With a median survival of almost 15 months, glioblastoma multiforme (GBM) continues to be one of the most difficult tumors to treat in the adult population (29,33, 34). The current standard of care dictates maximal surgical resection followed by radiation therapy and temozolomide (2, 24, 33). There are a variety of treatments undergoing experimental testing, such as multimodal chemotherapy (13, 21), enhanced drug delivery methods (3, 20), brachytherapy (11, 4), loco-regional chemotherapy (25), immunotherapy (35, 37) and gene/viral therapy (1, 5). A relatively unique concept substantially different from the pharmacologic/biologic/radiation approaches tested so far consists of using alternating electric fields as means to interfere with tumor cell mitosis, thus causing its destruction. Over the past 5 years, this concept has been rapidly translated from the bench to clinical trials.

**RATIONALE AND SCIENTIFIC BACKGROUND**

Cells contain ions and polar molecules, rendering them susceptible to the action of applied electrical fields (36). The impact of those fields on cellular physiology mainly depends on the magnitude of the potential between the electrodes (intensity) and the frequency of the current (8, 26). At very low frequencies (<1 kHz), alternating electric fields cause membrane depolarization (due to interference with the activity of ion channels), thereby inducing nerve, muscle, and heart stimulation (12, 23). As the frequency increases, the stimulatory effect decreases while heating becomes prominent, to the point of causing cellular destruction. This is the radiofrequency (3 kHz to 3 MHz range) and microwave (300 MHz to 300 GHz range) level (7, 22) that is at the basis of radioablation techniques used in cancer therapy (7, 19). Tumor-treating fields (TTFs) consist of electrical fields of very low intensity (1 to 2 V/cm) and medium frequency (100 to 300 kHz) that do not produce significant heating nor membrane depolarization/excitation (17). Such fields have been previously shown to induce reorganization of cellular microfilaments (6) and redistribution of membrane proteins (27). The proposed antitumor mechanism exerted by these specific fields has been explained as a synergy between: 1) distortion of microtubule assembly during the formation of the mitotic spindle, and 2) the formation of centripetal forces during mitosis substantially impeding the separation of mother and daughter cells, and ultimately resulting in membrane breakdown (16, 17). The first effect is due to the intrinsic polarity of β-tubulin, the constituent of microtubules: each molecule by virtue of its polarity produces a small electric field, which in turn orients and aligns the surrounding molecules of β-tubulin, leading to their polymerization. An external electrical field perturbing the forces responsible for β-tubulin orientation results in impairment of polymerization and failure of microtubule formation. The second effect would be based on the theory that in a quiescent, nondividing cells, the lines of force created by the external field are uniform within the cytoplasm and do not interfere with molecular movement or orientation; on the contrary, the abnormal cellular morphology assumed by the cell during mitotic cleavage would create a distortion of the field vectors generating forces pushing the molecules centripetally toward the furrow and impairing cellular division (17, www.novocuretrial.com). Based on the knowledge that tumors are composed of proliferating cells whereas quiescent cells are found primarily in normal tissues, thus provides the rationale for TTF’s selectivity against cancer cells.

**INITIAL EXPERIMENTS**

In 2004, Kirson et al. (17) first described how the application of a low-intensity (2 V/m), medium-frequency (100 to 300 KHz) alternating electric field resulted in disruption of cancer cell mitosis. The investigators were able to show that multiple tumor cell lines, when exposed to specifically tuned electric fields (which they named TTFs) for a period longer than 24 hours, were unable to undergo a proper mitotic process, remaining in a stunned, nonproliferative state for the time they were under the effect of the field, and, in some cases, up to 72 hours after the discontinuation of the treatment. Also, although TTFs were able to induce apoptosis in 25% of cultured glioma cells, quiescent cells did not seem to be affected. In vivo experiments carried over with mice harboring orthotopic intradermal melanomas revealed a halved growth rate for the tumors exposed to the TTF (17).

**THE TRANSLATION TO CLINICAL TRIALS**

Less than 3 years after the work by Kirson et al. (17), during which only one additional study was published, substantially confirming in vitro the antiproliferative effect of alternating electric fields (10), the
results of the first human application were published in 2007: in a single-arm pilot trial, 10 patients with recurrent GBM were treated with TTF (2 mV/200 KHz, produced by means of insulated surface electrodes in contact with shaved scalp) daily for an average of 18 hours per day until progression of the disease. No control patients were enrolled in the study. Median time to disease progression was 26.1 weeks, and median overall survival was 62.2 weeks, more than double that of historical controls (38). Importantly, no serious device-related side effects were reported, although 90% of patients experienced mild erythema at the site of electrode contact with the skin (16). Two years later, the same group reported the results obtained on 20 patients with GBM, 10 of whom had received TTFs at time of recurrence (group A), whereas the other 10 had received TTFs after the initial tumor resection and concomitantly with temozolomide treatment (group B). Results for group A substantially confirmed those obtained in the prior trial, with doubling of median time to disease progression and overall survival; as far as group B, the time to disease progression was 155 weeks (with 5 out of 10 patients still progression-free at time of publication), and median overall survival was greater than 39 months (with 8 out of 10 patients still alive at time of publication), compared with the 31 weeks and 14.6 months, respectively, of the historical control subjects. Again, no major toxicities were reported (18).

Finally, the results of a multicenter phase III clinical trial led by Dr. Stupp (University of Lausanne, Switzerland) have just been presented at the 2010 American Society of Clinical Oncology meeting: 237 patients with recurrent GBM were randomized to receive either TTF treatment alone (120 patients) or the best standard chemotherapy (117 patients). Median overall survival was not statistically different, with 6.6 versus 6.0 months for TTF and standard chemotherapy, respectively. Likewise, progression-free survival at 6 months and 1-year survival rate were similar for the two groups. Again, the treatment proved to be safe and well tolerated, and associated with a significantly lower incidence of hematological and systemic toxicities compared with the chemotherapy group (Table 1) (32). A prospective, multicentric trial is currently ongoing comparing the effect of TTF plus temozolomide versus temozolomide alone in patients with newly diagnosed GBM. The expected completion date is estimated for 2012.

**DISCUSSION**

As therapies for GBM are very much needed, TTF is receiving increased attention both in the academic environment as well as at the media and public opinion level (9). This has resulted from encouraging results and excellent product development by the involved biotechnological company (NovoCure Ltd., Haifa, Israel) (16-18, www.novocuretrial.com). From a clinical standpoint, two phase I clinical trials have been reported in the literature in a short period of time, showing encouraging outcomes (16, 18). However, because they are only phase I trials, no statistically relevant conclusions related to efficacy can be inferred. Even the reported long-term GBM survivors in the trial have also been reported in the literature, either sporadically or associated with various clinical trials/novel theraupe-
tic modalities. This has been associated with patient clinical character-
istics as well as genetic features of the tumor (28, 31). Clearly the re-
results provided by both phase I studies are exciting. However, as
often happens, the phase III trials seem to show that TTF was no
better than standard chemotherapy (32). The hope is that TTF in
combination with other treatments (temozolomide) may show a
significant advantage to temozolomide alone. It also remains to be
seen how acceptable to patients’ quality of life will be the current
mode of delivery necessitating multiple-hour applications of the
fields using paddles attached to shaved scalps.

Scientifically, it is unclear what the effect of TTF would be on
nonmitotic neoplastic cells, which generally constitute the bulk of
the neoplastic tumor. The interference with microtubule and
molecule orientation is also likely to impair neuronal and glial
functions as well. Cucullo et al. (10) have independently confirmed
that electric fields block cancerous cell proliferation, but have also
shown that normal astrocytes are affected as well. Studies describ-
ing the antimicrobial effect of TTF have confirmed that, indeed,
electric fields have an effect on noncancer and more primitive cells,
but it is unknown why this is so (for instance, bacteria do not use
microtubules for cellular division) (14, 15). The only human trial in
patients with nonneurological cancers (6 patients total) was limited
to the description that the treatment was safe and that 50% of pa-
ients had tumor regression (30).

In conclusion, TTFs represent a very interesting alternative to the
current monopoly of chemical-, biologic-, and radiation-based ex-
perimental therapies. Its initial testing in humans seems to be en-
couraging, although a phase III trial showing that TTFs do provide
significantly improved outcomes compared with current standard
therapy is likely to be needed for approval. Also, additional studies
elucidating the mechanisms of TTFs action not only in cancerous
but also in normal cells will be needed.

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Statins are structural analogs of \( \beta \)-hydroxy-\( \beta \)-methylglutaral coenzyme A reductase, a restrictive enzyme in the cholesterol pathway. Several studies have suggested possible benefits other than prevention of cardiovascular diseases and cholesterol control, including reduction of the incidence of stroke, dementia, and tumors (10). A neuroprotective effect in diseases such as Alzheimer, multiple sclerosis, and subarachnoid (SAH) and intracerebral hemorrhage has also been attributed to statins. Supposedly, the mechanisms underlying those effects include antiexcitotoxicity (e.g., N-methyl-D-aspartate receptor); improvement of microvascular perfusion (e.g., plasminogen activator inhibitor, tissue plasminogen activator); dilution of microthromboses (e.g., superoxide dismutase); and modulation of cytokines (e.g., through control of nuclear factor \( \kappa B \)), adhesion molecules (e.g., leukocyte-associated antigens, intercellular adhesion molecule), and immune cells (monocytes, macrophages) (10). Of special interest in SAH is the fibrinolytic effect. Many studies focus on the causes of delayed cerebral ischemia by vasospasm of large/medium vessels (Figure 1). However, often we found patients with severe angiographic vasospasm who had no detectable clinical repercussion and patients without angiographic evidence of vasospasm with neurologic deficits (2, 8, 9). Romano (9) found signs of microemboli in 38% of patients in the seventh day of vasospasm. Moreover, there was a close correlation between those findings and patients with ischemic symptoms (\( P = 0.003 \)). In a recent experimental work, Wang (15) found a decrease in microthrombi formation and downregulation of microclots in a prechiasmatic blood injection rat model. Analyses of these data give substantial support for use of statins in SAH.

Nevertheless, controversy about use of statins for SAH has been fueled by a systematic review performed by Vergouwen et al. (13) and three historical control studies (4, 5, 7). Vergouwen reviewed four studies (1, 6, 11, 12, 14) with a total of 190 patients, 94 randomized to statin treatment and 96 to placebo. They concluded that there is no statistical evidence to recommend the use of statins following SAH. However, several criticisms may be made on those papers. First, the groups selected in the studies had different major exclusion criteria; second, the definition of vasospasm, delayed cerebral ischemia, and functional outcome scale was not homogeneous; third, the end point evaluation went only as far as 6 months; fourth, historical control studies have an inherent data retrieval bias. Those studies have their merits; however, clinical recommendations must be done just after solid scientific data are obtained. It is not uncommon for the initial euphoria with new kinds of medical treatment to be followed by disappointment and a sense of abandon, especially when there is almost nothing interventional left for the physician to do. Most of us do not seem to agree with Voltaire: “The art of medicine consists in amusing the patient while nature cures the disease”.

Do Statins Play a Role After Subarachnoid Hemorrhage?

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Figure 1. Vasospasm is the main cause of morbidity after SAH. No satisfactory and effective medical treatment is available. Great expectations have been generated by recent published studies about the effectiveness of statins.

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