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November 2018

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Tumour Treating Fields (TTFs) for Paediatric Brain Tumours, Brain Metastases and other Novel Applications

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Abstract

Tumour treating fields (TTFs) are now FDA approved for high grade glioma treatment. Novel application of this treatment modality is being assessed for paediatric brain tumours and intracranial metastatic disease. Clinical trials are being conducted to test the efficacy of this treatment modality as adjuvant therapy to current standard of care. Here we will discuss the existing literature on TTF its role in pathologies other than GBM. In addition, aspects of safety, compliance and cost are also discussed.

Keywords: Brain Metastasis, Tumor Treating Fields, Alternating Electric Fields, Progression Free Survival, Overall Survival.

Introduction

In 2004, Kirson and Palti et al., hypothesized that alternating electric fields at the right frequencies would disrupt mitotic activity in cancer cells.[1] In 2007, they described the safety and efficacy of alternating electric fields of low intensity and intermediate frequencies on dividing cells in vitro and in vivo. In their experiments,they noted that externally applied transducer arrays significantly inhibited the growth intradermal melanoma (B16F1) in mice and intracranial glioma (F-98) in rats within one week of treatment. At 100-300 kHz, the alternating currents affect the mitotic spindle microtubules resulting in dielectrophoretic movement of molecules during anaphase and telophase, resulting in cellular disruption and apoptosis. The electric field strength of the treatment and its correlation with extent of tumour disruption has been shown in in vitro studies.[2] Only the dividing cells are affected while the quiescent cells are spared. The role of TTF in recurrent and newly diagnosed GBM is well recognized, and we have now begun to explore this treatment option for other brain tumours. However, other than efficacy, a major concern remains the safety, compliance and the cost of treatment, which has raised the argument that TTF remains largely impractical for majority of patients.

Review of Evidence

We queried the PubMed database with the phrases 'tumour treating fields in brain tumours' and 'alternating electric fields in brain tumours'. Abstracts of articles describing this treatment modality were reviewed. Articles addressing use of tumour treating fields for metastatic lesions were reviewed. Case reports were included if they were addressing a novel use of this tool.

Role in Paediatric Brain Tumours

In the paediatric brain tumour population, clinical trials are under way to better understand the effects of TTFs on recurrent high grade gliomas and ependymomas.[3] One case report is present in the current literature of a 13-year old patient with GBM who progressed through surgical resection, radiotherapy and chemotherapy. TTFs were used with subsequent stable disease observed radiographically and clinically for 7 months without any adverse effects.[4] Most recently, a case series of five patients with high grade gliomas was published by Green et al, with good tolerability and no treatment limiting toxicity noted.[5] In its current form and application, the use of TTF is greatly limited in paediatric patients due to compliance.

Role in Brain Metastases

The METIS trial is currently looking at patients with recent diagnosis of intracranial metastatic lesions, numbering 1-10, from non-small cell lung cancer, in addition to standard treatment with stereotactic radiosurgery.[6] The COMET trial recently closed, focusing on the same disease pattern.[7]

A group from Denmark is conducting a phase I feasibility trial, looking at the effects of small craniectomy or burr-holes in enhancing the delivery of the tumour treating fields.[8] In their pre-clinical computational work, Korshoej et al showed that removal of a craniotomy flap increased the strength of the electric fields upto 70% in the tumour, and caused growth arrest or regression in approximately

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50% of the tumour tissue.[9] They also noted that multiple small burr-holes were more effective than a single craniotomy. They concluded that a large part of the tumour should be located relatively close to the surface, it should be feasible to place a craniectomy or burr-holes immediately overlying the tumour, and TTF electrodes should be applied in close vicinity to the surgically made bony opening. It will be interesting to see the results of this trial in delivering enhanced treating fields to the tumour.

Other Potential Applications

Several trials are currently underway, not only for brain metastasis but also for solid organ tumours (LUNAR, STELLAR, INNOVATE, PANOVA).[10-13] Trials are also underway to assess the safety and feasibility of TTFs in recurrent high grade meningiomas as well as low grade gliomas.[14]

Safety, Compliance and Cost

The treatment modality offers very minimal toxicity profile compared to chemotherapy and radiation. The device is supposed to be worn continuously (>18 hrs/day) as the anti-tumour effects are halted immediately when the therapy is stopped. At least 4 weeks of continuous application is needed to halt/reverse tumour growth. The device delivers electric currents set at a frequency of 200 kHz, is applied to the patient's shaved scalp in a transducer array which is specified by the treating Oncologist. It is monitored by device specialists available around the clock for technical assistance.Guidelines are now available for Oncologists and patients to make treatment plans based on imaging findings.[15]

Compliance rates with therapy have been shown to directly correlate with overall survival (>75% (>18 hours daily) versus those with a <75% compliance rate (7.7 v 4.5 months. P=0.42).[16] Contact dermatitis can develop, and can be treated with topical steroids and good hygiene. Patients have to be instructed on scalp preparation and care.

Despite the advantages this treatment modality appears to offer, the costs are prohibitive, especially in an underdeveloped/developing country setting. Costs have been estimated to be approximately $20-23,000/month.[17]

Conclusion

Although TTF is now recognized as a potentially useful treatment modality for patients with GBM, its role remains less clear in other forms of brain tumours. However, several clinical trials are underway and their results are eagerly awaited. As it is required to be worn for more than 18 hours a day, for 4-weeks, its use appears limited due to compliance, especially in children. Cost is also a limiting factor, although as is true for all technological advances, it is likely to improve substantially with time.

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