Invited Commentary

Tumor-Treating Fields
Answering the Concern About Quality of Life

Lia M. Halasz, MD; Timur Mitin, MD, PhD

Since the 2005 publication of the randomized European Organization for Research and Treatment of Cancer/National Cancer Institute of Cancer trial that established concurrent radiotherapy (RT) and temozolomide for upfront treatment of glioblastoma (GBM),[1] little progress has been made. Thus, it was remarkable when the interim results for the EF-14 trial were published, documenting a 4.9-month increase in median overall survival with the addition of tumor-treating fields (TTFields) to standard therapy with combined RT and temozolomide.[2] These findings were strengthened by presentation of the mature analysis at the Society for Neuro-oncology Meeting in 2016, which confirmed that the median survival improved from 16 months after randomization to RT plus temozolomide to 21 months with the addition of TTFields to RT plus temozolomide.[3] The survival advantage continued at later times, such as the 2-year survival rate of 30% vs 42.5% (P = .001).

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Since its introduction, many physicians have remained skeptical about including TTFields as standard of care,[4] in part due to the novelty of the mechanism of action. The device generates low-intensity, intermediate-frequency (200 kHz) alternating electric fields that interfere with mitosis and disrupt the division of cells. Since its initial use for treatment of GBM, TTFields is now being tested for other cancer types, including metastatic non–small cell lung cancer,[5] and as an alternative to prophylactic cranial irradiation in small cell lung cancer (Oregon Health Sciences University/University of Washington trial, starting accrual in early 2018). Furthermore, physicians and patients have been concerned about the quality-of-life implications of wearing a mobile electrical device with 4 arrays of transducers continuously fixed to a shaved scalp for at least 18 hours a day. The battery pack for the device is large and heavy enough that it could interfere with daily activities. Quality of life remains a priority for many of our patients since clinical trials have shown incremental improvement in overall survival, but not cure.

An interim analysis of the EF-14 trial focusing on health-related quality of life (HRQoL), published by Zhu and colleagues,[6] suggested initial improvement in global HRQoL with TTFields in the first 6 months. Skin toxic effects concerns were higher among patients randomized to the combined TTFields, RT, temozolomide arm. The final analysis of these data, published by Taphoorn and colleagues[7] in this issue of *JAMA Oncology*, presents important data for evaluating the overall effect of TTFields on our patients. In contrast to the interim report, the investigators found no significant difference in HRQoL between the 2 treatment arms, except for itchy skin, which was worse with TTFields.

The finding of worsening itchy skin was not surprising given the known dermatologic adverse effects of the treatment. In the EF-14 trial, where TTFields was used with concurrent temozolomide shortly after RT, the rate of grade 1 and 2 skin toxic effects was 43%.[3] Because TTFields therapy is frequently being combined in the real-world setting with other agents, such as bevacizumab, the resultant skin toxic effects are not well studied and the incidence may be even higher. Hence, evaluation and appropriate and rapid management of skin toxic effects are critical to avoid significant treatment interruptions—and even discontinuation—to maximize TTFields therapy adherence and the resulting survival benefit.

One of the difficulties of this study,[7] which is common to many evaluations of HRQoL, is the low adherence to HRQoL assessments. Although 91.9% of patients had HRQoL assessments at baseline (before randomization), only 65.8% had assessments at 3 months and 41.7% at 12 months of follow-up. However, the authors performed sensitivity analyses with mixed-model analyses to account for missing data, which confirm their findings.

It is comforting to learn that the burden of carrying the device was not detrimental to patients' physical, social, or emotional functioning; however, overall it is important to remember that the trial participants were a highly selective group of patients. These individuals elected to take part in the trial, and thus represent a group of patients who are already open to wearing a device on their scalp daily for an indefinite time. In our experience, there are many social and cultural reasons that patients have for declining TTFields despite the data of improved survival. Many do not want the physical and visual cues that may remind them of their life-altering, life-limiting diagnosis. This factor may echo studies finding that patients with breast cancer rate alopecia as one of the most distressing treatment-related adverse effects because it can result in anxiety, depression, negative body image, lowered self-esteem, and reduced sense of well-being.[8]

With societal changes and the greater acceptability of wearable devices, ranging from fitness trackers to assistive technology, it will be interesting to see if patients become more open to utilizing TTFields. Moreover, whereas the patients participants in the EF-14 trial were using the first-generation TTFields system, weighing 2.7 kg, the currently used device weighs only 1.2 kg, which may lead to better tolerance of this daily therapy. Yet, in order for TTFields to gain popularity, it is not enough for patients alone to become more accepting; physicians will also need to be open to novel treatments. It is somewhat incongruous that we are so concerned about a therapy that has few adverse effects when many of our newly approved active cancer

molecules are associated with reduced patient safety even if they improve overall survival or HRQoL.[9] Overall, these new data on HRQoL, coupled with the overall survival results of EF-14, strengthen the inclusion of TTFields as an important treatment for our patients with GBM if they are willing to wear the device.

ARTICLE INFORMATION

Author Affiliations: Department of Radiation Oncology, University of Washington, Seattle (Halasz); Department of Radiation Oncology, Oregon Health and Sciences University, Portland, Oregon (Mitin).

Corresponding Author: Lia M. Halasz, MD, Department of Radiation Oncology, University of Washington, 1959 NE Pacific St, PO Box 356043, Seattle, WA 98195 (lhalasz@uw.edu).

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