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REVIEW

Tumor Treating Fields for Glioblastoma Multiforme: Effectiveness and Safety

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SUMMARY

Glioblastoma multifome (GBM) is the most common and most lethal primary brain tumor in adults. The standard treatment for GBM with good performance is maximal surgical resection followed by adjuvant chemoradiotherapy and adjuvant temozolomide therapy. In addition to this treatment, alternating electric fields or tumor treating fields (TTFields) are also recommended at category 1 level in the NCCN guidelines. In this review, the mechanism of action of alternating electric fields therapy in GBM, its efficacy in GBM and expected side effects will be discussed. TTFields is a treatment modality that acts on dividing cells by generating therapeutic levels of electric fields. Causing DNA damage and inhibiting DNA repair, activating apoptosis, autophagy and immunogenic death pathways, causing destruction of the cytoskeleton network, causing the formation of pores in the membrane and causing cellular destruction by disrupting cellular ion balance are the effects of alternating electric field therapy on cells. TTFields, which has also been tested in tumors such as lung cancer, pancreatic cancer and malignant mesothelioma, has proven to be a survival-enhancing treatment in primary and recurrent GBM patients. The risk of serious toxicity was found to be very low and the most common side effects were mild and moderate dermatologic toxicities. Having proven its efficacy and safety in GBM patients, TTFields is likely to benefit many more patients if cost issues can be overcome.

Keywords: GBM; toxicity; tumor treating fields.
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INTRODUCTION

Glioblastoma multifome (GBM) is the most common and most lethal primary brain tumor in adults. It has a highly aggressive course with a 5-year survival rate of 5–7%.[1,2] The disease, which is most commonly seen in the brain, can also be observed in the brain stem, cerebellum and spinal cord more rarely. The median age of onset is 64 years.[3] GBM can occur without a known precursor lesion (primary) or with the transformation of a low-grade tumor over time (secondary). Primary GBM is much more common than secondary GBM. Primary GBM, which has a worse prognosis, tends to occur at older ages than secondary GBM.[3–5] There are different genetic alterations that can be seen in GBM patients: Epidermal growth factor receptor (EGFR) overexpression, PTEN mutation and loss of chromosome 10 are especially typical for primary GBM, whereas isocitrate dehydrogenase-1 (IDH1) mutation, TP53 mutation and loss of 19q are seen especially in secondary GBM.[5,6] Especially the identification of IDH1 mutation status stands out as a reliable marker in the molecular differentiation of primary-secondary GBM. The standard treatment in GBM with

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good performance is adjuvant chemoradiotherapy and adjuvant temozolomide treatment after maximal surgical resection.[5,7,8] The agent of choice in chemoradiotherapy is temozolomide, as in adjuvant treatment. In addition to this treatment, alternating electric fields or tumor treating fields (TTFields) are also recommended at category 1 level in the NCCN guideline.[9] TTFields is a treatment modality that acts on dividing cells by generating electric fields at therapeutic levels.[10,11] Although alternating electric fields therapy is recommended at category 1 level by the NCCN for the treatment of GBM, many oncology physicians have questions about the efficacy of this treatment and may have difficulties in accessing this costly treatment. In this review, the mechanism of action of alternating electric fields therapy in GBM, its efficacy in GBM and expected side effects will be discussed.

TUMOR TREATING FIELDS THERAPY FOR GLIOBLASTOMA MULTIFORME: EFFECTIVENESS AND SAFETY

The effect of electric field on living cells was demonstrated for the first time in 1922 with a study showing the migration of bacteria in an electric field.[12] Alternating electric field can be used in medicine for nerve-muscle stimulation, acceleration of wound healing and treatment of various muscle and joint diseases.[13,14] Causing DNA damage and inhibiting DNA repair, activating apoptosis, autophagy and immunogenic death pathways, causing destruction of the cytoskeleton network, causing the formation of pores in the membrane and causing cellular destruction by disrupting cellular ion balance are the effects of alternating electric field treatment on cells; mitotic arrest and cell death occur in cells with the help of these mechanisms.[10,11] Giladi et al.[15] showed that TTFields inhibited the repair of radiotherapy-induced DNA damage in glioma cells. In the study conducted by Kirson et al.,[16] it was shown that alternating electric field application had an inhibitory effect on the growth of human and rat tumor cell groups. Analyses have shown that the cytotoxic effect of the electric field on dividing cells is maximum in the range of 150–200 kHz.[17] The treatment was found to have this effect on selectively dividing cells. These findings suggest that electric field therapy may also have a therapeutic role in malignant tumors. In GBM patients, TTFields is administered via a noninvasive and portable device that transmits alternating electric current to the brain via arrays placed on the scalp.

In the pilot study conducted by Kirson et al.[18] 200 kHz TTFields were applied to recurrent GBM patients. In a study of 10 patients, the median time to progression was 26 weeks and median overall survival was 62 weeks. These durations were reported to be approximately 2 times the reported durations for this patient group. The only instrument-related side effect was mild contact dermatitis and no serious side effects were observed. The study concluded that TTFields therapy is an effective and safe treatment modality for human cancers. In a pilot study by Salzberg et al.,[19] 100–200 kHz TTFields was applied to patients with locally advanced and/or metastatic solid tumors. The study included 6 patients who underwent multiple-line treatment. In 1 patient, partial response was observed, and in 3 patients tumor growth stopped during treatment. Disease progression was observed in 1 of the remaining 2 patients, and in the other patient with mesothelioma, regression was observed in the lesion near TTFields, while progression was observed in the lesion in the distant region. No serious treatment-related toxicity was detected. It was emphasized that TTFields is a safe and effective treatment modality that deserves further research. TTFields has also been tested in tumors such as lung cancer, pancreatic cancer and malignant mesothelioma and has been shown to be an effective and safe treatment modality.[20–23] In another study by Kirson et al.,[24] TTFields was administered in combination with temozolomide in newly diagnosed GBM patients. At the end of the study, progression-free survival was 155 weeks and overall survival was +39 months. TTFields treatment did not cause systemic toxicity and did not increase temozolomide-related side effects. It was concluded that TTFields added to chemotherapy increased chemotherapy sensitivity without increasing treatment-related toxicity. In a phase 3 study by Stupp et al.,[25] 200 kHz TTFields were compared with chemotherapy in patients with recurrent GBM. Although there was no significant difference between the groups in terms of overall survival, TTFields was found to be superior in terms of toxicity and quality of life. In a randomized study by Stupp et al.,[26,27] GBM patients were divided into temozolomide or temozolomide + TTFields arms after chemoradiotherapy. TTFields was applied at 200 kHz. As a result of the analysis, progression-free survival and overall survival were significantly higher in the TTFields group in both preliminary and final analysis. In a subgroup analysis of the EF-14 study, increased adherence to TTFields treatment was found to be an independent prognostic factor that increased survival in GBM.[28] In a secondary analysis

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of the EF-14 study, it was found that there was no decrease in quality of life in the group that added TTFields to temozolomide compared to the other group, but the side effect of skin itching was observed more in the group that received TTFields.[29] Fallah et al.[30] investigated the efficacy of bevacizumab + TTFields treatment in recurrent GBMs in a phase 2 study. In the study of 23 patients, median progression-free survival was 4.1 months and overall survival was 10.5 months. Grade 3–4 side effects thought to be treatment-related were observed in 2 patients. It was concluded that TTFields treatment is a safe and effective treatment. In a subgroup analysis study on Korean patients included in the EF-14 study, median overall survival and 1 and 2-year survival rates were significantly higher in the group that received TTFields treatment.[31] No serious toxicity was detected and skin irritation was observed in 30% of patients. The results demonstrate once again that TTFields is a safe and effective treatment.

Studies have shown that TTFields is a treatment approach with a low risk of serious toxicity. The most common treatment-related side effect is dermatologic toxicities.[26–33] Allergic dermatitis, irritant dermatitis, ulcers and mechanical lesions are side effects that can occur as dermatologic toxicity. Although topical corticosteroids may be sufficient in the management of dermatologic toxicities, topical-oral antibiotics may also be used in appropriate patients. Scalp cleansing, appropriate shaving and relocation of the instrument are recommended measures to reduce the risk of toxicity.[33]

TTFields is a very expensive treatment and its utilization rate can vary significantly from country to country due to the cost it brings to the healthcare system.[34] While the SEOM-GEINO and ASCO-SNO guidelines state that TTFields can be considered in newly diagnosed GBMs, it is recommended at category 1 level in the NCCN guideline.[9,35,36] Although there is no clear recommended treatment scheme for recurrent GBM, TTFields is one of the treatment options that can be preferred by current guidelines. TTFields, which has proven its efficacy and safety in GBM patients, is likely to benefit many more patients if cost issues are overcome.

CONCLUSION

TTFields is a treatment modality that has proven its efficacy and safety in newly diagnosed and recurrent GBM with its antimitotic and apoptotic effects.

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