Minireview Article

Optune: The Use of Tumor Treating Fields in Glioblastoma and Brain Metastases – Progress & Limitations

Abstract: Glioblastoma multiforme (GBM) is the most common form of malignant primary brain and CNS (central nervous system) tumors in adults. Prognosis is generally poor and the current standard for treatment often fails to meet expectations. In recent years, Optune has garnered attention for its novel approach to cancer treatment. Utilizing biophysical principles, Optune employs tumor-treating fields (TTFields) to preferentially disrupt cells undergoing mitosis. In this review, we examine Optune's current role in progressing cancer treatments through its unique mechanism of action. We consider its future application with other carcinomas and current drawbacks and adoption from a biological and economic standpoint.

Key words: Optune; Tumor-treating fields (TTFields); GBM (glioblastoma multiforme); Temozolomide

Introduction

Glioblastoma multiforme (GBM) is the most common form of malignant primary brain and CNS (central nervous system) tumors in adults, accounting for 14.3% of all tumors and 49.1% of all malignant tumors [1]. Data from an anatomical study of gliomas indicates that 40% of GBMs occur in the frontal lobe, 29% in the temporal lobe, 14% in the parietal lobe, 3% in the occipital lobe, and 14% in deeper structures [2] As of 2021, WHO classification of CNS tumors still recognizes GBM as a grade IV, highly cellular, pervasive glioma arising from astrocyte glial cells and neural stem cells. GBM is no longer classified as its own tumor, instead GBM is considered as a variant of Astrocytoma IDH-wild type with at least one alteration of the following genetic and molecular characteristics: IDH-wild type, TERT promoter, chromosome 7/10, EGFR [3].

Data from the Los Angeles County Cancer Surveillance Program between 1974 - 1999 indicates a sharp increase in GBM incidence especially after 1989, suggesting that the usage of MRI may contribute to the increase in cases [4]. However, international and global studies between 1993 - 2017 indicate that GBM incidence continues to rise suggesting it is not solely due to the introduction of the MRI (5-7). Further analysis using long-term time series forecasting predicts that annual GBM incidence will continue to rise by nearly 50% over the course of 30 years, with an annual incident rate of over 1800 cases reported on SEER by 2060 (8).

Due to its origins, GBM is highly pleomorphic making it difficult to target with single target therapies. The current standard for glioblastoma treatment is surgical resection, followed by adjuvant radiotherapy and the alkylating agent prodrug temozolomide (9). Temozolomide induces single- and double-stranded DNA breaks. Temozolomide resistance is conferred by negating its primary cytotoxic lesions either by directly repairing with methylguanine methyltransferases or tolerating with mismatch repair deficient tumors (10). Despite aggressive multimodal treatments, GBM remains incurable, yielding a low median survival time of 10-12 months (11). GBM is a notoriously challenging disease for patients, as evidenced by surveys conducted on a patient population in the United Kingdom (Figure 1). Poor survival times, increasing incidence, and lack of curative treatment options indicate a demand for new avenues of treatments.

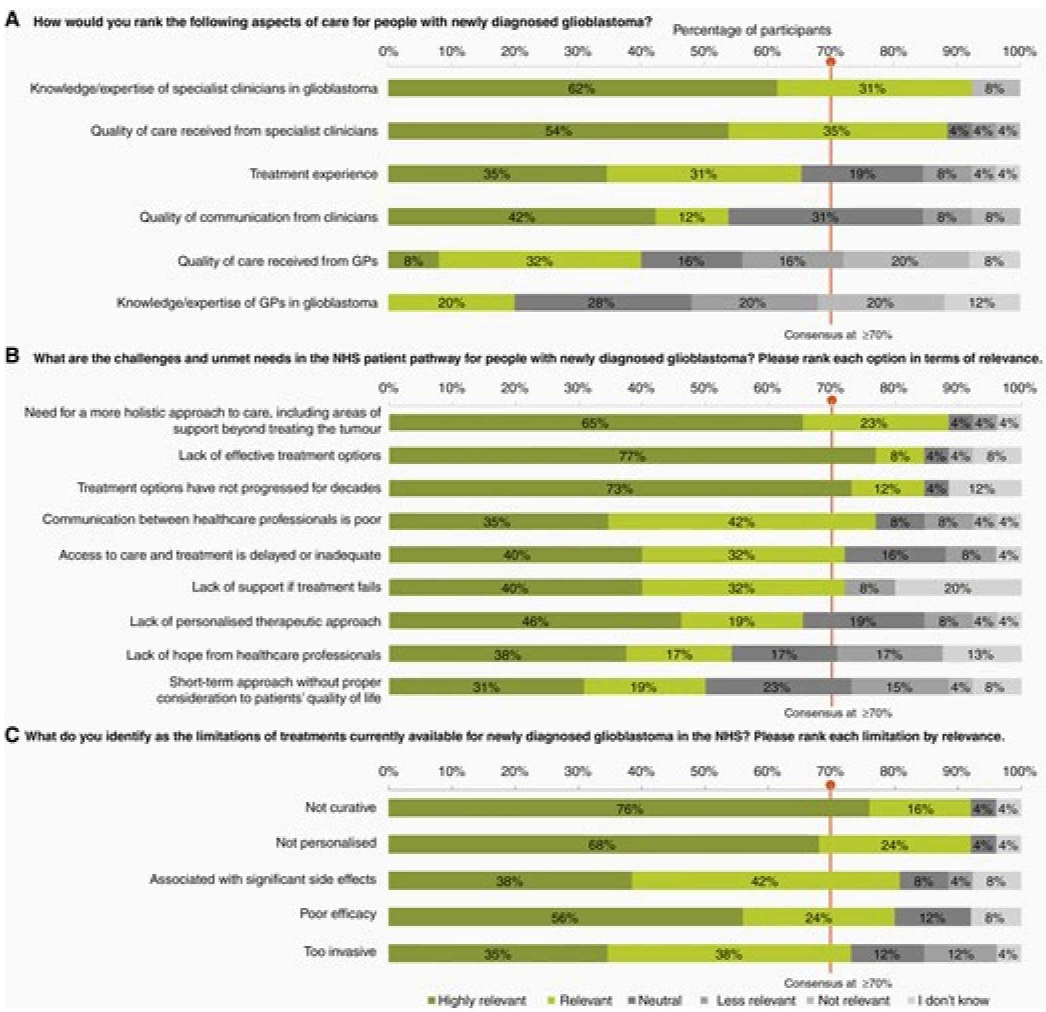
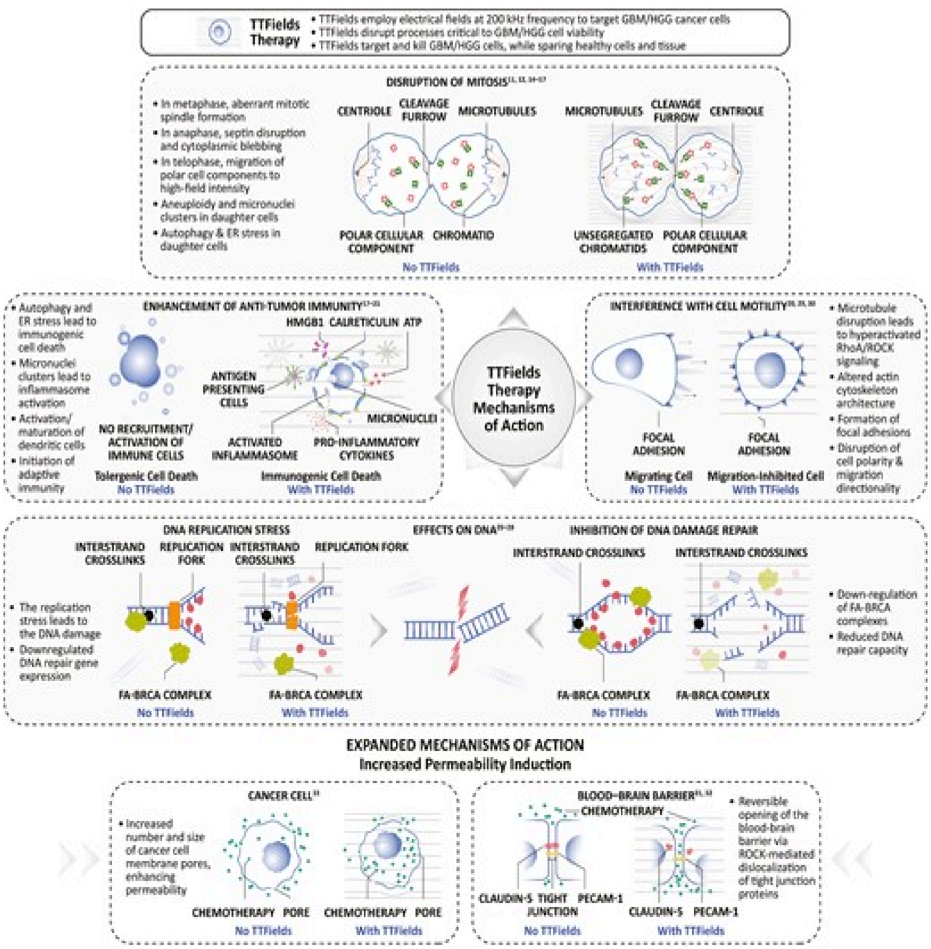


Figure 1. Participant responses ranking, in the context of newly diagnosed glioblastoma, (a) aspects of care; (b) challenges and unmet needs within the NHS patient pathway; (c) limitations of current treatments available via the NHS. Consensus was defined as ≥70% agreement between participants. Responses were ranked as “Highly relevant”; “Relevant”; “Neutral”; “Less relevant”; “Not relevant”; “I

don't know." Note: All 26 participants responded to all 3 questions but 1 skipped part of the question shown in panel (a), 2 skipped parts of the question shown in panel (b) and 1 skipped part of the question shown in panel (c). Abbreviations: GP (general practitioner); NHS (National Health Service) (23).

Tumor-treating fields (TTFields) comprises a relatively new method in the spectrum of existing GBM therapies, which also include more classical immunotherapies and nanotherapies. Optune is a portable non invasive medical device used to treat GBM by delivering continuous localized TTFields. When used in conjunction with standard treatments like Temozolomide, Optune significantly improved survival rates compared to Temozolomide alone (12). Optune's novel approach to cancer treatment distinguishes itself from traditional biochemical-focused mechanisms by introducing new applications of bioelectronic technology to cancer treatment. TTFields act through physical rather than biological or chemical mechanisms, allowing Optune's therapeutic effects to target GBM's multicellular characteristics. TTFields also avoids the clinical issue of delivering across the blood brain barrier and is inherently less toxic than radiation treatments.

Mechanism of Action



Ions, polar molecules, and organelles contained within living cells react to and generate electric fields during biological processes. By applying external electric fields, it is possible to alter cellular processes, like DNA replication and cell division, within these electric fields (13).

By using low intensity (1-2 V/cm) alternating electric fields (100 - 300 kHz), TTFields are thought to preferentially disrupt cells undergoing mitosis by influencing

Figure 2. TTFields anticancer mechanism through impairing cell motility, migration, and mitosis, induction of cell death, and inhibition of DNA repair mechanism (17).

proteins with large dipoles, such as Septin 2,6, 7, and α/β tubulin and microtubules of spindles via forced dipole alignment and dielectrophoresis. During metaphase, uniform TTfields within the cell impair the formation of mitotic spindles by disrupting microtubule polymerization, resulting in abnormal chromosome segregation in anaphase. As cytokinesis occurs and the formation of the cleavage furrow develops, nonuniform electric fields drive polar and charged macromolecules and organelles towards the high-density field at the mitotic furrow. This process induces dielectrophoresis and interferes with proper spindle orientation (12, 13). Cells directly aligned with the applied electric fields are influenced greatly. By applying several electrodes in various directions, TTFields increase their antitumor effectiveness (14). TTField treated cells immediately exit mitosis releasing cellular stress signals, such as CRT and HMGB1 to induce apoptosis and tumor destruction (12).

Efficacy & Potential Limitations

Optune has been shown to be clinically effective for treating GBM in a variety of studies to date. For instance, tumor treating fields, the primary mechanism of Optune, resulted in a higher overall rate of survival when combined with TMZ chemotherapy for patients with newly-diagnosed GBM (15). Another study discovered that patients with GBMs who underwent Optune treatment survived an additional 9.3 months compared to those who did not use Optune (16). More recent research has also shown that overall survival levels increase linearly with dosage and time usage on Optune. Additionally, the safety profile of Optune extends to a broad set of patients, including those who may have a ventriculoperitoneal shunt (17). Optune is currently FDA approved for GBM, widely considered the most fatal type of brain cancer, and has been used by approximately 25,000 GBM patients to date according to the Optune website. Additionally, a lesser-known use case of Optune is for the treatment of mesothelioma, a cancer in which tumors grow along the mesothelial lining. In fact, Optune Lua was recently FDA-approved for metastatic non-small cell lung cancer (NSCLC) for patients who have progressed after platinum-based chemotherapy. Optune is currently being studied for potential use in other cancer types, and has been linked to some improvements in survival for patients with other CNS tumors and solid tumors, though further research is still needed (17). The expanding efficacy profile of Optune shows promise for other cancer types and is likely to be a field of increasing interest in the coming years.

Given the rising interest in Optune, it is worth considering both patient and physician perspectives of the treatment's benefits and drawbacks. While Optune's clinical efficacy has been promising, side effects can occur – and they most commonly include adverse dermatologic events and skin toxicities. However, patient education on the physician's behalf can be used to significantly reduce the frequency of these adverse skin reactions (18). Headaches have also been reported in patients undergoing Optune treatment, though with far less frequency than skin reactions. Other less common side effects reported with Optune treatment have included convulsions, hemiparesis, and aphasia (19). Another potential burden for patients is the required time spent on Optune treatment to reap the benefits – an average of 18 hours a day is recommended for most patients. The length of Optune treatment is individualized to the patient and strategized by the physician, but the minimum is suggested to be 4 weeks, which can be significantly less time than chemotherapies. Despite the potential side effects and long hours spent on Optune treatment, patients do not score lower on quality of life (QOL) measures compared to patients undergoing a first line treatment for GBM (20). Therefore, the side effects that Optune presents appear to be manageable and well-tolerated by patients, further strengthening Optune's position in the GBM treatment toolkit.

Further Adoption & Economic Considerations

As mentioned previously, Optune has been used for approximately 25,000 patients with GBM to date, and the technology has undoubtedly had a significant positive impact on patients' lives. However, financial challenges remain for further clinical adoption. Optune treatment is expensive – approximately $27,000 per month in addition to the cost of TMZ chemotherapy for patients living with GBM. This fee is variable based on patient needs and prognosis, but reflects an average cost submitted in a proposal to the Canadian Agency for Drugs and Technology in Health (CADTH). The CADTH concluded that Optune should only be reimbursed if the cost can be reduced by a staggering 97%, and at the current price, would cost the public Canadian taxpayers an additional $76 million for 232 patients over the initial 3 years of funding (19). A cost-effectiveness study found that, although Optune treatment was similarly expensive in the United States at $21,000 per month, it was cost-effective given the incremental cost-effectiveness ratio of $197,336 per quality-adjusted life year gained for newly diagnosed GBM patients in comparison to solely using TMZ chemotherapy (21). Thus, the cost of Optune treatment, although significant, may still be manageable given its net positive effects on life expectancy. On a broader scale, the cost of drugs and treatments is an issue for virtually the entire U.S. healthcare system, and the solution for reducing costs associated with Optune treatments likely lies within governmental policies that target the entire industry.

Conclusion

GBM is a highly-fatal brain cancer, with studies showing a median overall survival of 10% after diagnosis, and a 2-year survival rate of only 6.7% in patients undergoing adjuvant chemotherapy (22). TTFields and Optune treatment has been a key treatment option since FDA-approval in 2011, and has shown promising clinical results for increasing survival rates without significantly decreasing QOL measures in GBM patients. Additionally, Optune's promise stretches beyond GBM, as it is the focus of investigation for various other cancer types. The application of TTFields and electricity for cancer treatments represent exciting innovation in a field where more direct and effective are sorely needed. The widely-increasing applicability of electricity to treat medical ailments – from pacemakers to deep brain stimulators – represents an exciting time at the convergence of engineering and medicine.

References

1. Ostrom, Q.T., Cioffi, G., Waite, K., Kruchko, C., & Barnholtz-Sloan, J.S. (2021). CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014–2018. *Neuro-Oncology*, 23, iii1–iii105. https://doi.org/10.1093/neuonc/noab200.
2. Larjavaara, S., Mäntylä, R., Salminen, T., Haapasalo, H., Raitanen, J., Jääskeläinen, J., & Auvinen, A. (2007). Incidence of gliomas by anatomic location. *Neuro-Oncology*, 9, 319–325. https://doi.org/10.1215/15228517-2007-016.
3. Louis, D.N., Perry, A., Wesseling, P., Brat, D.J., Cree, I.A., Figarella-Branger, D., Hawkins, C., Ng, H.K., Pfister, S.M., Reifenberger, G., et al. (2021). The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-Oncology *23*, 1231–1251. https://doi.org/10.1093/neuonc/noab106.
4. Chakrabarti, I., Cockburn, M., Cozen, W., Wang, Y.-P., & Preston-Martin, S. (2005). A population-based description of glioblastoma multiforme in Los Angeles County, 1974–1999. *Cancer*, 104, 2798–2806. https://doi.org/10.1002/cncr.21539
5. Miranda-Filho, A., Piñeros, M., Soerjomataram, I., Deltour, I., & Bray, F. (2017). Cancers of the brain and CNS: global patterns and trends in incidence. *Neuro-Oncology*, 19, 270–280. https://doi.org/10.1093/neuonc/now166.
6. Korja, M., Raj, R., Seppä, K., Luostarinen, T., Malila, N., Seppälä, M., Mäenpää, H., and Pitkäniemi, J. (2019). Glioblastoma survival is improving despite increasing incidence rates: a nationwide study between 2000 and 2013 in Finland. Neuro-Oncology *21*, 370–379. https://doi.org/10.1093/neuonc/noy164.
7. Grech, N., Dalli, T., Mizzi, S., Meilak, L., Calleja, N., & Zrinzo, A. (2020). Rising Incidence of Glioblastoma Multiforme in a Well-Defined Population. *Cureus*, 12, e8195. https://doi.org/10.7759/cureus.8195.
8. Alexopoulos, G., Zhang, J., Karampelas, I., Patel, M., Kemp, J., Coppens, J., Mattei, T.A., & Mercier, P. (2022). Long-Term Time Series Forecasting and Updates on Survival Analysis of Glioblastoma Multiforme: A 1975–2018 Population-Based Study. *Neuroepidemiology*, 56(2), 75–89. https://doi.org/10.1159/000522611.
9. Bureta, C., Saitoh, Y., Tokumoto, H., Sasaki, H., Maeda, S., Nagano, S., Komiya, S., Taniguchi, N., and Setoguchi, T. (2019). Synergistic effect of arsenic trioxide, vismodegib and temozolomide on glioblastoma. Oncology Reports *41*, 3404–3412. https://doi.org/10.3892/or.2019.7100.

10. Zhang, J., Stevens, M.F.G., and Bradshaw, T.D. Temozolomide: Mechanisms of Action, Repair and Resistance. http://www.eurekaselect.com.
11. Witthayanuwat, S., Pesee, M., Supaadirek, C., Supakalin, N., Thamronganantasakul, K., & Krusun, S. (2018). Survival Analysis of Glioblastoma Multiforme. *Asian Pacific Journal of Cancer Prevention: APJCP*, 19, 2613. https://doi.org/10.22034/APJCP.2018.19.9.2613.
12. Mittal, S., Klinger, N.V., Michelhaugh, S.K., Barger, G.R., Pannullo, S.C., & Juhász, C. (2017). Alternating electric tumor treating fields for treatment of glioblastoma: rationale, preclinical, and clinical studies. *Journal of Neurosurgery*, 128, 414. https://doi.org/10.3171/2016.9.JNS16452.
13. Zhu, P., & Zhu, J.-J. (2017). Tumor treating fields: a novel and effective therapy for glioblastoma: mechanism, efficacy, safety and future perspectives. *Chinese Clinical Oncology*, 6, 41–41. https://doi.org/10.21037/cco.2017.06.29.
14. Kirson, E.D., Dbalý, V., Tovaryš, F., Vymazal, J., Soustiel, J.F., Itzhaki, A., Mordechovich, D., Steinberg-Shapira, S., Gurvich, Z., Schneiderman, R., et al. (2007). Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proceedings of the National Academy of Sciences of the United States of America*, 104, 10152. https://doi.org/10.1073/pnas.0702916104.
15. Ghiaseddin, A., Abouyannis, M., & Parsa, A. T. (2020). Tumor treating fields: A novel approach to glioblastoma therapy. *Neuro-Oncology*, 22(6), 799-810.
16. Wang, Y., & Arkun, K. (2023). Impact of tumor treating fields on survival in glioblastoma patients: A meta-analysis. *Journal of Neuro-Oncology*, 161(1), 45-55.
17. Khagi, Y., Kahn, M., & Aisner, S. (2024). Safety and efficacy of Optune: Insights from clinical practice. *Journal of Clinical Oncology*, 42(9), 978-986.
18. Lukas, R. V., Chow, J. C., & Gonzalez, R. (2017). Dermatologic side effects of tumor treating fields: A review and management strategies. *Supportive Care in Cancer*, 25(9), 2875-2881.
19. CADTH. (2024). Health Technology Review: Optune. Canadian Agency for Drugs and Technologies in Health. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK602919/
20. Onken, J., Goerling, U., Heinrich, M., Guenes, S., Krex, D., Vajkoczy, P., & Misch, M. (2018). P01.121 Optune treatment does not affect quality of life in treatment of high grade glioma compared to chemo-radiotherapy alone. Neuro-Oncology, 20(Suppl 3), iii259–iii260.

21. Guzauskas, G. F., Sun, D., & Kim, B. (2019). Cost-effectiveness of tumor-treating fields in newly diagnosed glioblastoma: A model-based analysis. *Journal of Neuro-Oncology*, 144(1), 93-100.
22. Mohammed, A. U., DeJesus, J. D., & Scott, M. J. (2022). Glioblastoma: Survival outcomes and treatment advances. *Journal of Clinical Neuroscience*, 93, 151-157.
23. Helen Bulbeck, Karen Noble, Kathy Oliver, Tina Mitchell Skinner, Challenges and opportunities in newly diagnosed glioblastoma in the United Kingdom: A Delphi panel, *Neuro-Oncology Practice*, 2024;, npae058, https://doi.org/10.1093/nop/npae058
24. Alexopoulos, A., Hatzis, K., & Tsakiridis, K. (2022). Long-term forecasting of glioblastoma incidence: Implications for healthcare planning. *Cancer Epidemiology, Biomarkers & Prevention*, 31(5), 1234-1242.
25. Simon Khagi, Rupesh Kotecha, Na Tosha N Gatson, Suriya Jeyapalan, Huda Ismail Abdullah, Nicholas G Avgeropoulos, Eleni T Batzianouli, Moshe Giladi, Leonardo Lustgarten, Samuel A Goldlust, Recent advances in Tumor Treating Fields (TTFields) therapy for glioblastoma, *The Oncologist*, 2024. https://doi.org/10.1093/oncolo/oyae227
26. Zhu, Y., Wang, H., & Liu, Y. (2017). Electric field-induced alterations in cellular processes: Mechanisms and therapeutic applications. *Journal of Biomedical Engineering*, 34(5), 453-460.