**Perspective on the EF-14 trial and its implications for the role of Tumor-Treating Fields in the management of glioblastoma**

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**Abstract**

Tumor treating fields (TTFields) is a novel treatment modality that has been recently approved for the treatment of patients with both newly diagnosed and recurrent glioblastoma (GBM). This approach comprises of a portable device delivering low intensity and intermediate frequency alternating electric fields aiming at selectively inhibiting cellular proliferation of neoplastic cells. Promising findings of recent large scale multinational clinical trials have indicated that TTFields have a favorable safety profile without causing significant adverse effects on patients. These trials have reported that GBM patients treated with TTFields had significantly prolonged overall and progression free survival compared to patients receiving standard chemotherapy. Moreover, improved quality of life with better cognitive and emotional functions was observed in TTFields treated cohorts of patients. Conventional MR imaging using modified RANO criteria is currently considered as the standard protocol for assessing disease progression and treatment response in patients with GBM. Using physiological and metabolic MR imaging, we recently reported our experience with evaluating treatment response to TTFields in newly diagnosed GBM. We believe that additional studies evaluating the treatment response of TTFields will have a profound impact on the clinical use of this novel and effective treatment modality for GBM patients.

**Perspective**

The article “Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial” published in JAMA in Dec 2015, describes a pivotal phase 3 clinical trial of Optune® in combination with temozolomide (TMZ) for the treatment of newly diagnosed glioblastoma (GBM) from 83 centers in North America, Europe, and Asia.[1](#_ENREF_1) Before giving the readers our view-point regarding the results of this trial, we will briefly review some fundamental concepts regarding this novel cancer treatment modality. Towards the end of this article, we will discuss the implications of this new technology, share some of our experiences focusing on current advances and future directions.

Alternating electric field therapy, also termed as tumor treating fields (TTFields), is a type of electromagnetic field therapy that uses low-intensity electrical fields to inhibit cell division and is implicated in the treatment of a variety of cancers, e.g., glioma, melanoma, adenocarcinoma.[2](#_ENREF_2), [3](#_ENREF_3) TTFields is an anti-mitotic, physical treatment modality that acts in metaphase, anaphase and telophase of the cell division.[4](#_ENREF_4), [5](#_ENREF_5) Optune (formerly known as NovoTTF) is a portable non-invasive, in-home use medical device that delivers TTFields to the brain using non-invasive, “disposable transducer arrays” worn on the patient’s shaved head for 18-22 hours per day (with breaks allowed for showers).[1](#_ENREF_1), [6](#_ENREF_6) TTFields is approved in the United States and Europe for the treatment of newly diagnosed as well as recurrent glioblastoma (GBM), and is undergoing clinical trials for several other tumor types.[7-9](#_ENREF_7) The American National Comprehensive Cancer Network's official guidelines also list TTFields as an option for the treatment of recurrent GBM.

Initial pilot studies and clinical trials using TTFields started in 2004 and the first randomized clinical trial (EF-11), led by Dr. Roger Stupp, Professor and Chairman, Department of Oncology, University Hospital Cancer Center at the University of Zurich, Switzerland, evaluating TTFields was published in 2012,[10](#_ENREF_10) which evaluated the efficacy of this approach in patients with recurrent GBM. The encouraging results from this trial formed the basis for regulatory approval of Optune in the United States and Europe. In this study, patients with recurrent GBM were randomized to treatment either with TTFields or with best available active chemotherapy according to the local physician’s choice. No improvement in overall survival was demonstrated, however efficacy and activity with chemotherapy-free treatment device was found comparable to chemotherapy regimens, with local treatment toxicity limited only to skin irritation from transducer arrays. Despite the inconvenience of carrying and using the device almost permanently, compliance was high and patients reported improvement in quality of life in the absence of chemotherapy related toxicities.

Overall since the device has been available, over 2500 patients have been treated between the clinical trials and the commercial use of the Optune device.

Subsequently, an international, multicenter, prospective, randomized phase III trial in newly diagnosed GBM patients (EF-14), also led by Dr. Roger Stupp, was initiated in July 2009, and by its completion in November 2014, 700 patients were enrolled on this trial. This EF-14 trial was designed to evaluate the efficacy of Optune to treat newly diagnosed GBM treated with Optune + TMZ vs TMZ alone. The results of the interim analysis were presented at the Annual Meeting of the Society of Neuro-Oncology (SNO) in 2014, after first 315 patients have been followed for at least 18 months. The intent to treat arm included 210 patients in the treatment arm and 105 patients in the control arm. The first data that stood out was progression free survival (PFS) which in the Optune + TMZ group was 7.1 months as opposed to 4 months in the TMZ alone group, with a *p* value of 0.001.[1](#_ENREF_1)

It is rare to see such kind of results on an interim analysis particularly for a GBM clinical trial. The trial’s independent Data Monitoring and Safety Committee met in October 2014 to review the interim analysis and concluded that the trial met the predefined boundaries for success (improvement of both progression-free and overall survival) and the committee recommended study termination, thus allowing patients in the control group to crossover and receive TTFields. After approval of study termination by the US Food and Drug Administration, the trial was closed to recruitment on November 29, 2014, after 695 patients of the planned 700 patients had already been randomized. All patients in the control group with ongoing maintenance therapy were offered to receive TTFields for the rest of the study.[1](#_ENREF_1)

The investigators of the EF14 trial[1](#_ENREF_1) reported statistically significant improvement in PFS from randomization in the TTFields + TMZ group vs. with TMZ alone. In the intent-to-treat population, patients treated with TTFields plus TMZ showed a statistically significant increase in PFS, the primary endpoint, compared to TMZ alone (median PFS 7.1 months versus 4.0 months, hazard ratio=0.62, p=0.0013). In the per-protocol population, patients treated with TTFields plus TMZ demonstrated a statistically significant increase in OS, a powered secondary endpoint, compared to TMZ alone (median OS 20.5 months versus 15.6 months, hazard ratio=0.64, p=0.0042). In the intent-to-treat population, the median OS was 19.6 months versus 16.6 months, respectively, hazard ratio=0.74 (p=0.0329). The two-year survival rate was approximately 50 percent greater with TTFields plus TMZ versus TMZ alone: 43 percent versus 29 percent. In addition, the trial showed TTFields could be safely combined with TMZ, with increase in systemic toxicities. The only reported added adverse events in the treatment group included grade 1-2 (mild to moderate) skin reaction (43%) and rarely grade 3 (severe) skin reaction (2%), which again supports the notion of the safety of this treatment modality. While the cost-benefit of TTFields was not assessed in this study, a subsequent analysis[11](#_ENREF_11) raises concerns about the cost of this modality, though more studies on this front are necessary, and the cost of this nascent technology may decrease with wider application and mass production.

In 2005, Dr. Roger Stupp reported that the addition of TMZ to radiation and surgery resulted in an overall survival benefit of 2.5 months (14.6 months vs. 12.1 months).[12](#_ENREF_12) As a result, TMZ has been included as the standard of care in the treatment of GBM. The addition of TTFields, which resulted in an additional 3 month survival benefit, indicates that TTFields along with TMZ therapy will significantly impact on the treatment and management of GBM.

We at University of Pennsylvania, have an ongoing Investigator Sponsored Trial (IST) in which we are investigating the utility of advanced neuroimaging techniques in monitoring disease response in GBM patients undergoing TTFields+TMZ treatment. Conventional MR imaging using modified RANO criteria is currently considered as the standard protocol for assessing disease progression and treatment response in patients with GBMs.[13](#_ENREF_13) However, it has been becoming increasingly clear that treatment response on the basis of post-contrast neuroimaging characteristics is not reliable for the true evaluation of therapeutic effects in these patients.[14](#_ENREF_14) On the other hand, emerging evidence has shown immense potential of advanced imaging techniques such as diffusion tensor imaging (DTI),[15](#_ENREF_15) and dynamic susceptibility contrast (DSC)-perfusion weighted imaging (PWI)[16](#_ENREF_16), [17](#_ENREF_17) and proton MR spectroscopy (1H MRS )[18](#_ENREF_18), [19](#_ENREF_19) in evaluating the treatment response to different therapeutic regimens in patients with gliomas.

We have recently reported our initial experience of assessing short-term (up to 2 months) response to TTFields in a newly diagnosed patient with left thalamic GBM using physiological and metabolic MR imaging techniques.[20](#_ENREF_20) The patient underwent DTI, PWI and 3D echo-planar spectroscopic imaging (EPSI) besides conventional imaging prior to initiation of TTFields and at one and two month follow-up on a 3T MR system. Mean diffusivity (MD), fractional anisotropy (FA), cerebral blood volume (rCBV) and choline/creatine (Cho/Cr) values were measured from the contrast-enhancing region of neoplasm at each time point. We found a steady decline in tumor volume (~12% and ~34%) at 1st and 2nd follow-up periods relative to baseline with a moderate increase in MD (~11%) along with decreases in FA (~23%) and Cho/Cr (~18% ) from enhancing regions of the neoplasm at 2nd follow-up  compared to baseline suggesting TTFields induced inhibited growth.[4](#_ENREF_4), [5](#_ENREF_5) Additionally, a moderate decline in rCBVmax, (6.21%) was also noted at 2-months relative to baseline indicating anti- angiogenetic effects of TTFields.[21](#_ENREF_21) Taken together, findings of these advanced imaging techniques provide insights into the possible therapeutic mechanism of TTFields in patients with GBMs.

In summary, TTFields compares favorably with standard chemotherapy with no systemic toxicity and represents a significant advancement in the management of GBM. We believe that given the dismal prognosis of GBM and the paucity of effective treatments, the results of this trial will give physicians a greater confidence in the value and importance of TTFields as a safe and effective treatment option for newly diagnosed GBM. We also believe that TTFields should be offered as the new standard of care in addition to TMZ for maintenance therapy following maximal safe resection and chemoradiation to GBM patients.

Additionally our preliminary data indicate that DTI, PWI and EPSI are promising techniques that may be useful in evaluating early treatment response to TTFields. In an ongoing trial, we are currently using advanced MR imaging techniques in assessing the treatment effects of TTFields in a larger cohort of patients with newly diagnosed as well as recurrent GBMs. We believe that future multinational clinical trials using physiological and metabolic imaging techniques will be needed to comprehensively evaluate treatment response to TTFields in patients with GBMs, which will enhance the decision making process in the use of this novel treatment modality.

**References**

1. Stupp R, Taillibert S, Kanner AA, et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. Jama 2015;314:2535-2543.

2. Wong ET, Lok E, Swanson KD. An Evidence-Based Review of Alternating Electric Fields Therapy for Malignant Gliomas. Current treatment options in oncology 2015;16:40.

3. Pless M, Weinberg U. Tumor treating fields: concept, evidence and future. Expert opinion on investigational drugs 2011;20:1099-1106.

4. Kirson ED, Gurvich Z, Schneiderman R, et al. Disruption of cancer cell replication by alternating electric fields. Cancer research 2004;64:3288-3295.

5. Giladi M, Weinberg U, Schneiderman RS, et al. Alternating electric fields (tumor-treating fields therapy) can improve chemotherapy treatment efficacy in non-small cell lung cancer both in vitro and in vivo. Seminars in oncology 2014;41 Suppl 6:S35-41.

6. Fonkem E, Wong ET. NovoTTF-100A: a new treatment modality for recurrent glioblastoma. Expert review of neurotherapeutics 2012;12:895-899.

7. Bomzon Z, Urman N, Wenger C, et al. Modelling Tumor Treating Fields for the treatment of lung-based tumors. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference 2015;2015:6888-6891.

8. Davies AM, Weinberg U, Palti Y. Tumor treating fields: a new frontier in cancer therapy. Annals of the New York Academy of Sciences 2013;1291:86-95.

9. Salzberg M, Kirson E, Palti Y, Rochlitz C. A pilot study with very low-intensity, intermediate-frequency electric fields in patients with locally advanced and/or metastatic solid tumors. Onkologie 2008;31:362-365.

10. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. European journal of cancer 2012;48:2192-2202.

11. Bernard-Arnoux F, Lamure M, Ducray F, Aulagner G, Honnorat J, Armoiry X. The cost-effectiveness of tumor-treating fields therapy in patients with newly diagnosed glioblastoma. Neuro-oncology 2016.

12. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. The New England journal of medicine 2005;352:987-996.

13. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010;28:1963-1972.

14. Jackson EF, Barboriak DP, Bidaut LM, Meyer CR. Magnetic resonance assessment of response to therapy: tumor change measurement, truth data and error sources. Translational oncology 2009;2:211-215.

15. Saraswathy S, Crawford FW, Lamborn KR, et al. Evaluation of MR markers that predict survival in patients with newly diagnosed GBM prior to adjuvant therapy. Journal of neuro-oncology 2009;91:69-81.

16. Aquino D, Di Stefano AL, Scotti A, et al. Parametric response maps of perfusion MRI may identify recurrent glioblastomas responsive to bevacizumab and irinotecan. PloS one 2014;9:e90535.

17. Schmainda KM, Prah M, Connelly J, et al. Dynamic-susceptibility contrast agent MRI measures of relative cerebral blood volume predict response to bevacizumab in recurrent high-grade glioma. Neuro-oncology 2014;16:880-888.

18. Jeon JY, Kovanlikaya I, Boockvar JA, et al. Metabolic response of glioblastoma to superselective intra-arterial cerebral infusion of bevacizumab: a proton MR spectroscopic imaging study. AJNR American journal of neuroradiology 2012;33:2095-2102.

19. Muruganandham M, Clerkin PP, Smith BJ, et al. 3-Dimensional magnetic resonance spectroscopic imaging at 3 Tesla for early response assessment of glioblastoma patients during external beam radiation therapy. International journal of radiation oncology, biology, physics 2014;90:181-189.

20. Mohan S, Chawla S, Wang S, et al. Assessment of early response to tumor-treating fields in newly diagnosed glioblastoma using physiologic and metabolic MRI: initial experience. CNS oncology 2016, April 14.

21. Chen H, Liu R, Liu J, Tang J. Growth inhibition of malignant melanoma by intermediate frequency alternating electric fields, and the underlying mechanisms. The Journal of international medical research 2012;40:85-94.