

Tumor treating fields for glioblastoma: Review

Uysal B

Gulhane Training and Research Hospital, Department of Radiation Oncology, Ankara, Turkey

Abstract

Tumor treating fields (TTF) is delivered with an original device causing antimitotic activity in tumor cells of glioblastoma patients. Low intensity and intermediate frequency alternating electric fields are effective over metaphase. Tumor treating fields is a novel modality approved by FDA (Federal Drug Association) for newly diagnosed and also recurrent glioblastoma. Frequency of 200 kHz is given with transducer applied on scalp of patient. Phase 3 trial showed the efficacy of this modality alone equivalent compared to chemotherapy. Skin toxicity is the major side effect of this therapy. TTF is now used in recurrent glioblastoma but future perspective shows that this unique modality can be delivered in different solid tumors.

Background

Glioblastoma is the most aggressive and common primary brain tumor in adult population. 18,000 new cases of glioblastoma are diagnosed every year in the United States. Treatment of patients with glioblastoma enrolls chemoradiotherapy and adjuvant chemotherapy for 6-12 months following a maximal surgical resection or a biopsy. Median survival time is approximately 6-7 months and overall survival is 15-16 months in literature. Chemoradiation and surgery techniques have been updated but this doesn't change the prognosis of glioblastoma patients. Firstly, surgery can damage the brain tissue and secondly chemoradiation can be toxic to healthy brain parts.

Neither increasing the dose of temozolomide nor bevacizumab usage had concluded with survival improvement. Tumor Treating Fields (TTF) is a recent and new treatment endamaging tumor cells with low-intensity, intermediate- frequency (200 kHz) alternating electric fields by transducer applied on a scalp. TTF causes apoptosis of tumor cells (Table 1).

Discussion

TTF is also called as alternating electric fields approved by FDA (federal drug association). Skin toxicity is the major adverse effect but not a big issue compared to the toxicities of chemotherapy [1]. TTF was used in newly diagnosed glioblastoma in an article by Zhu et al. quality of life, cognitive and functional status were analyzed in this study. First group was delivered temozolomide and second group got temozolomide and TTF. Second group was better in quality of life for

first 9 months and other characterizations for comparative evaluation were similar. TTF group had reported just itchy skin [2].

FDA approved TTF with its speciality on disrupting mitosis and inhibiting tumor growth over various tumor types in 2011 and 2015. Cell cycle arrest and apoptosis is shown by TTF [3]. Antimitotic activity can be seen between frequencies of 100 kHz and 300 kHz [4].

Novel therapies such as immune modulatory therapies and electrical field treatment seems to improve survival. Future advances in molecular biology and nanotechnology may hopefully give better results for the management of this grade 4 disease [5].

Postacquisition T1 and T2 MRI sequences were anatomically segmented and then solved to determine the distribution of the electric fields and rate of energy deposition at the gross tumor volume (GTV) and other intracranial structures. The main aim is to analyze the physical parameters of TTF. A personalized approach for TTF treatment can be developed when patient and tumor-related factors are associated into the planning [6].

TTF is probably a radiosensitizer when concurrent TTF and RT used together. The removal and replacement of TTF from the scalps of patients daily before and after RT is mostly problematic. Effect of concurrent usage of RT and TTF at the same time was evaluated and it was concluded that more attention is needed for skin toxicities [7].

TTF and chemotherapy combination after recurrence improved overall survival compared to sole chemotherapy for the glioblastoma patients in the EF14 trial [8]. Management of newly diagnosed glioblastoma was discussed in ASCO (American Society of Clinical Oncology) meeting and approved by FDA [9].

TTF is a noninvasive effective and safe procedure that prolonging progression free and overall survival in glioblastoma patients [10].

Table 1. Indications and contraindications of TTF

Indications	Contraindications
22 years of age or older newly diagnosed Glioblastoma	Deep brain stimulators
Radiological recurrence after receiving chemotherapy	Spinal cord stimulators
	Vagus nerve stimulators
	Pacemakers
	Defibrillators
	Programmable shunts
	Hydrogel allergy
	Skull defects

Correspondence to: Uysal B, Gulhane Training and Research Hospital, Department of Radiation Oncology, Ankara, Turkey. E-mail: drboraaysal@windowslive.com

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Technicians, nurses are needed for education on detailed information of TTF usage and the possible complications and also adverse effects of this procedure [11].

Pulsed-dose bevacizumab and TTF was combined for the bevacizumab recurrent glioblastoma patients and the results support TTF and pulsed-dose bevacizumab in an article by Ansstas et al. [12].

Molecular targets of TTF enrolling alfa/beta-tubulin and the septin 2, 6, 7 heterotrimer were evaluated in an article. TTF may trigger antitumor immune response [13].

Maintenance therapy include temozolomide usage for 6 courses after chemoradiotherapy. TTF and temozolomide concomitant usage was compared with temozolomide only and progression-free and overall survival was significantly prolonged [14].

Although glioblastoma is a mortal disease, the efficacy of TTF with other combinations like chemotherapy, immunotherapy and radiotherapy should be supported with novel literature [15]. Potential tumor resistance is a really important topic needed to be researched for these WHO grade 4 dismal tumors [16].

TTF is a novel and promising therapy for glioblastoma patients. However, there is a problematic issue about skin adverse effects. Topical management with corticosteroids or antibiotics prevent skin areas effected from TTF. Quality of life should be maintained when managing this strategy [17].

TTF is evaluated in solid tumor brain metastases, nonsmall cell lung cancer, ovarian and pancreatic cancer with ongoing and future trials. Researchers wait for improving results from these trials same as newly diagnosed or recurrent glioblastoma [18,19].

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