Few advances have been made in the treatment of glioblastoma multiforme since 2005 when Stupp et al demonstrated a 2-month improvement in median survival with the addition of temozolomide to standard radiation treatment and established the current standard of care. Glioblastoma remains a nearly always fatal diagnosis with a median survival of 14 to 16 months and progression of disease frequently seen within the first 6 months after treatment completion. Multifarious approaches to overcome the innate therapeutic resistance of glioblastoma have been exercises in futility, including radiation dose escalation, attempts to overcome or exploit hypoxia within tumors, interference with tumor-driven angiogenesis, targeting EGFR overexpression, and all manners of cytotoxic chemotherapies.

A newer, locoregional approach to target cancer cells that largely avoids the potential for systemic toxic effects employs alternating electromagnetic fields, or tumor treating fields (TTF). In vitro studies with cancer cell lines have demonstrated that the use of TTF arrests cell division and kills tumor cells via multiple mechanisms, including misalignment of microtubule subunits during division, aberrant chromosomal segregation, and cytoplasmic blebbing during anaphase.2 These effects are more pronounced in rapidly pro...
liferating cancer cells than in normal quiescent tissue and have been documented in various tumor types, including glioma, melanoma, breast, and non–small-cell lung cancer (NSCLC), with the varying histologic types showing unique sensitivities to frequencies of 100 to 200 kHz. Investigations have shown that cellular damage is increased when the axis of mitotic division is aligned with the electric field, with a greater effect when using fields aligned in multiple directions. This area of study is still new and there is ongoing research into the optimal placement of transducers based on individual patient and tumor characteristics.

The clinical effectiveness and feasibility of TTF was initially tested in 10 patients with recurrent glioblastoma, and their 6-month progression-free survival and median survival were double that of historic controls. A subsequent phase 3 trial of TTF vs physician’s choice chemotherapy was then conducted also in recurrent glioblastoma. Although this study did not meet its primary end point of improving overall survival, the median overall survival (6.6 months vs 6.0 months, respectively) and progression-free survival (2.2 months vs 2.1 months) established TTF as noninferior to chemotherapy. Furthermore, the quality of life and toxic effect profiles favored treatment with TTF, and the US Food and Drug Administration approved TTF for use in recurrent glioblastoma multiforme.

Exciting results were recently published in JAMA by Stupp et al on the earlier use of TTF in newly diagnosed glioblastoma. This phase 3 trial randomized patients to standard chemoradiation followed by temozolomide with or without TTF and met its primary end point of improving overall survival, as well as several secondary end points. The preplanned interim analysis evaluated the outcomes of the first 315 patients and demonstrated an overall survival benefit of 20.5 vs 15.6 months and led to the closure of the study when 695 of the planned 700 patients were enrolled. These results were maintained in the analysis of the full cohort, presented at ASCO 2015, demonstrating an improvement in survival of 19.4 vs 16.6 months. Similarly, the arm including TTF demonstrated a statistically significant benefit in progression-free survival at the interim analysis of 7.2 vs 4.0 months that was also seen in the analysis of the entire set of patients. Because of the favorable results seen at the interim analysis, patients in the temozolomide-alone arm were allowed to cross over and receive TTF treatment, and this resulted in a very small cohort that received temozolomide alone as a basis for comparison.

In this study, MGMT promoter methylation data was collected in the majority of patients (72%), and was used as a stratification criterion. The 2 arms were balanced in regards to methylation status, with 32% and 35% of patients with MGMT methylation in the experimental and control arms, respectively. Local control and survival outcomes in the methylated vs unmethylated group were not reported in this publication, and it will be interesting to see if methylation also serves as a predictive factor for TTF efficacy.

Despite the low rate of additional toxic effects when TTF is given with temozolomide, there continues to be a barrier to its acceptance, related to the inconvenience of wearing this device and its attached battery pack for 18 hours of the day. In part, this is owing to the continued stigma of cancer, similar to reluctance of many patients in accepting alopecia-causing treatments. While a shaved head may be an unavoidable requirement in using this device, investigations into maintaining effectiveness while reducing the hours of usage to the evening hours or during sleep may increase the willingness of patients to undergo this treatment. One avenue of research may be using chemotherapeutic agents to synchronize cells in mitosis, so a shorter application of the TTF may be timed to match the drug effects.

The antitumor effects of TTF do not appear to be limited to glioblastoma and is a promising avenue for further research. Giladi et al recently published data on the in vitro and in vivo effectiveness of concurrent chemotherapy in conjunction with TTF in NSCLC, where the addition of TTF improved the effectiveness of all tested chemotherapies. A phase 2 trial (NCT02507232) of TTF in conjunction with temozolomide for low-grade gliomas will soon be open to recruitment and will assess the response rate, progression-free survival, and toxic effects of combined treatment. It is not yet clear whether antigen release from TTF-killed tumor cells may improve the results of immunotherapeutic approaches to control tumors both locally and abscopally, an effect that has been seen in patients treated with radiosurgery and immune-modulating agents.

There are multiple ongoing studies involving TTF in the treatment of brain metastases, pancreatic and ovarian cancer, and mesothelioma. There is much hope that appropriately designed and powered clinical trials will reveal more about this treatment approach—it may eventually be soundly integrated into management paradigms for a variety of tumors and clinical scenarios.