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Tumour Treating Fields (TTFs) for recurrent and newly diagnosed glioblastoma multiforme

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Abstract

In the last decade, significant advances have been made in Glioblastoma Multiforme treatment with the novel use of alternating electrical fields, also termed as tumour treating fields (TTFs). This modality has shown promising results in recurrent and newly diagnosed GBM patients, and according to some, may soon be considered an addition to the previously known 'trifecta' of GBM standard of care, i.e., surgery, chemo and radiation therapy.Here we review the existing data on TTF for both recurrent and newly diagnosed GBM. This review does not discuss the limitations of TTF, especially from compliance and cost point of view.

Keywords: Glioblastoma, Tumour Treating Fields, Alternating Electric Fields, Progression Free Survival, Overall Survival

Introduction

In the first in vivo study involving Tumour Treating Fields (TTF) was tested in ten patients with recurrent GBMs using non-invasive transducer arrays attached to the scalp, with significant improvement noted in time to tumour progression (TTP) [26.1 vs 9.5 weeks], progression free survival (PFS) at 6 months [50% vs 15.3%,], and overall survival (OS) [median 62.2 vs 29.3 weeks], without any systemic toxicity.[1] In 2009, the same group performed a second pilot trial to understand the efficacy of TTFs in newly diagnosed patients in combination with standard adjuvant TMZ, and again noted very promising results (Median PFS [155 vs 31 weeks] and improved median OS [> 39 vs 14.7 months]).[2]

Review of Evidence

We queried the PubMed database with the phrases 'tumour treating fields in glioblastoma' and 'alternating electric fields in brain tumours'. Abstracts of articles describing this treatment modality were reviewed. Articles addressing use of tumour treating fields in high grade gliomas were reviewed.

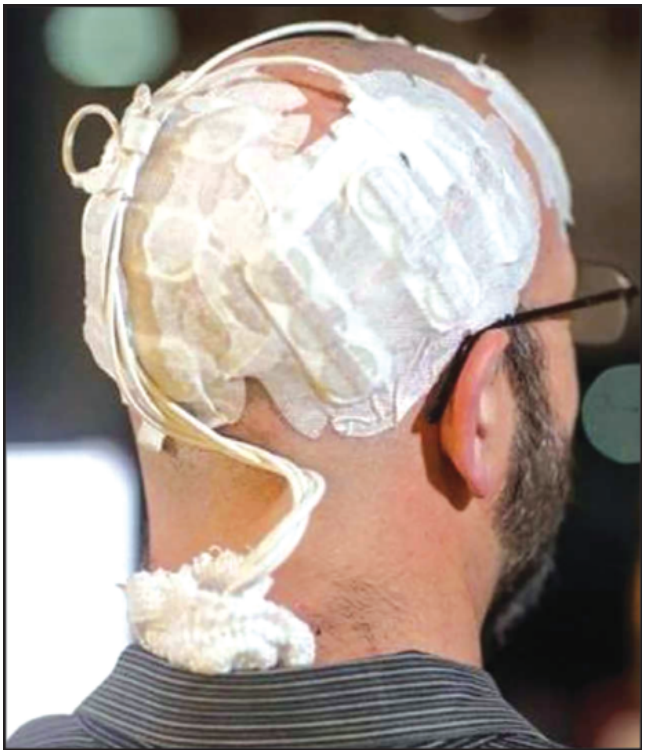

Figure: An example of TTF applied on a patient.[13]

Role in Recurrent GBM

Median time to recurrence for GBMis approximately seven months and median survival 15-18 months. Repeat craniotomy and Bevacizumab have shown to be beneficial in the recurrent setting.[3] Despite this, about 60% of patients relapse on Bevacizumab, can have serious side effects, develop resistance to the drug, and also fail to respond to any further chemotherapy.[4]

In 2012, Stupp et al published their results on the first Phase III trial of 237 patients studying the effects of TTFs alone, compared with standard chemotherapy

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regimens in recurrent GBM.[5] Thirty-six patients received bevacizumab, 36 received nitrosureas, 12 received temozolomide, and 33 received other agents. It was noted that TTFs alone were comparably effective and had lower toxicity profile and better quality of life. This landmark study led to the FDA approval of NovoTTF-100A™ System (Novocure, Ltd., Haifa, Israel) as stand alone treatment for recurrent GBMs. Subsequently several post-hoc analyses of this trial were conducted which showed subsets of patients in whom TTFs alone resulted in improved OS compared to second line chemotherapy (11.8 vs 9.2 months).[6] Rulesh et al, in 2012, published their series of twenty patients with recurrent GBM who had been treated with TTFs between 2004 and 2007.[7] They reported four long term survivors who were still alive at the time of publication. According to the authors, this was the first clinical study to have looked at the use of TTFs in recurrent GBM. However, the data reported on the original patients was quite limited and molecular characteristics of tumours in the survivors were not elucidated, hence not many conclusions can be drawn from it. Two trials are currently for recurrent GBM refractory to bevacizumab, and bevacizumab naive recurrent GBM.[8,9]

Role in Newly Diagnosed GBM

Stupp et al published their first randomized control trial on this subject in 2015.[10] In this study, they used TTFs in combination with maintenance TMZ and compared this group with standard TMZ administration. 695 patients from 83 centers across the world were included between July 2009 and November 2014. Significant improvement in progression free survival and overall survival was noted: 7.1 months (95% CI, 5.9-8.2 months) in the TTF plus TMZ group and 4 months (95% CI, 3.3-5.2 months) in the TMZ alone group. P= 0.001. Median overall survival was 20.5 months (95% CI, 16.7-25.0 months) in the TTF plus TMZ group and 15.6 months (95%CI, 13.3-19.1 months) in the TMZ group P= 0.004). Given this improvement in survival, it has been suggested to include this as part of standard of care for newly diagnosed GBM, in addition to the Stupp Protocol.[11]

In non-methylated MGMT promoter, TMZ is not considered a treatment option due to its resistance. A recent study by Clark et al effectively showed the utility of TTFs in both methylated and non-methylated cells.[12] As such, in patients with non-methylated MGMT promoter, the application of TTFs after radiation should be effective. It is also interesting to note that tumour cells may develop some resistance to TTFs.

Conclusion

The introduction and popularization of tumour treating fields is a remarkable development in GBM treatment since the introduction of the Stupp protocol in 2005. It offers an entirely new area for research and possible options for treatment. So far, studies have shown promising results with this treatment modality, with the added benefit of minimal toxicity and improved quality of life compared to standard chemoradiation options.

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