A Shock to the System: Tumor-Treating Fields Plus Temozolomide for Glioblastoma

Glioblastoma continues to be a uniformly fatal disease despite decades of aggressive research. Newly diagnosed adult patients continue to face 15% and 4.3% 2- and 5-yr survival rates, respectively. Current standard of care consists of upfront maximal safe resection (or biopsy for diffuse and unresectable lesions) followed by radiotherapy, with concomitant oral temozolomide (TMZ) chemotherapy, with 6 to 12 mo of maintenance TMZ thereafter. With this approach, modern trials have demonstrated overall survival from time of diagnosis of 14.6 to 16.7 mo. Tumor-treating fields (TTFields) have emerged as a novel nonpharmacologic adjunct that has shown promise in preclinical and clinical trials. TTFields work by delivering low-intensity alternating electric fields via a noninvasive scalp mounted transducer array. TTFields therapeutic effect results from arresting mitosis and inducing apoptosis in rapidly dividing cells resulting in increased sensitivity to chemotherapy. Stupp and colleagues previously presented an interim analysis of a phase 3 randomized clinical trial of TTFields plus TMZ versus TMZ alone in newly diagnosed glioblastoma with promising results. They now report in JAMA the final analysis with a median follow-up of 40 mo.

The authors designed a multicenter, international, open-label randomized clinical phase 3 trial with centers in North America, Europe, Korea, and Israel. The study population included patients >18 yr old with Karnofsky performance scores (KPS) >70 and newly diagnosed, histologically confirmed supratentorial glioblastoma who were randomized in a 2:1 ratio between TFField plus TMZ and TMZ maintenance therapy alone. Patients with rapid radiographic progression following standard radiochemotherapy, infratentorial tumor location, and severe comorbidities were excluded from enrollment. A total of 695 patients were enrolled in 83 centers and randomized with stratification by extent of resection and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status. The primary end point was progression-free survival with a secondary end point of overall survival conducted in an intent-to-treat manner. Twenty-six patients in the control group crossed over to undergo TFField therapy following the publication of the interim analysis and included in the control group as randomized.

Baseline characteristics between experimental and control groups were well balanced with a median follow-up of 40 mo and a minimum follow-up of 24 mo. Median progression-free survival was 6.7 mo in the experimental group versus 4.0 mo in the control group with a Hazard ratio of 0.63. Median survival duration from randomization was 20.9 mo versus 16.0 mo with a Hazard ratio of 0.63 for the experimental and control groups respectively. At 2-, 3-, and 5-yr following randomization 43%, 26%, and 13% of patients were alive in the experimental group compared to 31%, 16%, and 5% in the control group. Between group findings remained consistent when adjusted for KPS, age, MGMT promoter methylation status, geographic region, tumor location, and extent of resection. Patients that lacked MGMT promoter methylation had significantly shorter survival in both groups, though the use of TTFields plus TMZ was associated with improved survival regardless of promoter methylation. No statistically significant difference in adverse events was noted between groups, with the exception of localized skin toxicity in the experimental group. Mild skin irritation occurred in 52% of patients and severe skin involvement in 2%.

This randomized phase 3 clinical trial provides an important addition to the care of patients afflicted with glioblastoma. Based on the strength of the evidence, the addition of TTFields to radiochemotherapy may emerge as the standard of care for newly diagnosed and recurrent glioblastoma patients. Some criticism has emerged regarding the decision to calculate survival data from randomization rather than diagnosis, but when the data were adjusted for this decision, the survival benefit remains robust and significant. Additionally the control group was not truly blinded, as for ethical and practical reasons a sham device was not employed, thus potentially contributing to a placebo effect. Factors that may impact the adoption of TFF therapy include patient tolerability of the device and insurance coverage of the expense. While the need to wear the scalp-mounted transducer array for >18 h a day may appear onerous, 75% of patients in this trial were able to achieve 75% adherence, suggesting good tolerability. From a neurosurgical standpoint, current rates of skin complications may become clinically significant for wound healing purposes if the technology is more widely adapted. Further technological refinement may ultimately lead to improved tolerability and decreased rates of localized skin complications. TTFields in addition to standard of care radiation and chemotherapy provides a valuable new adjunct in the care of patients with glioblastoma.

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REFERENCES


