**TRIAL SUMMARY: A new treatment paradigm**


During the oral central nervous system (CNS) sessions at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting, Stupp et al. presented the results of the EF14 randomized phase III trial. This trial investigated a novel treatment modality consisting of tumour treating fields (TTFields), a device that emits low-amplitude alternating (1–3 V/cm, 200 kHz) electric fields, in the management of newly diagnosed glioblastoma. From 2009 to 2014, 695 grade IV astrocytoma (glioblastoma) patients from 83 sites worldwide (including Canada), were randomized 2:1 after completion of concurrent chemoradiotherapy to receive either 6 cycles of adjuvant temozolomide (TMZ) chemotherapy with TTFields (TTF/TMZ), or TMZ alone. The device was applied more than 18 hours a day until tumour progression, to a maximum of 24 months. The TMZ-alone control arm did not have a sham device.

The results of the first preplanned interim analysis were presented at the Society of Neurooncology meeting (SNO) in 2014, and reported a statistically significant difference in the median overall survival (OS) of 19.6 months in the TTF/TMZ arm vs 16.6 months in the TMZ-alone arm (p=0.034) in the first 315 patients. At ASCO 2015, a confirmatory analysis of all 695 patients was reported. Patient characteristics, including Karnofsky Performance Score (KPS), Mini-Mental State Examination (MMSE) score, the extent of resection, steroid requirement and MGMT methylation status, were similar in both arms. The median progression-free survival (PFS) was 7.1 vs 4.2 months (p=0.0010) and the median OS was 19.4 vs 16.6 months (p=0.022), favouring the TTFields arm. Other than a skin reaction to the electrodes or tape (44%), the device did not result in increased grade 1/2 or 3/4 adverse events.

**COMMENTARY:** In preclinical models, the electric fields generated with TTFields were seen to disrupt cell membranes, interfere with the assembly of organelles and mitosis, either directly or by interrupting spindle checkpoints, and possibly overcome multiple drug resistance pathways. By applying the polarizing electric forces approximately 200 times a second, the TTFields seek to delay the mitotic rate and induce apoptosis. Glioblastoma is uniquely positioned to benefit from such a locoregional treatment modality as the tumour bulk is situated in a confined site, the brain, and results in morbidity and mortality.

This trial represents the first successful evaluation of a noninvasive device therapy in the treatment of not only glioblastoma, but also advanced solid tumours in the first-line setting. This is a paradigm-shifting therapeutic intervention with mild, well-tolerated side effects. The median OS achieved with this device therapy approaches 20 months, which is unprecedented in glioblastoma trials to date, despite the recommended early closure of the trial after the first interim analysis due to clinical benefit and subsequent crossover. The device was approved by the US Food and Drug Administrative (FDA) in 2011 in the recurrent glioblastoma setting, and in 2015 was incorporated into the National Comprehensive Cancer Network (NCCN) guideline for the treatment of recurrent glioblastoma (Category 2B). With the efficacy results presented at ASCO 2015, it is anticipated that the device will also be included as recommended standard-of-care treatment in the first-line setting. However, a number of factors need to be taken into consideration.

Economically, the devices come at a staggering cost of $21,000 per patient-month, and will continue to incur costs until disease progression as per the trial design. Currently, it is unclear whether Canada would be able to obtain the devices for purchase and future reuse to reduce recurring costs, as the devices are presently only available for hire. Although the median survival benefit is a modest 3 months, benefit may have been diluted by crossover, and considering that the current standard of systemic therapy, TMZ, only adds about 2.5 months of OS benefit to radiotherapy alone, this observed magnitude of benefit with TTFields is still clinically relevant in glioblastoma. The effectiveness of the device as it relates to economic evaluation will likely be enhanced by the minimal side effects and reported improvements in quality of life. Until Health Canada and Pan-Canadian Oncology Drug Review (pCODR) evaluations are complete, Canadian centres have a window of opportunity to consider opening further trials to confirm the results and test the device in other settings, thereby enhancing patient access and developing clinical expertise.
As for oral systemic treatments, adherence is a critical factor in the device's efficacy. For instance, the patient registry data (PRiDE) of 457 patients with recurrent glioblastoma receiving TTFields revealed that the patients who wore the device for more than 18 hours a day (≥75% daily adherence) achieved a median OS of 13.5 months compared with 4.0 months for those who wore the device for less than 18 hours a day. The EF14 phase III trial mandated use for a minimum of 18 hours/day; therefore, the reported survival benefit is less likely to be achieved with lower daily usage. In another followup study, those who achieved an objective response had an adherence rate of 92% (22 hours/day use), while those with disease stabilization had 85% compliance (20.4 hours/day use) and the cohort average was 79% (19 hours/day use). Given that local discomfort secondary to the device as well as the potential stigma associated with wearing an external device may impact device utilization, patient education and ongoing device monitoring will be an integral part of ensuring adherence. The device-recorded “on” time log is expected to aid with monitoring adherence.

Another interesting factor relates to the use of concurrent or prior therapy such as dexamethasone or bevacizumab. Retrospective data from the phase III trial in the recurrent setting showed that patients taking less than 4.1 mg of dexamethasone per day achieved a median OS of 7.2 months, a highly significant difference (p=0.0001). These data suggest a possible interaction between device efficacy and other therapies known to reduce intracranial edema, and further studies are needed to elucidate this correlation.

Overall, the TTFields represents a novel and unique treatment modality that has demonstrated a robust survival benefit in a large phase III trial in newly diagnosed glioblastoma, a disease for which therapeutic options are limited. While questions remain with regard to cost-effectiveness, adherence monitoring and interactions with other drugs, this trial heralds a new standard of care and therapeutic paradigm in the management of glioblastoma.

**References**


