



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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Comment on: 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;314:2535-43.

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 multiforme (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. One of these trials reported that GBM patients treated with TTFields had significantly prolonged overall and progression free survival (PFS) 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.

Keywords: Tumor-treating fields (TTFields); glioblastoma; diffusion tensor imaging (DTI); proton MR spectroscopy

Submitted Jun 13, 2016. Accepted for publication Jun 28, 2016.

doi: [10.21037/tcr.2016.07.49](https://doi.org/10.21037/tcr.2016.07.49)

View this article at: <http://dx.doi.org/10.21037/tcr.2016.07.49>

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 multiforme (GBM) from 83 centers in North America, Europe, and Asia (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 (2,3). TTFields is an anti-mitotic, physical treatment modality that acts in metaphase, anaphase and telophase of the cell division (4,5). 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) (1,6). TTFields is approved in the United States and Europe for the treatment of newly diagnosed as well as recurrent GBM, and is undergoing clinical trials for several other tumor types (7–9). 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), 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 2,500 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).

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).

The investigators of the EF14 trial (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 *vs.* 4.0 months from randomization, 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 *vs.* 15.6 months, hazard ratio =0.64, P=0.0042). In the intent-to-treat population, the median OS was 19.6 *vs.* 16.6 months, respectively, hazard ratio =0.74 (P=0.0329). The 2-year survival rate was approximately 50% greater with TTFields plus TMZ *vs.* TMZ alone: 43% *vs.* 29%. In addition, the trial showed TTFields could be safely combined with TMZ, without 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) 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 *vs.* 12.1 months) (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 months 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). 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). On the other hand, emerging evidence has shown immense potential of advanced imaging techniques such as diffusion tensor imaging (DTI) (15), and dynamic susceptibility contrast (DSC)-perfusion weighted imaging (PWI) (16,17) and proton MR spectroscopy (1H MRS) (18,19) 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). 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 (4,5). Additionally, a moderate decline in rCBVmax, (6.21%) was also noted at 2-month relative to baseline indicating anti-angiogenic effects of TTFields (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.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xian-Xin Qiu, MD, PhD candidate (Department of Neurosurgery, the Children's Hospital of Medical College, Zhejiang University, Hangzhou, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2016.07.49>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Mohan S, Chawla S, Skolnik A, Poptani H. Perspective on the EF-14 trial and its implications for the role of tumor-treating fields in the management of glioblastoma. *Transl Cancer Res* 2016;5(S2):S272-S275. doi: 10.21037/tcr.2016.07.49