Alternating electric field therapy for Glioblastoma

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Tumor electric fields therapy (TTFields) is emerging as a novel anti-cancer physiotherapy. Despite recent breakthroughs of TTFields in glioma treatment, the average survival time for glioblastoma patients with TTFields is <2 years, even when used in conjugation with traditional anti-cancer therapies.

Tumor electric field treatment at optimal frequency, strength, and output mode markedly inhibits the cell viability, proliferation, and invasiveness of primary glioblastoma cells in vitro independent of different genetic traits of the cells. Moreover, a random sequence electric field output confers considerable anti-cancer effects against glioblastoma in vivo. [1)]

Kumaria reviews possible mechanisms by which alternating electrical fields may confer an anti-glioma effect. As the scalp and skull are poor conductors of an electrical field, a case is made here for implantable electrodes, perhaps placed at the time of tumor debulking. Such a system may deliver an electrical field directly to the tumor resection cavity and with greater precision [2)].

Tumor-treating fields (TTFields) are a cancer treatment modality that uses alternating electric fields of intermediate frequency (~100-500 kHz) and low intensity (1-3 V/cm) to disrupt cell division. TTFields are delivered by transducer arrays placed on the skin close to the tumor and act regionally and noninvasively to inhibit tumor growth. TTFields therapy is U.S. Food and Drug Administration approved for the treatment of glioblastoma multiforme, the most common and aggressive primary human brain cancer [3)].

Ornelas et al. critically appraised the evidence for the use of TTFields as adjunctive treatment to newly diagnosed Glioblastoma. The objective was addressed through the development of a structured, critically appraised topic. They incorporated a clinical scenario, background information, a structured question, literature search strategy, evidence summary, clinical bottom lines, and expert discussion. Participants included consultant and resident neurologists, a medical librarian, clinical epidemiologists, and content experts in the field of neurooncology. A randomized controlled trial was selected for critical appraisal. Patients with newly diagnosed Glioblastoma completing standard radiation and chemotherapy with temozolomide (TMZ) were subsequently randomized to receive maintenance TMZ with TTFields, or TMZ alone. With the addition of TTFields, median progression-free survival was 6.7 months compared with 4 months without the addition of TTFields (95% confidence interval, 0.52-0.76; P<0.001) and overall survival was 20.9 months compared with 16.0 months without the addition of TTFields (95% confidence interval, 0.53-0.76; P<0.001). TTFields may increase both progression-free and overall survival in patients receiving standard chemoradiation therapy for Glioblastoma [4)].

Mechanistically, TTFields have been proposed to impair formation of the mitotic spindle apparatus and cytokinesis. In order to identify further potential molecular targets, here the effects of TTFields on Calcium signaling, ion channel activity in the plasma membrane, cell cycle, cell death, and clonogenic survival were tested in two human glioblastoma cell lines in vitro by fura-2 Ca2+ imaging, patch-clamp cell-attached recordings, flow cytometry and pre-plated colony formation assay. In addition, the expression of voltage-gated Ca2+ (Cav) channels was determined by real-time RT-PCR and their significance for the cellular TTFields response defined by knock-down and pharmacological blockade. As a result, TTFields stimulated in a cell line-dependent manner a Cav1.2-mediated Ca2+ entry, G_1 or S phase cell cycle arrest, breakdown of the inner mitochondrial membrane potential and DNA degradation, and/or decline of clonogenic survival suggesting a tumoricidal action of TTFields. Moreover, inhibition of Cav1.2 by benidipine aggravated in one glioblastoma line the TTFields effects suggesting that Cav1.2-triggered signaling contributes to cellular TTFields stress response. In conclusion, the present study identified Cav1.2 channels as TTFields target in the plasma membrane and provides the rationale to combine TTFields therapy with Ca2+ antagonists that are already in clinical use [5)].

While the development of tumor-treating fields (TTFields), electric fields with alternating low and intermediate intensity has facilitated glioblastoma treatment, clinical outcomes of TTFields are reportedly inconsistent. However, combinatorial administration of chemotherapy with TTFields has proven effective for glioblastoma patients. Sorafenib, an anti-proliferative and apoptogenic agent, is used as first-line treatment for glioblastoma. A study aimed to investigate the effect of sorafenib on TTFields-induced anti-tumor and anti-angiogenesis responses in glioblastoma cells in vitro and in vivo. Sorafenib sensitized glioblastoma cells to TTFields, as evident from significantly decreased post-TTFields cell viability ($p < 0.05$), and combinatorial treatment with sorafenib and TTFields accelerated apoptosis via reactive oxygen species (ROS) generation, as evident from Poly (ADP-ribose) polymerase (PARP) cleavage. Furthermore, use of sorafenib plus TTFields increased autophagy, as evident from LC3 upregulation and autophagic vacuole formation. Cell cycle markers accumulated, and cells underwent a G2/M arrest, with an increased G0/G1 cell ratio. In addition, the combinatorial treatment significantly inhibited tumor cell motility and invasiveness, and angiogenesis. The results suggest that combination therapy with sorafenib and TTFields is slightly better than each individual therapy and could potentially be used to treat glioblastoma in clinic, which requires further studies [6)].

Tumor-treating fields plus TMZ represent a major advance in the field of Glioblastoma treatment, and should be considered for patients with newly diagnosed Glioblastoma with no contraindications. As a disease with such a poor prognosis, treatment of Glioblastoma should go beyond improving survival and aim at preserving and even improving the quality of life of both the patient and the caregiver [7)].

Tumor treating fields (TTFields) are low intensity (1 ? 2 V/cm), intermediate frequency (100 ? 200 kHz) alternating electric fields administered using insulated electrodes placed on the skin surrounding the region of a malignant tumor. TTFields were shown to destroy cells within the process of mitosis via apoptosis, thereby inhibiting tumor growth. TTFields have no effect on non-dividing cells.

TTFields disrupt cell division through physical interactions with key molecules during mitosis. This non-invasive treatment targets solid tumors.

This novel treatment modality has shown promise in a variety of tumor types. It has been evaluated in randomized phase 3 trials in glioblastoma (Glioblastoma) and demonstrated to prolong progression free survival (PFS) and overall survival (OS) when administered together with standard maintenance temozolomide (TMZ) chemotherapy in patients with newly diagnosed Glioblastoma. TTFields are continuously delivered by 4 transducer arrays consisting each of 9 insulated electrodes that are placed on the patient's shaved scalp and connected to a portable device.

Hottinger et al., summarize the preclinical data and mechanism of action, the available clinical data, and further outlook of this treatment modality in brain tumors and other cancer indications [8].

This non-invasive treatment by Novocure uses “Tumor Treating Fields” (NovoTTF) to treat cancerous growths and is now available for adult patients with recurring brain tumors (Glioblastoma recurrence or Glioblastoma).

Reviews

In a large prospective randomized Phase III trial TTFields was compared with best standard care (including chemotherapy): TTFields significantly improved median overall survival (OS) compared with standard therapy (7.8 vs 6.1 months) for the patients treated per protocol. Importantly, quality of life was also better in the TTFields group. The second indication was a Phase II study in second-line non-Small-cell lung cancer, where TTFields was administered concomitantly with pemetrexed. This combination resulted in an excellent median OS of 13.8 months. Interestingly, the progression-free survival (PFS) within the area of the TTFields was 28, however, outside the TTFields the PFS was only 22 weeks.

The proof of concept of TTFields has been well demonstrated in the preclinical setting, and the clinical data seem promising in various tumor types. The side effects of TTFields were minimal and in general consisted of skin reaction to the electrodes. There are a number of ways in which TTFields could be further evaluated, for example, in combination with chemotherapy, as a maintenance treatment, or as a salvage therapy if radiotherapy or surgery is not possible. While more clinical data are clearly needed, TTFields is an emerging and promising novel treatment concept [9].

Case series

To evaluate the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with glioblastoma.

After completion of chemoradiotherapy, patients with glioblastoma were randomized (2:1) to receive maintenance treatment with either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229) (median time from diagnosis to randomization, 3.8 months in both groups). The study enrolled 695 of the planned 700 patients between July 2009 and November 2014 at 83 centers in the United States, Canada, Europe, Israel, and South Korea. The trial was terminated based on the results of this planned interim analysis.

Treatment with TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. Temozolomide (150-200 mg/m2/d) was given for 5 days of each 28-day cycle.

The primary end point was progression-free survival in the intent-to-treat population (significance threshold of .01) with overall survival in the per-protocol population (n = 280) as a powered secondary end point (significance threshold of .006). This prespecified interim analysis was to be conducted on the first 315 patients after at least 18 months of follow-up.

The interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 randomized to temozolomide alone, and was conducted at a median follow-up of 38 months (range, 18-60 months). Median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P = .001). Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n = 196) and 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n = 84) (HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004).

In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival [10)].

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