience, women tend to have greater reservations about this therapy than men, most likely because the head must be shaved. However, when patients are informed that TTFields can effectively control their recurrent glioblastoma, most are willing to sacrifice

their hair to wear the device. It is possible for patients to wear a wig on top of the device, as long as it allows enough aeration for heat to dissipate.

The battery lasts for 4 to 6 hours. When patients are sedentary or sleeping at night, they can use a power cord that plugs into a wall socket, so that they do not need to wake up every 4 to 6 hours at night to change the battery. Patients can carry the generator and the battery pack in a backpack, allowing them to maintain their mobility and independence. Future improvements may include a lighter generator and battery pack, which will substantially decrease the weight and hopefully make the portability of this device even better. In October 2015, a second-generation TTFields device became available in Europe. This new system weighs 2.7 pounds.

Patient Compliance

The key to effective therapy is to wear the device at least 75% of the time. Tumor cells do not divide in a synchronized fashion. Therefore, TTFields must be present to catch the tumor cells when they are actively dividing in mitosis.

At the Beth Israel Deaconess Medical Center in Boston, Massachusetts, we take a hands-on approach to the incorporation of TTFields therapy into patient management in order to increase patient compliance. We typically advise patients to wear the TTFields device for at least 75% of a 24-hour period (ie, 18 hours daily), based on the data previously described showing that this compliance rate improves median overall survival.[5] Patients do not need to wear the device continuously for 18 hours; they can break it up throughout the day. In addition, patients might wish to wear the device for more than 18 hours a day, in order to accumulate enough hours to have one day when they do not wear the device at all.

A main issue of use occurs when patients travel on commercial airlines. Currently, lithium ion batteries are not permitted on most commercial airlines. The device manufacturer can contact a particular airline to seek permission for the patient. The transducer arrays will set off metal detectors, so manual screening at security is required for patients wearing them. To avoid these obstacles, the device manufacturer has an organized system in which the device, generator, and battery pack are sent to the patient's destination.

Optimizing TTFields Therapy

Optimization of the efficacy of the TTFields modality has been an intense area of investigation. In the phase 3 trial, a radiologic response was reported in 14.0% (n=14) of patients in the TTFields arm vs 9.6% (n=7) of the chemotherapy arm (P=.19).[2] An initial analysis evaluated the characteristics of responders and nonresponders in both treatment cohorts to identify any predictive factors.[9] The median duration of response was 7.3 months in the TTFields arm compared with 5.6 months for chemotherapy (P=.0009). Among the radiologic responders, baseline low-grade histology was reported in 5 of the TTFields group vs none in the chemotherapy group.

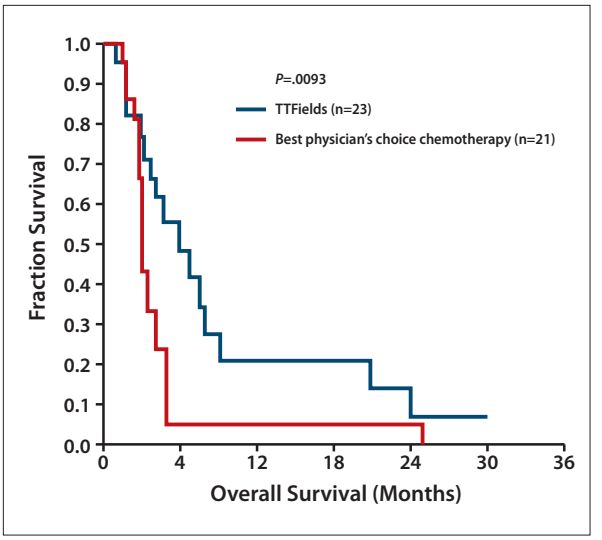

Figure 8. An analysis determined that the dosage of dexamethasone should be limited to 4.1 mg/day or less when used with tumor treating fields. Adapted from Wong ET et al. *Br J Cancer*. 2015;113(2):232-241.[10]

Dexamethasone, which is frequently used to treat the neurologic symptoms caused by glioblastoma, appeared to impact response. In the cohort of patients who received TTFields therapy, the mean cumulative dexamethasone dose was 35.9 mg for responders vs 485.6 mg for nonresponders (P<.0001). This marked difference prompted a subsequent analysis that defined the optimal cumulative dexamethasone dose for patients using TTFields.[10] The optimal dose, 4.1 mg/day or less, was associated with a median overall survival of 11.0 months (Figure 8). Among patients who received higher dosages, overall survival was 4.8 months (x^2=34.6; P<.0001). Emerging evidence has suggested that dexamethasone may exert inhibitory actions on the patient's antitumor immunity, which may account for this agent's effect on TTFields. Under normal conditions, TTFields therapy disrupts the tumor cell membrane and leads to endoplasmic reticulum stress. These effects cause the tumor cell to become visible to the immune system. A dexamethasone dosage of 4.1 mg/day or less allows the immune system to exert an effect on the tumor. Therefore, it is critically important to limit the dexamethasone dosage to 4.1 mg/day while patients are receiving TTFields therapy. Among patients who cannot tolerate this low dose, an alternative might be to replace dexamethasone with bevacizumab. This strategy is supported by data from 2 trials (the RTOG 0825 [Temozolomide and Radiation Therapy With or Without Bevacizumab in Treating Patients With Newly

Diagnosed Glioblastoma] study and the AVAglio [A Study of Avastin (Bevacizumab) in Combination With Temozolomide and Radiotherapy in Patients With Newly Diagnosed Glioblastoma] study), which showed that progression-free survival improved with the addition of bevacizumab to radiotherapy and temozolomide chemotherapy in patients with newly diagnosed glioblastoma.[11,12] (However, overall survival did not improve.) This effect on progression-free survival may be a result of the antiedema effects of bevacizumab. There is the potential that bevacizumab could replace dexamethasone for symptom palliation.

Importantly, the effect of the dexamethasone dosage on overall survival was also observed among patients receiving chemotherapy. Among patients receiving a dosage of less than 4 mg/day, the overall survival was 8.9 months, vs 6.0 months with the higher dosages (x^2=10.0; P<.0015). This finding suggests that a lower dexamethasone dose should be considered for all glioblastoma patients, not just those receiving TTFields therapy.

Other Emerging Treatment Strategies in Glioblastoma

There are several other new treatment strategies in glioblastoma. Immunotherapeutic agents have gained prominence during the past few years. The immunotherapies of greatest interest for treatment of glioblastoma include the checkpoint inhibitors, consisting of antibodies directed against cytotoxic T-lymphocyte–associated protein 4 (CTLA-4; such as the approved agent ipilimumab) or the PD-1/PD-ligand 1 interaction (including the approved agents nivolumab and pembrolizumab).

Another notable type of immunotherapy is vaccine-based. For glioblastoma, this strategy includes removal of a small piece of the tumor at the initial diagnosis, followed by leukapheresis to harvest the patient's dendritic cells. These dendritic cells are then sensitized in vitro to the patient's tumor specimen, so that when they are reinjected into the patient, the cells are able to effect a cytotoxic T-cell–driven immune response. Gene therapy–based immunotherapy treatments are also currently under investigation. Immunotherapy is an exciting area of treatment, with great promise in glioblastoma. It is possible that in the future, immunotherapy strategies may be added as an adjunct to boost the antitumor immune response in patients undergoing treatment with TTFields.

Disclosure

Dr Wong has a sponsored research agreement from Novocure for investigating the basic biologic effects of TTFields on tumor cells.

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Future Directions in the Use of Tumor Treating Fields and Other New Technologies in Glioblastomas and Other Cancers

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Despite advancements in surgery, radiation, and chemotherapy, patients with newly diagnosed glioblastoma have limited treatment options, and less than 10% are alive 5 years after diagnosis.[1] The poor prognosis can be attributed to several factors, such as the heterogeneous microenvironment in which the glioblastoma tumor develops, and the diverse pathways and mutations underlying the development of these tumors.[2] In addition, most medical therapies have poor blood-brain barrier penetration, further limiting their efficacy in glioblastoma.

As previously discussed, the EF-14 trial assessed the efficacy of TTFields in patients with newly diagnosed glioblastoma. At a median follow-up of 12 months, the addition of TTFields to maintenance temozolomide resulted in a significant improvement in median progression-free survival compared with maintenance temozolomide alone (7.1 vs 4.2 months; hazard ratio, 0.69; *P*=.0010).[3] The combination resulted in improved overall survival among patients treated with TTFields therapy plus maintenance temozolomide vs maintenance temozolomide alone (19.4 vs 16.6 months; hazard ratio, 0.75; 95% CI, 0.60-0.96; *P*=.0222).

The most common adverse event in the TTFields arm was grade 1 or 2 skin reaction at the treatment site (reported in approximately 45%). All other treatment-related adverse events in the combination arm were similar to those seen in the temozolomide-alone arm. There was no increase in neurologic side effects (such as seizures) with the addition of TTFields therapy.

As previously discussed by Dr Toms, the phase 3 trial of TTFields therapy in patients with recurrent glioblastoma demonstrated that this modality was associated with a similar overall survival compared with chemotherapy, as well as a clinically meaningful effect on quality of life.[4]

Ongoing and Future Studies of TTFields in Glioblastoma

Studies are evaluating TTFields in combination with other therapeutic modalities. In vitro studies have shown an additive or synergistic effect when TTFields are used with chemotherapy in high-grade glioma, breast adenocarcinoma, and NSCLC.[5] TTFields therapy appears to act synergistically with a number of chemotherapies in preclinical models.[5]

Further studies of TTFields in patients with newly diagnosed glioblastoma include a phase 2 trial of the combination of TTFields with bevacizumab plus temozolomide in patients with newly diagnosed, unresectable glioblastoma.[6]

A phase 2, multicenter, investigator-initiated study is evaluating the combination of TTFields together with bevacizumab in patients with recurrent glioblastoma.[7] Another ongoing clinical trial is investigating the combination of TTFields therapy with bevacizumab and carmustine for the treatment of patients in first relapse of glioblastoma.[8] A pilot study is evaluating the combination of TTFields with bevacizumab and hypofractionated stereotactic irradiation in patients with recurrent glioblastoma who are bevacizumab-naive.[9] A phase 2 study will attempt to identify any genetic signatures among patients with recurrent glioblastoma that may predict response to TTFields therapy.[10]

There was an interesting post hoc observation in the EF-11 study: among patients who had progressed on bevacizumab, median overall survival was 6.0 months with TTFields therapy (n=23) vs 3.3 months with chemotherapy (n=21; hazard ratio, 0.43; 95% CI, 0.22-0.85; x^2 *P*=.016; Figure 9).[11] Building on this observation, there is a planned Radiation Therapy Oncology Group (RTOG) foundation study that will evaluate the benefit of TTFields and bevacizumab in patients with recurrent glioblastoma who have progressed on bevacizumab.

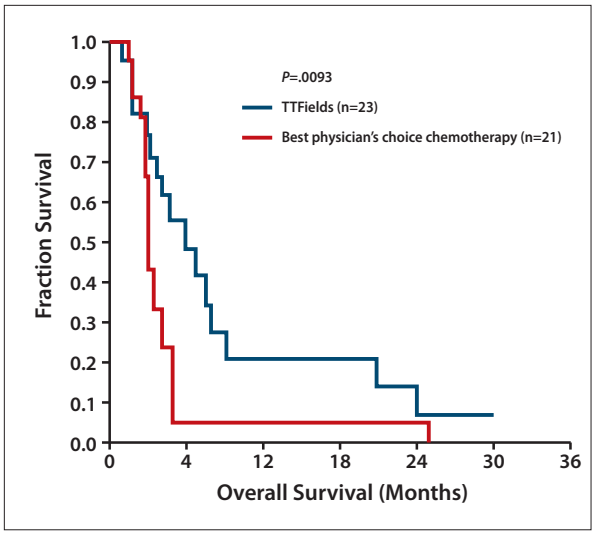

Figure 9. A post hoc observation in the EF-11 study found that among patients who had progressed on bevacizumab, median overall survival was 6.0 months with tumor treating fields therapy vs 3.3 months with chemotherapy. Adapted from Kanner AA et al. *Semin Oncol.* 2014;41(suppl 6):S25-S34.[11]

TTFields are undergoing evaluation in other central nervous system tumors. There are currently no medical treatments proven to be effective for patients with progressive meningioma that has not responded to surgery and/or radiation. TTFields are under evaluation in a pilot study for recurrent atypical and anaplastic meningioma.[12]

Ongoing Studies of TTFields in Other Tumor Types

Preclinical studies have demonstrated that TTFields have activity in many cell lines, which suggests that this modality may have activity in other tumor types in addition to glioblastoma.[13] The STELLAR (Safety and Efficacy of TTFields Concomitant With Pemetrexed and Cisplatin or Carboplatin in Malignant Pleural Mesothelioma) study is evaluating the safety and efficacy of TTFields therapy administered concomitantly with pemetrexed and cisplatin or carboplatin as first-line treatment in patients with malignant pleural mesothelioma.[14] This study is a prospective, single-arm, nonrandomized, open-label, phase 2 trial that aims to enroll 80 patients. The primary study outcome is overall survival. Secondary outcome measures include progression-free survival, response rate, and toxicity.

The PANOVA (Safety Feasibility and Effect of NovoTTF-100L Together With Gemcitabine for Front-Line Therapy of Advanced Pancreatic Adenocarcinoma) trial is evaluating the safety, feasibility, and efficacy of TTFields used in combination with gemcitabine for the first-line treatment of advanced pancreatic adenocarcinoma.[15] This open-label pilot study enrolled 20 patients. The primary endpoints are adverse events and feasibility. Secondary endpoints include median and 6-month progression-free survival, median and 1-year overall survival, and overall response rate. The study was started in November 2013. An analysis presented at the 2015 ASCO meeting provided preliminary data on safety. Adverse events occurred in 80% of patients. Among the 45% of patients who experienced dermatitis, 78% experienced a mild or moderate skin toxicity. There were 9 serious adverse events, but none were related to TTFields; 78% were attributed to the underlying cancer and other treatments. More than half of the patients (55%) enrolled were still receiving TTFields at the time the study was presented.[16] Enrollment is ongoing for an additional 20 patients who will receive concomitant TTFields, gemcitabine, and nab-paclitaxel.

The safety, feasibility, and effect of TTFields in combination with weekly paclitaxel is under investigation in the INNOVATE (Safety, Feasibility and Effect of TTFields Concomitant With Weekly Paclitaxel in Recurrent Ovarian Carcinoma) study of patients with recurrent ovarian carcinoma.[17] This prospective, single-arm, nonrandomized, open-label, pilot phase 1/2 trial aims to enroll approximately 30 patients. The primary endpoints are adverse events and skin toxicity that leads to premature discontinuation. Key secondary endpoints include progression-free survival, overall survival, and response rate.

The COMET (Effect of NovoTTF-100A in Non-Small Cell Lung Cancer [NSCLC] Patients With 1-5 Brain Metastases Following Optimal Standard Local Treatment) study is evaluating TTFields therapy in patients with NSCLC who have 1 to 5 brain metastases following optimal standard local treatment.[18] This randomized, phase 2 trial aims to treat 60 patients with either TTFields or the best standard of care. The primary endpoint is the time to local and distant progression in the brain. Secondary endpoints include overall survival, progression-free survival, the 6-month disease control rate in the brain, neurocognitive function, quality of life, and adverse events.

Clinical Studies of Other Emerging Treatment Strategies in Glioblastoma

Immunotherapies, especially the checkpoint inhibitors (antibodies directed against CTLA-4 or the PD-1/PD-ligand 1 interaction), represent an exciting advancement in oncology. Immunotherapies (antibodies directed against CTLA-4 and PD-1) were first approved for the treatment of melanoma. More recently, antibodies directed against PD-1 have gained approval for NSCLC. Several clinical trials are under way to investigate their activity and safety in patients with glioblastoma.

CheckMate 143 is a randomized, phase 3 clinical trial in which approximately 440 patients with recurrent glioblas-

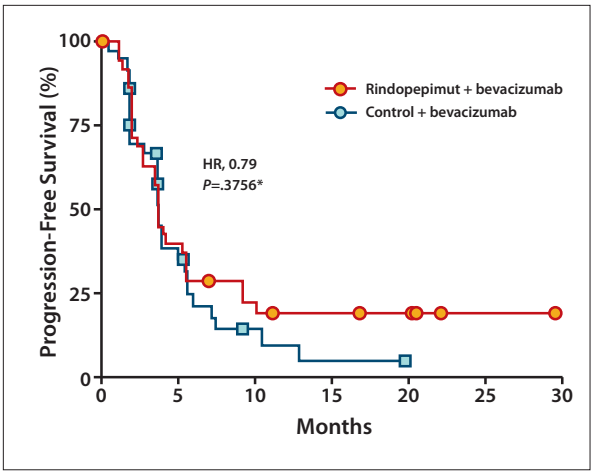

Figure 10. Progression-free survival in the phase 2 ReACT trial, in which glioblastoma patients in first or second relapse with EGFRvIII were randomized to bevacizumab plus a double-blinded injection of rindopepimut or control. *Log rank test (2-sided). EGFR, epidermal growth factor receptor; ReACT, A Study of Rindopepimut/GM-CSF in Patients With Relapsed EGFRvIII-Positive Glioblastoma. Adapted from Reardon DA et al. ReACT: overall survival from a randomized phase II study of rindopepimut (CDX-110) plus bevacizumab in relapsed glioblastoma [ASCO abstract 2009]. *J Clin Oncol.* 2015;33(suppl).[22]

toma received nivolumab (an anti–PD-1 antibody) alone, nivolumab plus ipilimumab (an anti–CTLA-4 antibody), or bevacizumab alone.[19] The primary endpoints are safety and overall survival. Secondary endpoints are progression-free survival and response rate. The trial has completed enrollment. A phase 2 trial will assess the PD-1 checkpoint inhibitor pembrolizumab both alone and in combination with bevacizumab for the treatment of patients with recurrent glioblastoma.[20] In the estimated 79 patients, the primary study outcomes are 6-month progression-free survival and the maximum tolerated dose. Secondary outcomes include safety and tolerability, progression-free survival, overall survival, and radiographic response. There are other ongoing studies in both newly diagnosed and recurrent glioblastoma evaluating the role of these checkpoint inhibitors.

Vaccine-based approaches, such as rindopepimut, ICT-107, SL-701, dendritic cell vaccine therapy, and HSPPC-96, are also being evaluated in clinical trials. Approximately 25% of glioblastoma patients harbor EGFRvIII, which is a constitutively active *EGFR* deletion driver mutation associated with poor survival in glioblastoma.[21] In the phase 2 ReACT (A Study of Rindopepimut/GM-CSF in Patients With Relapsed EGFRvIII-Positive Glioblastoma) trial, glioblastoma patients in first or second relapse with EGFRvIII were randomized 1:1 to bevacizumab plus a double-blinded injection of rindopepimut or control (keyhole limpet hemocyanin). Among the intent-to-treat population, the progression-free survival at 6 months was 28% (10/36) in the vaccine arm vs 16% (6/37) in the placebo arm (P=.1163; 1-sided x^2 test; Figure 10).[22]

The randomized, phase 3 ACT IV (Phase III Study of Rindopepimut/GM-CSF in Patients With Newly Diagnosed Glioblastoma) trial is evaluating the efficacy and safety of the addition of rindopepimut to temozolomide in patients with recently diagnosed glioblastoma treated with surgery, radiation, and temozolomide.[23] The accrual to the study has been completed. Several hundred patients were randomly assigned to receive rindopepimut (given along with granulocyte-macrophage colony-stimulating factor as a vaccine adjuvant) or keyhole limpet hemocyanin (used as a control), each with temozolomide.

Given the low and nonoverlapping toxicity profile of TTFields with immunotherapy, it will be interesting to see the potential efficacy of these novel therapies in combination with TTFields therapy in glioblastoma.

Disclosure

Dr Ahluwalia has received research or grant support from BMS, Novocure, Spectrum Pharmaceuticals, Boehringer Ingelheim, Novartis, and Tracon Pharmaceuticals. He has served as a consultant for Caris Life Sciences, Monteris Medical, and Incyte.

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Clinical Use of Tumor Treating Fields: Discussion

Eric T. Wong, MD, Steven A. Toms, MD, and Manmeet S. Ahluwalia, MD

H&O Do TTFields use magnets?

Eric T. Wong, MD TTFields do not use magnets in the traditional sense (ie, refrigerator magnets). Instead, they use electromagnetic waves, which do use magnetism. TTFields use the electromagnetic spectrum. Specifically, the alternating electric field disrupts the movement of charged particles. The human body has many charged molecules that have zero net charge; they have a positive charge on one end of the molecule and a negative charge on the other end. In an alternating electric field, although there is no net translational movement (ie, moving from point A to point B), there is rotational movement. The dipole will move around because of the alternating electric field or the charged environment that is imposed onto the dipole.

H&O Do TTFields use radiation?

Eric T. Wong, MD Again, not in the sense of what is commonly thought of as radiation, which is typically ionizing radiation. This type of high-energy radiation enters into the patient's body in a straight path, and the intensity of the radiation energy disrupts electrons along the way. In contrast, TTFields have a lower energy intensity, and they do not disrupt electrons. Nevertheless, the active frequency of 150 to 200 kHz will affect specific molecules that have a particular dipole moment, such as septin. It is likely that there are other large, charged molecules that are also under the influence of the alternating electric field.

H&O Is there any increase in seizures with TTFields?

Manmeet S. Ahluwalia, MD Based on the information we have from multiple clinical trials, there has been no observation of increased frequency of seizures with TTFields.

H&O Is the benefit in the phase 3 study explained by the placebo effect?

Eric T. Wong, MD No. In the registrational, randomized, phase 3 clinical trial, the control group consisted of those patients who received their physicians' best choice of chemotherapy.[1] The majority of the patients who received chemotherapy were treated with either an alkylating agent or bevacizumab. It is important to realize that all of these patients received treatment with some proven efficacy. Therefore, although TTFields treatment resulted in the same outcome as chemotherapy, this treatment modality maintained patient survival not because of the placebo effect but because of a true effect on the tumor.

This question raises an important point concerning the impact of dexamethasone. Our post hoc analysis identified an optimal dosage of 4.1 mg/day or less, and higher dosages decreased the efficacy of TTFields (and chemotherapy). For patients treated with a lower dosage of dexamethasone, TTFields therapy resulted in better survival than chemotherapy. Among patients who received higher dosages, TTFields therapy was associated with a shorter survival time compared with chemotherapy. These findings suggest that there is a

specific population of patients who are highly responsive to the TTFields effect, and the dose of dexamethasone is an important parameter in treating this population.

H&O What is the pseudoprogression of radiation?

Eric T. Wong, MD Pseudoprogression of radiation refers to a phenomenon that is frequently seen after patients receive temozolomide and ionizing radiation for the treatment of newly diagnosed glioblastoma. The patients' tumor enhancement on MRI after treatment appears worse than on the pretreatment scan. It occurs because the patient's tumor is so susceptible to the effects of the radiation that it becomes highly enhancing. To help my patients understand this phenomenon, I relate the radiation to sunburn. Some individuals are more susceptible to sunburn than others. When the sunburn is very bad, or when the patient is especially susceptible, the skin becomes extremely red and hot, and it sloughs off. The same thing can happen to the tumor in the brain. Patients with pseudoprogression have in fact shown an overwhelming response to the treatment, rather than tumor progression.

H&O Can TTFields therapy be combined with other modalities of treatment?

Eric T. Wong, MD Definitive data are currently lacking. In my opinion, TTFields can be combined with cytotoxic chemotherapy. The optimal type and schedule of cytotoxic chemotherapy remains to be determined.

Among the cytotoxic chemotherapies, I would probably chose lomustine. In 3 separate randomized clinical trials, lomustine (in combination with other agents) was shown to have efficacy against recurrent glioblastoma, including progression-free survival rates that were comparable to the benchmark.[2-4]

We recently published a case report of this strategy.[5] We treated a patient who was basically told to go to hospice because she had no other treatment options. The patient came to us in a wheelchair with an extremely large tumor. We immediately initiated TTFields therapy. We restarted bevacizumab therapy in order to wean the patient off of dexamethasone. In addition, we added a multidrug regimen consisting of 6-thioguanine, lomustine, capecitabine, and celecoxib. After 2 cycles of lomustine, the patient experienced a partial response. From this outcome, we can conclude that TTFields therapy not only works just as well as systemic chemotherapy, but in patients receiving low doses of dexamethasone, it can offer increased benefit over traditional chemotherapy alone. When traditional chemotherapy is combined with bevacizumab and TTFields therapy, it can augment the response even more.

H&O What are some common questions from patients about TTFields?

Steven A. Toms, MD The most common questions from patients concern whether they can still live their normal life while wearing the device, and if other people will stare at them. Wearing the device does not appear to impact daily activities. I compare the battery pack to a large, somewhat heavy purse, a light backpack, or a computer bag. The batteries last 2 to 3 hours, so several batteries must be taken when the patient is away from home for an extended time. When patients are at home and wearing the device while sedentary, such as while they are sleeping or watching television, we ask them to keep the device plugged in to an electrical outlet. The device can be covered fairly well by wigs, scarves, and hats. Although people may express curiosity about the device, most patients are able to handle this attention.

We also receive questions about insurance. Most insurance plans cover the TTFields device. With the FDA approval, more plans are covering it. The manufacturer offers assistance to alleviate the financial burden to the patient.

Disclosures

Dr Wong has a sponsored research agreement from Novocure for investigating the basic biologic effects of TTFields on tumor cells. Dr Ahluwalia has received research or grant support from BMS, Novocure, Spectrum Pharmaceuticals, Boehringer Ingelheim, Novartis, and Tracon Pharmaceuticals. He has served as a consultant for Caris Life Sciences, Monteris Medical, and Incyte. Dr Toms is a member of the strategic advisory boards of Medtronic and Novocure.

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Slide Library

Modalities for Cancer Treatment

Traditional Modalities
- Surgery
- Radiation therapy
- Chemotherapy

Emerging Modalities
- TTFields
- Immunomodulatory therapies
- Viral-mediated gene therapies

TTFields, tumor treating fields.

TTFields: Mechanism of Action

- TTFields are thought to exert dielectrophoretic forces on cellular components, thereby altering their normal functions
- Basic science research proposed that alternating electric TTFields lead to the destruction of tumor cells during mitosis[1]
- TTFields disrupt mitosis during the metaphase to anaphase transition
- TTFields inhibit cytokinesis, the process at the end of mitosis in which a cell with 2 nuclei separates into 2 individual cells

1. Gera N et al. *PLoS One*. 2015;10(5):e0125269.

TTFields: Clinical Trial Data

Trial	Population	Outcome
EF-11[1]	Recurrent glioblastoma	TTFields appeared to be as effective as chemotherapy
EF-14[2]	Newly diagnosed glioblastoma	The addition of TTFields to maintenance temozolomide resulted in a significant improvement in median progression-free survival compared with maintenance temozolomide alone in the intent-to-treat group

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TTFields: FDA Approvals

- The initial approval of TTFields, in 2011, was as monotherapy for adult patients (ages 22 years and older) with recurrent glioblastoma multiforme who had received chemotherapy and shown signs of progressive disease
- On October 5, 2015, this indication was expanded to include patients with newly diagnosed glioblastoma who have undergone surgical biopsy or resection and have completed radiation therapy with concomitant temozolomide

FDA, US Food and Drug Administration.

Immunotherapy for Glioblastoma

Checkpoint inhibitors consist of antibodies:
- Directed against CTLA-4
  - Ipilimumab
- Directed against the PD-1/PD-ligand 1 interaction
  - Nivolumab
  - Pembrolizumab

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed death 1.

Vaccine-Based Approaches in Clinical Trials

- Rindopepimut
- ICT-107
- SL-701
- Dendritic cell vaccine therapy
- HSPPC-96

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Technological Advances in the Treatment of Cancer: Combining Modalities to Optimize Outcomes

CME Post-Test: *Circle the correct answer for each question below.*

1. What is the most common form of primary brain cancer in adults?

   a. Glioblastoma
   b. Pituitary adenomas
   c. Primitive neuroectodermal tumors
   d. Vestibular schwannomas

2. What does the Stupp protocol consist of?

   a. Bevacizumab plus a daily immunomodulatory agent, followed by adjuvant temozolomide
   b. Radiotherapy plus daily temozolomide, followed by adjuvant temozolomide
   c. Stereotactic radiosurgery plus daily bevacizumab, followed by an adjuvant PD-1 inhibitor
   d. Temozolomide plus a checkpoint inhibitor, followed by adjuvant bevacizumab

3. Approximately how many glioblastoma patients harbor EGFRvIII?

   a. 10%
   b. 15%
   c. 20%
   d. 25%

4. During the mitotic cycle, errors that occur during which transition typically result in aberrant mitotic exit and cell death?

   a. Early interphase to prophase
   b. Later metaphase to anaphase transition
   c. Early prometaphase to metaphase
   d. Later telophase to cytokinesis

5. What frequency is used with TTFields in glioblastoma?

   a. 75 kHz
   b. 200 kHz
   c. 300 kHz
   d. 375 kHz

6. In the phase 3 E-11 trial, what was the median progression-free survival for patients who received TTFields?

   a. 1.8 months
   b. 2.2 months
   c. 3.1 months
   d. 4.6 months

7. In the phase 3 E-14 trial, what was the median overall survival among patients treated with TTFields and temozolomide?

   a. 16.7 months
   b. 17.8 months
   c. 18.2 months
   d. 19.4 months

8. What is the most common adverse event associated with TTFields?

   a. Seizures
   b. Memory loss
   c. Skin irritation occurring under the transducer arrays
   d. Muscle soreness

9. Which agent should be limited to 4.1 mg/day when used with TTFields?

   a. Bevacizumab
   b. Dexamethasone
   c. Nivolumab
   d. Temozolomide

10. Which agent is an anti–PD-1 antibody?

    a. Bevacizumab
    b. Ipilimumab
    c. Nivolumab
    d. Rindopepimut

Project ID: 10974

Evaluation Form: Technological Advances in the Treatment of Cancer: Combining Modalities to Optimize Outcomes

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 10974**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

❒ MD/DO ❒ PA/PA-C ❒ NP ❒ RN ❒ PharmD/RPh ❒ PhD
❒ Other, please specify:

2. What is your area of specialization?

❒ Oncology, Hematology/Oncology ❒ Oncology, Medical ❒ Oncology, Radiology

3. Which of the following best describes your *primary* practice setting?

❒ Solo Practice ❒ Group Practice ❒ Government
❒ University/teaching system ❒ Community Hospital
❒ HMO/managed care ❒ Non-profit/community ❒ I do not actively practice
❒ Other, please specify:

4. How long have you been practicing medicine?

❒ More than 20 years ❒ 11-20 years ❒ 5-10 years ❒ 1-5 years
❒ Less than 1 year ❒ I do not directly provide care

5. Approximately how many patients do you see each week?

❒ Less than 50 ❒ 50-99 ❒ 100-149 ❒ 150-199 ❒ 200+
❒ I do not directly provide care

6. How many patients do you currently see each week with cancer?

❒ Fewer than 5 ❒ 6-15 ❒ 16-25 ❒ 26-35 ❒ 36-45 ❒ 46-55
❒ 56 or more ❒ I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Explain the need for additional anticancer treatment modalities beyond the existing strategies of surgery, chemotherapy, and radiation therapy
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Describe the proposed mechanisms of action for novel anticancer treatment modalities, such as tumor treating fields
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Evaluate efficacy and safety data from clinical studies of novel anticancer treatment modalities
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Identify patients who would be appropriate candidates for clinical trials of novel anticancer treatment modalities
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Combine new treatment modalities, such as tumor treating fields and immunotherapy, with existing strategies, such as surgery, chemotherapy, and radiation therapy
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The content was evidence based
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The educational material provided useful information for my practice
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity enhanced my current knowledge base
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? *(choose only one of the following options)*

❒ I do plan to implement changes in my practice based on the information presented
❒ My current practice has been reinforced by the information presented
❒ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? *(check all that apply)*

❒ Apply latest guidelines ❒ Choice of treatment/management approach
❒ Change in pharmaceutical therapy ❒ Change in current practice for referral
❒ Change in nonpharmaceutical therapy ❒ Change in differential diagnosis
❒ Change in diagnostic testing ❒ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

❒ Very confident ❒ Somewhat confident ❒ Unsure ❒ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

❒ Formulary restrictions ❒ Insurance/financial issues ❒ Time constraints
❒ Lack of multidisciplinary support ❒ System constraints
❒ Treatment-related adverse events ❒ Patient adherence/compliance
❒ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

❒ Yes ❒ No, please explain:

15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

Request for Credit (*required fields)

Name* _____

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Organization _____

Specialty* _____

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I certify my actual time spent to complete this educational activity to be:

❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Project ID: **10974**