Harnessing Technology to Enable Hope for GBM

Tumor Treating Fields

In this article, Dr Daniel Tan introduces Tumour Treating Fields, a promising therapy for patients with glioblastoma multiforme.

Glioblastoma multiforme or GBM is a feared, lethal and aggressive brain tumour that arises from glial cells, which are supporting cells of neurons. Tumours of glial cells are known as gliomas, and GBM is classified as a grade IV diffuse astrocytic and oligodendroglia tumour by the World Health Organization.

According to the American Association of Neurological Surgeons, the incidence of GBM is about 3 per 100,000 persons and accounts for about 50 per cent of all primary brain tumours in the United States. It usually affects adults aged between 45 and 70 and the median age of diagnosis is 64 years. It is more common in men and survival is poor with a median survival of only 14.6 months even after receiving standard of care treatment.

Although relatively rare, GBM is well-recognised because of prominent persons it has stricken, such as US presidential candidate John McCain, and current US President Joe Biden's son, Beau Biden. Additionally, it strikes healthy adults in their prime, whose rapid neurological deterioration after a recent diagnosis tend to leave a deep impression on their relatives and friends.

GBM remains silent until it causes symptoms related to its location within the brain. The most common ones include:

- Headaches that persist for days or even weeks
- Changes in vision (blurred, or double vision)
- Changes in thinking and learning
- Personality changes
- New onset of seizures

Unfortunately, GBM while treatable, remains incurable.

Standard Treatment

The mainstay of the treatment for GBM has remained unchanged for more than a decade. According to the Stupp trial published in 2005, the addition of temozolomide chemotherapy given concurrently with adjuvant radiotherapy and then adjuvantly for six months led to an improved median overall survival of 14.6 months versus 12.1 months compared with radiotherapy alone, with minimal additional toxicity. Since then, studies attempting more intense chemotherapy or radiotherapy have not been able to improve survival and as such, the Stupp regime has remained the standard of care for close to two decades.

New Treatment Option For GBM: Tumour Treating Fields

In October 2015, the U.S. Food and Drug Administration (FDA) approved the use of a new treatment called Tumour Treating Fields (TTF) in combination with temozolomide chemotherapy for the treatment of newly diagnosed GBM. This was based on a randomized international trial called EF-14, which showed that those who had TTF after their radiation therapy together with the adjuvant chemotherapy had a median overall survival of 20.5 months versus 15.6 months in the control arm. This spectacular result led to the early stopping of the trial at a planned interim analysis, and longer-term follow-continued to show this benefit among trial participants.

In fact, in 2011, the FDA approved TTF therapy for recurrent GBMs based on an earlier trial called EF-11, which compared the efficacy of TTF therapy with a broad range of investigator's choice systemic therapies, and TTF showed

equivalent survival with a lower incidence of serious side effects.

Hence, while 'new' to many, TTF has been approved in clinical use for almost a decade in GBM, yet its utilisation has been limited, despite positive results in high-quality trials.

What is TTF?

TTFs are low intensity, intermediate frequency, alternating electric fields whose overall effects are interference with and prolongation of cell division, and disruption of cytokinesis in rapidly dividing cells, resulting in apoptosis. TTFs targets cancer cells with a high therapeutic index due to their unique electrical polarity, geometric shape, and rapid replication rate. The optimal electrical frequency for the most effective cell kill varies by tumour type. For example, recurrent GBM, are sensitive to TTFs at an intensity of 1 to 3 V/cm and frequency of 200 kHz.

Delivery of TTF

For GBM, two orthogonal pairs of transducer arrays are placed on the shaved scalp of patients and these deliver low intensity, intermediate frequency, alternating electric fields to the tumour.

The device should be worn at all times (analyses in the trials showed better outcomes in patients whose time on therapy was 18 hours a day or greater) and requires an electrical power source, either via a direct AC plug or a portable battery. The second-generation device weighs only 2.7 pounds (including a battery) with the aim that the lighter weight may improve patient compliance. Regular shaving of the scalp is essential for optimal penetration of the electrical fields. Due to copyright issues, pictures and more details of the delivery device can be found at www.optune.com.

Eligibility Criteria

Both Newly Diagnosed GBM Patients and Recurrent GBM Patients are eligible for TTF treatment.

Benefits Of Adding TTF to Standard GBM Treatment

In Newly Diagnosed Patients, when TTF was added to chemotherapy, 43 per cent of patients were alive at two years compared with 31 per cent who were on chemotherapy alone. 13 per cent of patients who had TTF treatment in addition to chemotherapy were alive at five years compared to 5 per cent among those who had chemotherapy alone. These patients were also able to maintain their mental, emotional and physical well-being longer than those on chemotherapy alone.

Side Effects

TTF treatment is very safe and is well tolerated with a low risk of adverse events. The most common side effect patients experience is device-related scalp irritation, which can be managed by topical ointments and periodic relocation of the arrays.

Reasons for the silence

As mentioned above, TTF therapy is not new. Within the neuro-oncology speciality, there are several postulated reasons for its slow adoption. Some blame it on the newness of the technology that renders it unfamiliar to clinicians schooled in the three traditional approaches to cancer therapy i.e. Surgery, Radiation, and Chemotherapy. Others attribute it to the patient compliance needed for efficacy i.e. shaving the head, constant wearing of the device, and its logistical (battery life) and social implications (visible on the scalp).

In Singapore, this author had been engaging the manufacturers since 2018 to make the Optune device available here and in the region. While keen to extend their presence, the manufacturers have expressed the desire to expand first into major markets and to clear regulatory and reimbursement hurdles since this is a new class of product. Hence, our region will have to wait in the queue.

Access to TTF

Nevertheless, TTF treatments are available to our local and regional patients via our close collaboration with clinical partners in markets where the device is available. Our patients can be prescribed TTF by our overseas colleagues, while we will work closely together with them to ensure continuity of care and management of potential side effects.

TTF For Other Cancers

TTF is being actively investigated in other cancers such as meningiomas, lung cancer, pancreatic cancer, and ovarian cancer. Recently, the FDA has also approved under the Humanitarian Device exemption pathway the use of TTF for unresectable, locally advanced, or metastatic malignant pleural mesothelioma. This was based on a small study, where these patients were given TTF together with chemotherapy and achieved one-year survival of 62 per cent, and two-year survival of 42 per cent.

Conclusion

Glioblastoma multiforme is a rapidly progressing, lethal cancer of the brain. Technological innovation has led to the first proven and significant extension of survival for GBM patients in decades, with minimal additional toxicity. The efficacy of TTF on such an aggressive and lethal tumour type heralds hope for further breakthroughs in less aggressive tumours. At the same time, TTF demonstrates that advanced technologies, alongside developments in the more glamorous pharmaceutical realm, is still able to provide effective breakthroughs for our patients. Indeed, cancer is best treated by a combination of multiple modalities, and by keeping an open and active mind, we can harness technology to enable hope for our patients. While currently unavailable locally, TTF can still be accessed by our local patients through our clinical collaborations with close continuity of care.

References

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About the Author

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