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Australia and New Zealand Horizon Scanning Network

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AN INITIATIVE OF THE NATIONAL, STATE AND
TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

Tumour Treating Fields (TTF) for glioblastoma multiforme (GBM)

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**Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical**



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College of Surgeons**

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PRIORITISING SUMMARY

REGISTER ID S000096

NAME OF TECHNOLOGY TUMOUR TREATING FIELDS (TTF)

PURPOSE AND TARGET GROUP PATIENTS WITH GLIOBLASTOMA MULTIFORME (GBM)

STAGE OF DEVELOPMENT (IN AUSTRALIA)

- | | |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- Yes
- No
- Not applicable

INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
The Netherlands	✓		
Czech Republic	✓		
Israel	✓		
Switzerland	✓		
France	✓		
United States	✓		
Austria	✓		
Germany	✓		

IMPACT SUMMARY

The Tumour Treating Fields (TTF) device (NovoCure Ltd., Haifa, Israel) delivers low-intensity, intermediate-frequency, alternating electric fields to treat cancer. The electric fields are delivered via electrodes placed onto the patient's shaved skin, and treatment is applied for between 2 and 4 weeks (Schroeder et al 2008). TTF has two modes of

action: arrest of cell proliferation and destruction of dividing cells. As only mitotic cells would be destroyed, TTF is thought to be highly specific for cancer (Schroeder et al 2008; Kirson et al 2004)

BACKGROUND

The World Health Organisation (WHO) categorises primary brain tumours based on their origin and histologic appearance. Meningiomas, derived from meningotheial cells, make up approximately 20% of primary brain tumours and neuroglial tumours, derived from astrocytes, oligodendrocytes, or ependymal cells, make up the remaining 80% (Chandana et al 2008).

The grade of gliomas is generally based on the World Health Organisation (WHO) classification system:

- Grade I lesions have low proliferative potential, and a cure may be possible following surgical resection.
- Grade II lesions are generally infiltrative in nature and often recur. Some grade II lesions may progress to higher grades of malignancy.
- Grade III lesions have histological evidence of malignancy. Patients generally receive adjuvant radiation and/or chemotherapy.
- Grade IV lesions are cytologically malignant, mitotically active, necrosis-prone and typically associated with a fatal outcome (Louis et al 2007).

Glioblastoma multiforme (GBM) a grade IV glioma and is the most common and aggressive type of glioma (Chandana et al 2008; Germano et al 2008; Louis et al 2007). Patients have a median survival rate of less than 12 months, and a five year survival rate of less than 5% (Germano et al 2008).

TTF may treat patients with GBM by delivering very low intensity, alternating electric fields through the patient's scalp. The electric fields stop cell proliferation by disrupting the formation of the mitotic spindle and rupturing cell membranes during mitosis (Schroeder et al 2008). In studies to date TTF has shown no effect on non-dividing, healthy cells in the same treatment region, meaning that normal brain cells are unaffected (Edelman 2008).

TTF has been promoted as an attractive treatment option for GBM as none of the present treatment modalities may be considered curative (Brandes et al 2008) as surgery, chemotherapy and radiation therapy aim to improve the patient's quality of life and extend survival. Proponents of TTF note that it may have further value through reducing the length of hospital stay as patients do not need to remain in the clinical setting whilst treatment takes place. This also allows patients living in remote areas to return home during treatment. TTF has been depicted as a well tolerated and pain-free, which is an advantage over existing treatment modalities. In addition to this, TTF may be an adjuvant therapy to chemotherapy. It has been proposed that TTF may enhance

the effects of chemotherapy without an associated increase in treatment toxicity (Kirson et al 2009).

CLINICAL NEED AND BURDEN OF DISEASE

As the most common malignant brain tumour is GBM, we may assume that it comprises the majority of cases of brain cancer (Chandana et al 2008). In 2005, the number of new cases of brain cancer in Australia was 1,422 accounting for 1.4% of all new cancer cases (AIHW 2008). The age standardised incidence rate of brain cancer in 2005 was 6.8 per 100,000. In addition, brain cancer was responsible for 1050 deaths in 2005, accounting for 2.7% of all deaths from cancer in Australia (AIHW 2008). It was the ninth most common causes of death in cancer for women in 2005 (436, 2.6% of total). In the 2006-2007 time period there were 4,855 brain cancer-related hospital separations in Australia, out of a total of 377,021 cancer-related hospital separations. The average length of stay (including same-day separations) for brain cancer-related hospital separations was 11.4 days, compared with an average of 4.8 days for all cancers (AIHW 2008).

DIFFUSION

The use of TTF has been trialled in animal models (Kirson et al 2009; Kirson et al 2007). While the procedure is still at an early stage of development, three human trials of the TTF device for the treatment of brain tumours have been conducted (Kirson et al 2009; Kirson et al 2007; Salzbarg et al 2008).

The TTF device is not presently listed on either the US Food and Drug Administration or the Australian Therapeutic Goods Administration. An international phase III randomised controlled trial comparing TTF to the best standard of care is underway.

COMPARATORS

Management of GBM is concerned with providing symptomatic relief and increasing the patient's survival (Hart et al 2008). The three main interventions include:

- 1) Surgery: curative surgery is generally not possible. Surgery aims to reduce the tumour, allowing decompression of the brain (Brandes et al 2008).
- 2) Radiotherapy: achieves an approximate doubling of overall survival compared with surgery alone or followed by chemotherapy (Brandes et al 2008).
- 3) Chemotherapy: either single agent or multi-agent regimes try to penetrate the blood brain barrier and maximise tumour responsiveness. Chemotherapy may provide a 6% increase in 1-year survival (95% CI 3–9%, from 40% to 46%) and an increase in median survival time of 2 months (CI 1–3 months) (Brandes et al 2008). Additionally, glucocorticosteroids may reduce peri-tumoural oedema and improve neurological symptoms and survival.

SAFETY AND EFFECTIVENESS ISSUES

Study description

Three studies were identified (Salzberg et al 2008; Kirson et al 2007; Kirson et al 2009) for inclusion in this prioritising summary. Salzberg et al (2008) reported on six patients with cancer who received TTF, although only one patient had GBM. This patient's data has been separated, where possible, for inclusion in this horizon scanning summary. The patient received TTF continuously for a minimum of four weeks.

Kirson et al (2009) reported on a total of 20 patients with GBM, divided into two groups. Group 1 (n=10) had recurrent GBM treated with TTF following failure of maintenance chemotherapy (Temozolomide). This cohort had been previously reported by Kirson et al (2007). Data from the more recent publication (Kirson et al 2009) will be used preferentially for discussion; however, information contained in the original study (Kirson et al 2007) will be included where appropriate. To assess the progression free survival in these 10 patients, the authors made comparisons to a matched group of concurrent control patients (n=18) who received salvage chemotherapy at recurrence. Group 1 received continuous TTF treatment until disease progression or for a maximum of 18 months. Meanwhile, group 2 (n=10) consisted of patients were at least 4 weeks post radiation therapy, and were treated with TTF combined with maintenance standard chemotherapy. To assess the progression free survival in these patients, authors made comparisons to a matched group of concurrent control patients (n=32) who received chemotherapy only. Group 2 received continuous treatment for an average of one year. Overall survival in all 20 patients was compared to matched historical control data. The studies used varying TTF to treat patients. Kirson et al (2009) used 4 electrodes to deliver 200 kHz, 0.7 V/cm fields, while Salzberg et al (2008) used 4 electrodes to deliver 100-200kHz, 0.7 V/cm fields. Patients in the Salzberg et al (2008) study were allowed to disconnect for up to 60 min/day, while treatment duration was not reported upon by Kirson et al (2009). Kirson et al (2007) did not report the number of electrodes that were used to deliver 200 kHz, 1-2 V/cm fields, but reported that treatment duration was for 18 hours per day.

Safety

Salzberg et al (2008) found that adverse events were mild, and that there were no serious adverse events throughout the study. The only treatment-related adverse event was skin irritation beneath the electrodes. It was unclear whether this side effect was suffered by the one included patient with GBM.

Kirson et al (2009) found that there were no device-related serious adverse events, and the only treatment-related related adverse event was dermatitis. The dermatitis appeared during the second month of treatment in 90% (18/20) of patients and its severity decreased upon use of topical corticosteroids and periodic electrode relocation. The dermatitis persisted for the duration of treatment, resolving completely within days to weeks from the end of treatment. The duration of follow-up was 60 days after termination of therapy for the 10 patients who received TTF alone (group 1). Elevated liver enzymes were consistently reported but were attributed to anti-epileptic drug

usage. Two patients had non treatment-related partial seizures. In the 10 patients who received TTF with chemotherapy (group 2), the combination did not increase chemotherapy-related adverse events.

Kirson et al (2007) indicated that an electric field-based treatment may theoretically cause two types of toxicities. First, TTF could cause cardiac arrhythmias or seizures by stimulating excitable tissues. Secondly, TTF may damage other rapidly dividing, normal cells within the body such as small intestinal mucosa. Kirson et al (2007) noted that these events were not observed in their patients.

Efficacy

Salzberg et al (2008) narratively stated that the patient with GBM did not respond to the TTF treatment, but did not report any effectiveness data. The authors attributed this failure to the short treatment duration of 4 weeks, compared with 12 and 18 months reported in other cohorts. Salzberg et al (2008) did not suggest an optimal treatment time, but noted that better effects for GBM patients were reported in subsequent studies.

Kirson et al (2007) noted that patients treated with TTF exclusively (Group 1 in Kirson et al 2009) had substantially longer median time to disease progression relative to historical controls (26.1 weeks (range 3-124 weeks) vs. 9.5 ± 1.6 weeks). Meanwhile, the progression-free survival at 6 months in TTF patients was 50% vs. $15.3 \pm 3.8\%$ in historical controls. Two TTF patients were still progression free at study closure. The median overall survival of TTF treated patients was 62.2 weeks (range 20.3-124.0 weeks) vs. 29.3 ± 6 weeks in historical controls. Kaplan Meier estimates indicated that the 1-year survival rate for TTF treated GBM patients is 67.5%. The TTF resulted in one complete response (10%) which was tumour free 10 months after treatment ceased. Also, one patient (10%) had a partial response that was still responding 7 months after treatment ceased. Both patients were still progression free after more than 2 years from the commencement of treatment. One patient (10%) had a minimal response while four patients (40%) had stable disease for over 4 months before progressing. No data were supplied for the remaining three patients.

Kirson et al (2009) reported no unique outcomes for group one, but did report upon group two (patients treated with TTF and chemotherapy). The median progression free survival of the combination treated patients was 155 weeks vs. 31 weeks for concurrent controls treated with maintenance chemotherapy alone, 50% (5/10) of group 2 patients were progression free at the time of study publication. The median overall survival of combination treated patients was greater than 39 months vs. about 14.7 months for concurrent controls treated with maintenance chemotherapy alone. At the time of the study publication 80% of combined treatment patients were alive.

COST IMPACT

There is no cost-effectiveness information available on the TTF device. However, TTF may permit cost savings over current treatment modalities through a reduced length of hospital stay.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified from the retrieved material.

OTHER ISSUES

It should be noted that in both studies by Kirson et al, Drs Kirson, Schneiderman, Itzhaki, Mordechovich, Gurvich, Shmueli and Wasserman disclosed that they were employees of NovoCure Ltd. Dr Palti had a minority holding in NovoCure Ltd and for the 2007 study was listed as a member of the company board of directors. Additionally, in the 2007 study Dr Salzberg was listed as a clinical trial consultant to NovoCure Ltd.

SUMMARY OF FINDINGS

The included studies all had low patient numbers and there is paucity of good quality evidence. A larger study, a randomised controlled trial consisting of 236 patients is currently being conducted (Effect of NovoTTF-100A in Recurrent Glioblastoma Multiforme (GBM)). The RCT is expected to be completed in 2009. No serious adverse effects were encountered during TTF treatment in the studies included. However, it is unclear what fields are optimal for treating patients, as there was no standardisation between the studies. Kirson et al (2007) stated that 200 kHz, 1-2 V/cm fields were optimal for treating human gliomas, although no supporting references were provided. None of the studies conducted statistical analysis of their results despite claims of substantial improvement in time to progression and patient survival.

HEALTHPACT ACTION

Based on the limited evidence available, the effectiveness of TTF remains unproven. There is insufficient evidence to conclusively state if TTF has a positive impact upon increased patient survival, as all studies had small patient numbers. Although one study found that time to progression increased with TTF from 9.5 weeks to 26.1 weeks, this outcome was not assessed in a prospective control group. It is recommended that TTF technology is monitored for 24 months, and that any further applications of this technology should be noted.

NUMBER OF STUDIES INCLUDED

Total number of studies	3
Level IV intervention evidence	3

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SEARCH CRITERIA TO BE USED

TTF

Tumour Treating Fields

Tumor Treating Fields