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Optune in Glioblastoma: Revolutionizing Treatment with Tumor Treating Fields

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ABSTRACT

Introduction: Glioblastoma multiforme (GBM) is one of the most aggressive primary brain tumors in adults, known for its rapid progression and poor prognosis. Despite advancements in surgical resection, radiotherapy, and chemotherapy, the median survival for GBM patients remains limited. In recent years, Tumor Treating Fields (TTFields), commercially known as Optune, have emerged as an innovative, non-invasive therapeutic approach. TTFields utilize alternating electric fields to interfere with the mitotic processes of cancer cells, thereby inhibiting tumor growth. This paper aims to provide an in-depth review of the current understanding of TTFields therapy, assess its clinical efficacy, and explore future directions in GBM management.

Materials and methods: A systematic literature review was conducted, focusing on peer-reviewed articles published between 2017 and 2025. The search was performed using databases such as PubMed, JAMA, Lancet Oncology, Neuro-Oncology etc. Keywords included “glioblastoma,” “Tumor Treating Fields,” “Optune,” “clinical trials,” and “survival outcomes”.

Summary: The integration of TTFields therapy into the standard GBM treatment regimen represents a significant advancement in neuro-oncology. Clinical evidence indicates that TTFields, particularly in combination with temozolomide, can extend survival and delay disease progression in GBM patients.

Conclusions: TTFields therapy has emerged as a promising adjunctive treatment for glioblastoma, offering new hope for patients facing this highly aggressive disease. While current data support its efficacy and safety, further large-scale studies are needed to refine treatment protocols, identify predictive biomarkers, and assess long-term benefits. As research advances, TTFields may become an integral part of multimodal glioblastoma therapy, potentially improving both survival rates and quality of life for patients.

Keywords: glioblastoma, Tumor Treating Fields, Optune, clinical trials, survival outcomes

Introduction

Gliomas, one of the most common primary brain tumors, are associated with significant morbidity and mortality both in Europe and worldwide. According to data from 2020, the global incidence rate of gliomas was approximately 3.23 per 100,000 people per year, with higher rates observed in developed countries [1]. In Europe, the annual incidence of gliomas ranges between 4.7 and 5.7 per 100,000 individuals, with the highest rates reported in Northern and Western Europe [2].

Epidemiological trends from 2006 to 2021 indicate a slight but steady increase in the number of glioblastoma cases, potentially linked to advances in diagnostics and an aging population while the incidence of other types of gliomas remained stable. A correlation was observed

between chances of survival and histological group of diagnosed glioma and the age of the patient - lowest probability of 5-year survival was noticed in adults with glioblastoma and highest for oligodendroglioma [3]. Additionally, studies have shown that gliomas occur more frequently in men than in women, with a male-to-female ratio of approximately 1.6:1[4].

Glioblastoma: Pathogenesis, Symptoms, and Current Treatment Approaches

Glioblastoma (GBM) is the most aggressive primary brain tumor in adults, characterized by rapid growth, extensive infiltration of surrounding brain tissue, and a poor prognosis. Despite advances in treatment, the median survival time for GBM patients remains approximately 15 months, with only 5.5% surviving beyond five years after diagnosis [4].

Pathogenesis

The development of GBM is driven by complex genetic and environmental interactions. This malignancy is marked by significant molecular heterogeneity, resulting from genetic mutations and epigenetic modifications [5]. Key molecular alterations include mutations in IDH1/2 and TP53, as well as EGFR amplification, which contribute to tumor progression and therapy resistance. Mutations in the IDH1 and TP53 genes play a significant role in the development of glioblastoma multiforme (GBM). IDH1 mutations, commonly found in less aggressive gliomas, disrupt cellular metabolism and contribute to tumor growth, but they are also associated with better treatment outcomes. On the other hand, TP53 mutations, frequently observed in primary gliomas, impair DNA repair mechanisms, leading to more aggressive tumor growth and resistance to therapy. The presence of these mutations is crucial for prognosis and can influence therapeutic approaches [6]. Moreover, the tumor microenvironment, consisting of immune cells, stromal components, and vasculature, plays a critical role in supporting GBM growth and evading immune responses - research highlighted that macrophages promote angiogenesis, enhance invasion and facilitate tumor recurrence by secreting cytokines and growth factors. Their immunosupressive nature allows GBM cells to evade immune surveillance [7].

Clinical Symptoms

Glioblastoma symptoms vary depending on tumor location and size but typically result from increased intracranial pressure and local tissue infiltration [8]. Common clinical manifestations include:

- Persistent headaches – often worsening in the morning or with physical exertion [8].
- Nausea and vomiting – typically due to increased intracranial pressure [8].
- Neurological deficits – such as motor weakness, speech difficulties, visual impairments, and loss of coordination [8].
- Cognitive and behavioral change**s** – including memory impairment, attention deficits, and personality alterations [8].
- Seizures – occurring in approximately 30-50% of patients as a presenting symptom[8].

Diagnosis is established through a combination of neuroimaging and histopathological examination. Magnetic resonance imaging (MRI) with contrast enhancement is the gold standard for initial tumor visualization, often revealing a ring-enhancing lesion with central necrosis and surrounding edema. Definitive diagnosis requires a tissue biopsy, with molecular profiling increasingly used to guide personalized treatment strategies [8,9].

Current Treatment Strategies

The standard therapeutic approach for GBM consists of a combination of surgery, radiotherapy and chemotherapy:

- Surgical resection – The primary goal of surgery is to achieve the greatest possible tumor removal while preserving neurological function. Studies have shown that a greater extent of resection correlates with improved survival outcomes [10].
- Radiotherapy – Following surgery, patients undergo fractionated external beam radiation therapy (typically 60 Gy in 30 fractions), which helps control tumor progression [10,11].
- Chemotherapy – Concurrent and adjuvant administration of temozolomide (TMZ), an alkylating agent, remains the standard chemotherapeutic approach. Resistance to TMZ,

often due to methylation status of the *MGMT* promoter, remains a significant challenge [10,12].

Despite advancements in surgical oncology, radiotherapy, and chemotherapy, current treatments for GBM do not provide significant long-term survival benefits. As a result, alternative therapeutic strategies are being actively explored, including immunotherapy, molecularly targeted therapies [13], and innovative methods such as Tumor Treating Fields (TTFields), commercially known as Optune [14].

Treatment of gliomas with tumor treating fields (optune)

Tumor Treating Fields (TTFields) is an innovative, non-invasive cancer treatment that uses alternating electric fields (100–300 kHz) with an intensity of 1 V/cm to 3 V/cm to disrupt mitotic processes in cancer cells. The Optune device, developed by Novocure, has been FDA-approved for treating both newly diagnosed and recurrent glioblastoma (GBM) [15].
TTFields therapy operates at the molecular level by interrupting critical cancer-related processes, including mitosis, DNA replication and cell membrane function. These disruptions ultimately lead to cancer cell death and inhibit tumor growth [16].

Mitosis inhibition

TTFields have been found to disrupt mitosis by interfering with polar cellular components. Specifically, they impact tubulin, a key subunit in microtubules, reducing its polymerization and consequently impairing mitotic spindle formation during metaphase. Additionally, TTFields alter septin localization at the midline of the mitotic spindle in anaphase, leading to irregular mitotic exit. During telophase, the hourglass shape of the dividing cell generates a nonuniform electrical field, intensifying the alternating electric field at the cleavage furrow. This results in the movement of polar cellular components through dielectrophoresis. These disruptions ultimately trigger apoptosis or the formation of aneuploid daughter cells, which experience heightened endoplasmic reticulum (ER) stress and autophagy. Collectively, these mechanisms contribute to decreased cancer cell replication, inhibited proliferation, and reduced tumor growth [16].

TTFields strengthen antitumor immune responses by triggering immunogenic cell death

TTFields influence the immune system by inducing immunogenic cell death through endoplasmic reticulum (ER) stress and autophagy activation, thereby enhancing the systemic antitumor immune response. This therapy modifies the tumor microenvironment by promoting dendritic cell maturation, increasing cancer cell phagocytosis, and recruiting leukocytes. In cancer models, TTFields combined with immune checkpoint inhibitors (ICI) led to higher levels of cytotoxic T cells in the tumor and increased effector memory T cells in the spleen [16].

Additionally, TTFields can induce long-term antitumor immunity by activating the STING and AIM2 inflammasomes and the type 1 interferon (T1IFN) pathway. Studies show that in glioblastoma (GBM), TTFields activate adaptive immunity and influence gene expression related to T-cell activation. Furthermore, TTFields can reprogram macrophages from the M2 (tumor-promoting) phenotype to the M1 (pro-inflammatory) phenotype, enhancing the inflammatory response within the tumor [14,16].

Augmented permeability of cellular structures

TTFields treatment has been linked to several other cellular alterations. One notable effect is its ability to transiently and reversibly increase blood-brain barrier (BBB) permeability both in vitro and in vivo. This is believed to occur through a molecular pathway involving microtubule disruption, which activates Rho kinase, leading to the phosphorylation of claudin-5, a component of tight junctions. This phosphorylation causes tight junction proteins, such as claudin-5 and ZO-1, to relocate into the cytoplasm. As a result, it is hypothesized that molecules that typically struggle to pass through the selective BBB may now penetrate more efficiently, potentially increasing local concentrations of certain therapies within the central nervous system [17,18]. Additionally, in vitro studies have shown that TTFields can induce pore formation in the plasma membrane of cancer cells, enhancing permeability to small molecules, which may be beneficial for various anticancer treatments, while sparing noncancerous cells [19].

Genomic stability maintenance response

TTFields therapy affects the DNA damage response by downregulating DNA repair genes, particularly those involved in the FA-BRCA pathway [20]. Exposure to TTFields increases DNA double-strand breaks, chromatid aberrations, shorter replicated DNA, and R-loop formation, indicating abnormal DNA replication. These changes make the cells more vulnerable to DNA-damaging agents and those that interfere with DNA repair [21].

Impaired cellular movement

TTFields therapy affects cancer cell migration by regulating microtubules and actin. Changes in microtubule organization activate the RhoA/ROCK pathway, leading to reduced cell polarity, which impacts the direction and speed of migration. Combined with immune system activation, these mechanisms may contribute to the antimetastatic effects of TTFields [22].

EF-14 Trial – Efficacy of TTFields in GBM Treatment

The EF-14 trial was a multicenter, randomized phase III study designed to assess the efficacy of Tumor Treating Fields (TTFields) in newly diagnosed glioblastoma (GBM) patients. Participants were randomly assigned to receive either standard therapy (radiotherapy and temozolomide) or standard therapy combined with TTFields, which were applied concurrently with temozolomide for at least 18 hours per day [23].

EF-14 Trial Findings

- Median Overall Survival (OS): Patients receiving TTFields demonstrated a median survival of 20.9 months, compared to 16 months in the standard therapy group (HR = 0.63; $p < 0.001$). This result indicates a 37% reduction in the risk of death for patients treated with TTFields [23].
- 2-Year Survival Rate: In the control group, 31% of patients survived for 2 years, while in the TTFields group, this rate was 43% [23].
- Median Progression-Free Survival (PFS): The median PFS was 4.0 months for the control group and 6.7 months for the TTFields group [23].

The results of the EF-14 trial demonstrated that TTFields significantly improve treatment outcomes for GBM patients, both in terms of overall survival and delaying disease progression. When combined with temozolomide, TTFields present an effective therapeutic option that is well tolerated by patients, with minimal adverse effects, most notably skin irritation at electrode application sites [23].

Optune – Clinical Application and Practical Considerations

TTFields are recommended for patients with:

- Newly diagnosed GBM, after tumor resection and completion of radiotherapy with temozolomide.
- Recurrent GBM, as a second-line treatment for patients unable to receive chemotherapy or as an adjunctive therapy.

Tumor Treating Fields (TTFields) therapy is approved in the United States (by the US Food and Drug Administration [FDA]), Canada, China, Israel, Japan, Australia, and several countries in Europe (the device is Conformité Européenne [CE]-marked by the European Union [EU]) [24-31].

How TTFields Are Applied

The Optune system consists of four transducer arrays placed on the patient's scalp. The device generates electric fields that penetrate the skull and disrupt cancer cell division. Arrays must be replaced regularly, and the patient's head must be shaved to ensure optimal device-skin contact. The placement of the TTFields array is customized based on the patient's anatomy, with a layout determined by the treatment planning software. The device's portability allows for its use at home and during daily activities, integrating seamlessly into patients' routines. The second-generation device, approved by the CE in 2015 and the US FDA in 2016, is more compact, lighter, and offers a longer battery life. It also uses less conspicuous, patient-friendly

tan arrays, enhancing comfort compared to the original version [31,32]. The therapy must be continuous – patients should wear Optune for at least 18 hours per day [23].

Safety Profile of TTFields

Optune is a well-tolerated therapy, with the most common side effect being skin irritation at the electrode application sites (up to 52% of patients, usually mild) [23]. Dermatological side effects associated with TTFields therapy include conditions like contact dermatitis, excessive sweating, dry skin, and itching, with rare occurrences of skin erosions, ulcers, and infections. While these reactions are typically mild to moderate, it's crucial to minimize their occurrence and promptly manage them to prevent therapy discontinuation. Recent guidelines stress the importance of careful array placement, removal, and repositioning, as well as regular skin checks. Topical treatments can help with minor irritations, while more severe cases should be addressed by a dermatologist [33].

TTFields therapy primarily leads to mild-to-moderate, manageable, and reversible skin irritation under the arrays, with no evidence of added systemic toxicities. In the EF-14 study (ndGBM), systemic adverse events were similar between the TTFields/TMZ and TMZ-alone groups, suggesting that the chemotherapy contributed to the systemic adverse effects [23].

These studies aim to assess the efficacy of TTFields beyond glioblastoma, potentially broadening their clinical applications. Additionally, ongoing research focuses on optimizing TTFields parameters, combining them with novel therapeutic agents, and improving patient adherence to maximize treatment benefits. As new therapeutic strategies continue to emerge, TTFields represent a promising approach in neuro-oncology, offering a non-invasive modality that can enhance current glioma treatments and improve patient survival outcomes [33].

Summary

Glioblastoma (GBM) remains one of the most aggressive and treatment-resistant primary brain tumors. Despite advancements in surgery, radiotherapy, and chemotherapy, patient prognosis remains poor. The introduction of Tumor Treating Fields (TTFields), commercially known as Optune, represents an innovative, non-invasive approach to GBM therapy. By

utilizing alternating electric fields, TTFields disrupt mitotic processes in cancer cells, inhibiting their proliferation while sparing healthy brain cells. Clinical evidence, particularly from the EF-14 trial, has demonstrated that TTFields combined with temozolomide significantly prolong overall survival (OS) and progression-free survival (PFS) in patients with newly diagnosed GBM. This therapy has also been approved for the treatment of recurrent GBM, providing an alternative for patients who have not responded to other treatments. TTFields have a favorable safety profile, with the most common adverse effect being localized skin irritation at electrode application sites. The non-invasive nature of this therapy, its lack of systemic toxicity, and its potential synergy with other treatment modalities make TTFields an attractive therapeutic option in both neurooncology and the broader field of oncology.

Conclusions

TTFields therapy represents a significant breakthrough in glioblastoma treatment, offering a clinically validated method to extend survival and improve patients' quality of life. While existing studies confirm its efficacy and safety, further research is needed to optimize treatment protocols, identify predictive biomarkers, and determine the long-term benefits of this therapy. As our understanding of TTFields continues to expand, integrating this modality into multimodal treatment strategies may further enhance therapeutic outcomes. Future research should focus on defining patient selection criteria, evaluating long-term treatment effects, and exploring applications beyond glioblastoma. The growing body of scientific evidence underscores TTFields' potential as a groundbreaking tool in neurooncology, opening new possibilities for cancer treatment.

Disclosure

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