Tumor treating fields for glioblastoma: Review

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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 endangering tumor cells with low-intensity, intermediate- frequency (200 kHz) alternating electric fields by transducer applied on a scalp. TTF causes apopitosis 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].

Table 1. Indications and contraindications of TFF

| 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 |

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].

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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 Anstas 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 Grad 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].

References
1. Lok E, Swanson KD, Wong ET (2015) Tumor treating fields Therapy device for glioblastoma: physics and clinical practice considerations. Expert Rev Med Devices 12: 717-726. [Crossref]
2. Zhu JJ, Demireva P, Kanner AA (2017) Health-related quality of life, cognitive screening, ad functional status in a randomised phase 3 trial (EF-14) of tumor treating fields with temozolomide compared to temozolomide alone in newly diagnosed glioblastoma. J Neurooncol 135: 545-552. [Crossref]
3. Zhu P, Zhu JJ (2017) Tumor treating fields: a novel and effective therapy for glioblastoma: mechanism, efficacy, safety and future perspectives. Chin Clin Oncol 6: 41. [Crossref]
4. Mrugala MM, Ruzevick J, Zlomanczuk P, Lukas RV (2017) Tumor Treating Fields in Neuro-Oncological Practice. Curr Oncol Rep 19: 53. [Crossref]
5. Toms SA, Tapinos N (2017) Recent Advances in the Treatment of Gliomas - Comprehensive Brain Tumor Center. R I Med J 100: 43-46. [Crossref]
6. Lok E, San P, Hua V, Phung M, Wong ET (2017) Analysis of physical characteristics of tumor treating fields for human glioblastoma. Cancer Med 6: 1286-1300. [Crossref]
7. Bender E, Kozak K, Howard S, Hayes L, Bayouth J, et al. (2017) The effect of Optune tmor treating fields transducer arrays on skin radiation dose during radiotherapy. J Clin Oncol 42: 172-175. [Crossref]
8. Kesari S, Ram Z (2017) Tumor treating fields plus chemotherapy versus chemotherapy alone for glioblastoma at first recurrence: a post hoc analysis of the EF-14 trial. CNS Oncol 6: 185-193. [Crossref]
9. Mehta M, Wen P, Nishikawa R, Reardon D, Peters K (2017) Critical review of the addition of tumor treating fields (TTFields) to the existing standard car for newly diagnosed glioblastoma patients. Crit Rev Oncol Hematol 111: 60-65. [Crossref]
10. Saria MG, Kesari S (2016) Efficacy and Safety of Treating Glioblastoma With Tumor-Treating Fields Therapy. Clin J Oncol Nurs 20: S9-S9S13. [Crossref]
11. Murphy J, Bowers ME, Barron L (2016) Optune®: Practical Nursing Applications. Clin J Oncol Nurs 20: 514-19. [Crossref]
12. Anstas G, Tran DD (2016) Treatment with tumor-treating fields therapy and pulse dose bevacizumab in patients with bevacizumab refractory recurrent glioblastoma: a case series. Case Rep Neurol 8: 1-9. [Crossref]
13. Swanson KD, Lok E, Wong ET (2016) An overview of alternating electric fields therapy (novoTTF therapy) for the treatment of malignant glioma. Curr Neurol Neurosci Rep 16: 8. [Crossref]
14. Stupp R, Taliiber S, Kanner AA, Kesari S (2015) Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. JAMA 314: 2535-2543. [Crossref]
15. Wong ET, Lok E, Swanson KD (2015) An evidence-based review of alternating electric fields therapy for malignant gliomas. Curr Treat Options Oncol 16: 40. [Crossref]
16. Rehman AA, Elmore KB, Mattei TA (2015) The effects of alternating electric fields in glioblastoma: current evidence on therapeutic mechanisms and clinical outcomes. Neurosurg Focus 38: 14. [Crossref]
17. Lacouture ME, Davis AM, Weinberg U, Palti Y (2013) Characterization and management of dermatological adverse events with the NovoTTF-100A system, a novel anti-mitotic electric field device for the treatment of recurrent glioblastoma. Semin Oncol 41: 1-14. [Crossref]
18. Davies AM, Weinberg U, Palti Y (2013) Tumor treating fields: a new frontier in cancer therapy. Ann N Y Acad Sci 1291: 86-95. [Crossref]
19. Pless M, Weinberg U (2011) Tumor treating fields: concept, evidence and future. Expert Opin Investig Drugs 20: 1099-1106. [Crossref]