Management of Recurrent or Progressive Glioblastoma Multiforme with Low-intensity, Medium-frequency Alternating Electric Fields

a report by
Yoram Palti

Professor of Physiology and Biophysics, Technion, Israel Institute of Technology

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Physicians and scientists are investigating the use of specially tuned, low-intensity, intermediate-frequency electric fields to disrupt cancer cell growth. These fields, known as tumour-treating fields (TTFields), represent an entirely new cancer treatment modality unlike medical, radiation or ablation therapies. Physicians are currently conducting the most advanced clinical study of TTFields in a US Food and Drug Administration (FDA)-approved phase III, pivotal, multicentre clinical trial for patients with recurrent or progressive glioblastoma multiforme (GBM). The study is being performed under an FDA-approved investigational device exemption (IDE). The trial is ongoing at eight centres in Europe and twelve centres in the US and is based on an extensive mass of pre-clinical data, a comprehensive description of which can be found in *Cancer Research*.[1] The current phase III trial also builds on the results of a pilot clinical trial for recurrent GBM patients, the results of which were recently published.[2]

Scientific Background

It is generally accepted that low-intensity (1V/cm), medium-frequency (100–300kHz) alternating electric fields have no meaningful biological effects. This assumption is based on the fact that the evidence collected to date suggests they do not cause significant temperature elevation or stimulate excitable tissues such as nerves, muscles in general, the heart muscle or cardiac pacemakers, as they reverse polarity before reaching the threshold of excitation; however, this fact is true only for quiescent cells. Proliferating or dividing cells may be significantly affected by such fields.

There are two major mechanisms by means of which the frequency-tuned TTFields specifically affect dividing cells. The first mechanism relates to the non-uniform electric field distribution within dividing cells (see *Figure 1B*) compared with the uniform field in quiescent cells (see *Figure 1A*). The non-uniformity, which is expressed in field focusing at the narrow cytoplasmatic bridge connecting the two daughter cells, exerts a force on all charged bodies – such as intracellular organelles – or dipoles – such as most macromolecules. This force, directed towards the bridge regardless of the field polarity, results in movement of the said charged elements in a process called dielectrophoresis. This movement disrupts the internal cell structure and results in its destruction. The second mechanism relates to the force the field exerts on the microtubule chains and individual dimmers interfering with the polymerisation– depolymerisation process taking place in the spindle during division. This interference interrupts the normal division process. The end result is that the cancer cell proliferation rate is attenuated and the cells are destroyed without affecting the normal quiescent cells.

Since the TTFields treatment is based on a physical rather than a chemical modality, its affinity and activity is independent of highly specific cell receptors. Therefore, it is hoped that it will affect a wide range of cancer cell types. Indeed, it was preliminarily found to arrest the proliferation of and destroy all 15 types of cancer cell lines tested.

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The Technology

Physicians are currently using the NovoTTF device – which was developed by NovoCure Ltd of Haifa, Israel – to conduct clinical trials studying the effect of TTFields on solid cancer tumours. The NovoTTF is a non-invasive, battery-operated, wearable medical device that patients carry in a specialised over-the-shoulder bag. Patients receive continuous treatment throughout the day. The device automatically controls the field intensity, while monitoring the local temperature, and keeps a continuous detailed log of the treatment parameters. The patient has no control over the treatment parameters. The device is designed to disrupt the division of cancer cells in the brain using 200kHz, two-directional, alternating electric fields delivered by means of insulated electrodes applied to the surface of the scalp by hypoallergenic bandages.

Pilot Study Results

The *Proceedings of the National Academy of Sciences* recently published the results from an initial pilot study for patients with recurrent glioblastoma treated with TTFields alone. In this single-arm trial, treatment was performed with the NovoTTF device on 10 recurrent GBM patients. Patients were eligible at any recurrence following standard treatments (surgery or biopsy, chemotherapy and radiation) and all patients had previously received temozolomide. Efficacy analysis was performed by comparing the following end-

Yoram Palti is a Professor of Physiology and Biophysics at the Technion, Israel Institute of Technology and the Founder of NovoCure Ltd. He was formerly an Associate Professor of Physiology at the University of Maryland School of Medicine. He was also Head of the Rappaport Institute for Research in the Medical Sciences, the research arm of the Technion Medical School, for 12 years. Professor Palti is an expert in electrophysiology and biomedical engineering and is the author of more than 30 patents and 70 scientific papers.

points to a composite of clinical literature of controlled, prospective, chemotherapy trials published since 1999: time to tumour progression (TTP); progression-free survival (PFS) at six months; and overall survival (OS). At the time of this publication the median length of TTP was 26.1 weeks; PFS at six months was 50%; and median OS was 62.2 weeks (see *Figure 2*). This is more than double the corresponding reported rates in historical control groups reported in the composite of clinical literature; namely, approximately 9.5 weeks, 15.3% and 29.3 weeks, respectively.

The patients received treatment for a total of 280 weeks without a single treatment-related adverse event. The only device-related side effect was a mild to moderate contact dermatitis beneath the delivering electrode gel. This dermatitis responded well to application of topical cream and periodic electrode relocation.

Ongoing Clinical Studies

Physicians are currently enrolling patients for a phase III pivotal study for the treatment of patients with recurrent or progressive GBM tumours, under an FDA-approved IDE. The trial is a randomised, controlled trial that expects to enrol 236 patients at eight centres in Europe and 12 centres in the United States. The trial is generally open to GBM patients whose tumours have recurred following standard treatments (surgery or biopsy, radiation, chemotherapy) and who are not candidates for further surgery or radiotherapy. Additional information on this trial has been published at www.novocuretrial.com. Physicians are also conducting pilot studies to preliminarily determine the safety and potential efficacy of the use of TTFields in the treatment of newly diagnosed GBM patients and for patients with breast cancer.

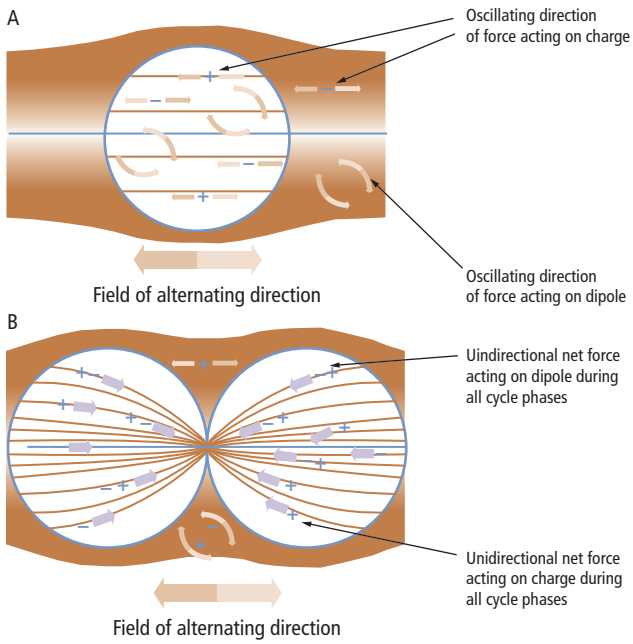
Additional Research Needed

TTFields disrupt cancer cell proliferation due to physical cell properties and are not believed to affect chemical processes within the cell. Accordingly, in the future physicians might be able to use TTFields as an adjunctive treatment to chemotherapy or antiangiogenesis agents such as Avastin. *In vitro* data developed by scientists at NovoCure – the company developing the NovoTTF device – strongly suggest that there is synergism between the effects of TTFields and chemotherapies, at least in the case of breast carcinoma and non-small-cell lung cancer. TTFields could potentially be used to boost the efficacy of chemotherapy agents or biological agents that act on a cellular chemistry level. More research is required on the potential of TTFields as an adjunctive oncology therapy.

Conclusion

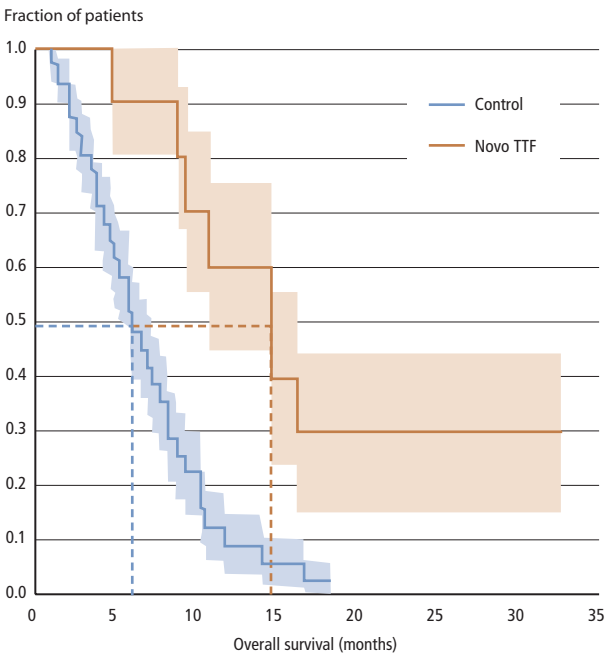
Rapidly emerging scientific and clinical data suggest that TTFields may be an important new treatment modality in the fight against numerous solid-tumour cancers. Published results from the first completed pilot study preliminarily suggest that physicians may in the future be able to use TTFields as a stand-alone therapy to treat recurrent or progressive GBM tumours. Further research will, however, be required to determine whether this use of TTFields is safe and effective. Additionally, given the unique, non-chemical mechanisms of action for TTFields, physicians should continue to study the potential for TTFields to be used in conjunction with chemotherapies or biological agents. ■

Figure 1: Comparison of Electric Fields in Quiescent Cells and Dividing Cells



Alternating current field distribution in and around quiescent (A) and dividing (B) cells. Inside quiescent cells the field is uniform and the oscillating electric forces result only in 'vibration' of ions and dipoles (the forces associated with each half cycle are denoted by the arrows). In contrast, the non-uniform field within dividing cells (B) induces forces pushing all dipoles towards the furrow.
Source: Kirson et al., 2004.[2]

Figure 2: Kaplan–Meier Overall Survival Curves



Brown trace = NovoTTF-treated patients ± standard error of mean (n=10). The median OS in these patients is 14.7 months versus 6.1 months in patients from a matched control group. Note that three of 10 patients remain alive.
Black tracing = historically matched control group.

1. Kirson ED, Gurvich Z, Schneiderman R, et al., Disruption of cancer cell replication by alternating electric fields, *Cancer Res*, 2004;64: 3288–95.
2. Kirson ED, Dbaly D, Tovarys F, et al., Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors, *Proc Natl Acad Sci U S A*, 2007;104:10152–7.