Health Policy Advisory Committee on Technology

Technology Brief

Tumour treating fields for glioblastoma multiforme

May 2012
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This brief was prepared by Mrs Caryn Perera and Mr Heath White from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).
REGISTER ID  WP068

NAME OF TECHNOLOGY  TUMOUR TREATING FIELD (TTF)

PURPOSE AND TARGET GROUP  PATIENTS WITH Glioblastoma Multiforme (GBM)

STAGE OF DEVELOPMENT IN AUSTRALIA

- Yet to emerge
- Experimental
- Investigational
- Nearly established

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- Yes
- No
- Not applicable

INTERNATIONAL UTILISATION

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<thead>
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<th>COUNTRY</th>
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2012 SAFETY AND EFFECTIVENESS ISSUES

Although no peer reviewed studies were identified, a detailed description of the methodology and results of a pivotal study (level II intervention evidence) involving
the NovoTTF-100A System which was submitted to the Food and Drug Administration (FDA) in March 2011 (FDA 2011a) was included. Two conference abstracts relating to the pivotal study were also identified. One abstract was excluded due to data overlap; however, the other provided efficacy data for a specific subgroup with better baseline prognostic characteristics (Ram et al 2010), and was included.

FDA Pivotal Study (FDA 2011a)

This pivotal study designated EF-11 was a randomised multi-centre clinical trial comparing the safety and effectiveness of NovoTTF-100A to the best standard of care effective chemotherapies (BSC) for recurrent glioblastoma multiforme (GBM). The objective of the study was to demonstrate the non-inferiority of NovoTTF-100A compared with BSC.

Twenty-eight US and European centres provided data (range: 1-21 patients per centre), for a total of 237 enrolled patients (120 TTF patients, 117 BSC patients). The randomisation schedule was stratified by clinical site and by patients who did or did not undergo re-operation for their recurrence to avoid an unequal distribution of operated patients between groups. The compounds comprising the BSC varied between centres and consisted of one of the six following chemotherapies: Platinum based chemotherapy (Carboplatin), Nitrosureas (BCNU), Procarbazine, Procarbazine plus lomustine and vincristine (PCV), Temozolomide and bevacizumab (following FDA approval in May 2009).

For the analysis of results, the intent-to-treat population was comprised of six defined groups:

1. TTF patients who never started therapy (n=4)
2. TTF patients who received less than 4 weeks of therapy (n=23)
3. TTF patients treated Per Protocol (n=93)
4. BSC patients who never started therapy (n=26)
5. BSC patients with protocol violations (n=12)
6. BSC patients treated Per Protocol (n=79)

Patients were analysed with regards to efficacy using four different systems: intent-to-treat (ITT – all 6 groups), per protocol (PP – groups 3 and 6), modified ITT-1 (mITT-1 – groups 3, 4, 5 and 6) and modified ITT-2 (mITT-2 – groups 3, 5 and 6). For safety, all patients in groups 2, 3, 5 and 6 (i.e. all patients who had received one or more treatments) were included.

In the ITT population, there were no significant differences between the two groups with regard to baseline demographics such as tumour location, tumour area, reoperation for recurrence status, prior low-grade glioma, age and weight. However, the proportion of patients with frontal tumour position was significantly higher in
the BSC group ($p=0.0018$). In contrast, the Karnofsky Performance Score (KPS) was significantly higher in the TTF group ($p=0.0456$). Patients in the TTF group were treated for an average of 1.6 months longer than patients in the BSC group (no $p$-value provided).

The percentage of patients with adverse events (AE) was similar in the TTF (64/116, 55%) and BSC (54/91, 59%) groups (no $p$-value provided). The rate of severe complications was also similar in the TTF (19/116, 16%) and BSC (17/91, 19%) groups (no $p$-value provided). When AEs were classified by body system, statistically significant differences between the two groups were observed in four of the 19 categories analysed (Table 1).

### Table 1  Adverse events by body system (safety population)

<table>
<thead>
<tr>
<th>System organ class</th>
<th>TTF, n (%)</th>
<th>BSC, n (%)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>9 (7.8)</td>
<td>27 (29.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>5 (4.3)</td>
<td>11 (12.1)</td>
<td>0.0376</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>21 (18.1)</td>
<td>1 (1.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>5 (4.3%)</td>
<td>17 (18.7)</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

TTF: Tumour treating fields; BSC: best standard chemotherapy

The top ten AEs reported for each group are presented in Table 2. In the TTF group there was one death at 42 days; however, this was not directly related to the procedure. No other deaths were reported.
Table 2  Top ten adverse events by procedure (safety population)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>TTF, n (%)</th>
<th>Adverse event</th>
<th>BSC, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16 (13.8)</td>
<td>Nausea</td>
<td>16 (17.6)</td>
</tr>
<tr>
<td>Rash under electrode</td>
<td>16 (13.8)</td>
<td>Diarrhoea</td>
<td>12 (13.2)</td>
</tr>
<tr>
<td>Convulsion</td>
<td>9 (7.8)</td>
<td>Thrombocytopenia</td>
<td>12 (13.2)</td>
</tr>
<tr>
<td>Malaise</td>
<td>9 (7.8)</td>
<td>Malaise</td>
<td>11 (12.1)</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>9 (7.8)</td>
<td>Headache</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Rash (non electrode)</td>
<td>5 (4.3)</td>
<td>Leukopenia</td>
<td>7 (7.7)</td>
</tr>
<tr>
<td>Mental status changes</td>
<td>5 (4.3)</td>
<td>Vomiting</td>
<td>7 (7.7)</td>
</tr>
<tr>
<td>Rash (non electrode)</td>
<td>4 (3.4)</td>
<td>Abdominal pain</td>
<td>7 (7.7)</td>
</tr>
<tr>
<td>Fall</td>
<td>4 (3.4)</td>
<td>Depression</td>
<td>5 (5.5)</td>
</tr>
<tr>
<td>Nervous system disorder AND</td>
<td>3 (2.6)</td>
<td>Convulsion</td>
<td>4 (4.4)</td>
</tr>
<tr>
<td>urinary incontinence</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TTF: Tumour treating fields; BSC: best standard chemotherapy

The primary endpoint of the study was overall survival (OS). There was no significant difference in OS between the TTF and BSC groups, with the exception of the PP and mITT-1 populations, when analysed using the Wilcoxon rank test, which showed that OS was significantly higher following TTF (Table 3).

Table 3  Overall survival (all populations)

<table>
<thead>
<tr>
<th>Population</th>
<th>TTF, median months (95% CI)</th>
<th>BSC, median months (95% CI)</th>
<th>Logrank ($p$)</th>
<th>Wilcoxon ($p$)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>6.3 (5.6-7.8)</td>
<td>6.4 (5.2-7.4)</td>
<td>0.98</td>
<td>0.72</td>
<td>1.0 (0.76-1.32)</td>
</tr>
<tr>
<td>PP</td>
<td>7.8 (6.7-9.5)</td>
<td>6.5 (5.3-7.4)</td>
<td>0.24</td>
<td>0.03</td>
<td>0.82 (0.59-1.14)</td>
</tr>
<tr>
<td>mITT-1</td>
<td>7.8 (6.7-9.5)</td>
<td>6.4 (5.2-7.4)</td>
<td>0.16</td>
<td>0.01</td>
<td>0.81 (0.60-1.09)</td>
</tr>
<tr>
<td>mITT-2</td>
<td>7.8 (6.7-9.5)</td>
<td>6.8 (5.7-8.4)</td>
<td>0.53</td>
<td>0.12</td>
<td>0.90 (0.66-1.23)</td>
</tr>
</tbody>
</table>

TTF: Tumour treating fields; BSC: best standard chemotherapy; ITT: Intention to treat; PP: per protocol; mITT-1: modified intention to treat-1; mITT-2: modified intention to treat-2

In determining the one-year survival rate, patients who were lost to follow-up, or for whom there was no survival information beyond 351 days post-randomisation, were excluded. The one-year survival rate based on the ITT population was similar between the two groups (Table 4). Although the one-year survival rate appeared higher in the TTF group in the PP population, no statistical analyses was provided to determine whether this difference was significant.
Table 4  One-year survival rate (ITT and PP populations)

<table>
<thead>
<tr>
<th>Population</th>
<th>TTF, n/N (%) [95% CI]</th>
<th>BSC, n/N (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>25/114 (21.9) [14.33, 29.53]</td>
<td>23/104 (22.1) [14.14, 30.09]</td>
</tr>
<tr>
<td>PP</td>
<td>25/90 (27.8) [18.52, 37.03]</td>
<td>16/74 (21.6) [12.24, 31.0]</td>
</tr>
</tbody>
</table>

TTF: Tumour treating fields; BSC: best standard chemotherapy; CI: confidence interval; ITT: intention to treat; PP: per protocol

Progression free survival, defined as being alive and progression free six months after treatment based on a composite of clinical and radiological data, was similar between the two groups in the ITT population; however, in the three remaining populations, progression free survival was significantly higher following TTF (Table 5).

Table 5  Progression free survival at 6 months (PFS6) (all populations)

<table>
<thead>
<tr>
<th>Population</th>
<th>TTF, n/N (%) [95% CI]</th>
<th>BSC, n/N (%) [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>22/103* (21.4) [13.44, 29.27]</td>
<td>14/92* (15.2) [7.88, 22.56]</td>
<td>0.1349</td>
</tr>
<tr>
<td>PP</td>
<td>22/84 (26.2) [17.2, 36.9]</td>
<td>9/71 (12.7) [4.94, 20.4]</td>
<td>0.0181</td>
</tr>
<tr>
<td>mITT-1</td>
<td>22/84 (26.2) [17.2, 36.9]</td>
<td>14/92 (15.2) [7.88, 22.6]</td>
<td>0.0357</td>
</tr>
<tr>
<td>mITT-2</td>
<td>22/84 (26.2) [17.2, 36.9]</td>
<td>13/83 (15.7) [8.60, 25.3]</td>
<td>0.0473</td>
</tr>
</tbody>
</table>

*TFS6 was determined for 103/120 TTF and 92/117 BSC patients, the remaining were indeterminate (no tumour assessments at the 6-month visit or later) or censored.

There were no significant differences in time to progression when comparing TTF and BSC in the ITT and mITT-2 populations; however, TTF treatment resulted in significantly longer time to progression in the PP and mITT-1 populations (Table 6). The one death in the TTF group (at 42 days) was censored and excluded from the time to progression analysis.

Table 6  Time to progression (all populations)

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>TTF, median months (95% CI)</th>
<th>n</th>
<th>BSC, median months (95% CI)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>120</td>
<td>9.3 (8.9, 10.1)</td>
<td>117</td>
<td>9.6 (8.6, 12.3)</td>
<td>0.84 (0.62, 1.13)</td>
<td>0.2444</td>
</tr>
<tr>
<td>PP</td>
<td>93</td>
<td>10.1 (9.1, 14.9)</td>
<td>79</td>
<td>9.7 (8.4, 13.1)</td>
<td>0.70 (0.50, 0.98)</td>
<td>0.0359</td>
</tr>
<tr>
<td>mITT-1</td>
<td>93</td>
<td>10.1 (9.1, 14.9)</td>
<td>117</td>
<td>9.6 (8.6, 12.3)</td>
<td>0.69 (0.50, 0.95)</td>
<td>0.0224</td>
</tr>
<tr>
<td>mITT-2</td>
<td>93</td>
<td>10.1 (9.1, 14.9)</td>
<td>91</td>
<td>9.7 (8.7, 13.1)</td>
<td>0.73 (0.53, 1.00)</td>
<td>0.0508</td>
</tr>
</tbody>
</table>

TTF: Tumour treating fields; BSC: best standard chemotherapy; HR: hazard ratio; CI: confidence interval; ITT: intention to treat; PP: per protocol; mITT-1: modified intention to treat-1; mITT-2: modified intention to treat-2
Ram et al (2010)

This conference abstract involved the same patient population as the EF-11 study (FDA 2011), but presented results for a specific subgroup of patients with better prognostic baseline characteristics (KPS ≥ 80%; age ≤ 60 years; first to third recurrence).

No safety data were reported.

In patients treated according to protocol, the median OS time was 7.8 months and 6.1 months in those patients treated with TTF and BSC, respectively (n=185, p=0.01). In the subpopulation with better prognostic baseline characteristics, OS was greater in the TTF group than the BSC group (median 8.8 months versus 6.6 months; n=110, p<0.01). One year survival was 35 and 20 per cent and PFS6 was 25.6 and 7.7 per cent in TTF and BSC patients, respectively (no p-value provided). Quality of life was equivalent or superior in TTF patients; however, no specific data were provided regarding this outcome.

2012 Cost Impact

The manufacturer of the NovoTTF-100A device provided ASERNIP-S with an unpublished study comparing the cost of treatment emergent hospitalisations for TTF patients with that of BSC patients in the EF-11 trial. This analysis demonstrated that there were fewer hospitalisations in the TTF group (29/116, 25.0%) compared with the BSC group (54/91, 59.3%) (p<0.0001). Patients in the BSC group had a higher mean length of stay (8.7 0 ± [SD] 6.52 days) compared with patients in the TTF group (7.07 ± 5.53 days (p=0.23). In addition, patients in the BSC group required more in-hospital procedures (mean 1.57 ± 1.30) compared with patients in the TTF group (1.07 ± 0.84) (p=0.035). The average Centres for Medicare and Medicaid Services diagnosis related group (MS-DRG) cost per hospitalisation was lower in the TTF group ($7,589.10 ± $1,190.74) compared with the BSC group ($8,949.32 ± $3,831.80) (p=0.019). Once the average hospitalisation cost was adjusted to take into account the number of patients in each group, the average MS-DRG cost per patient was $1,897.28 for TTF patients compared with $5,310.58 in the BSC group, an average cost saving of $3,413.31 per TTF patient compared with BSC patients.

No other cost information for the NovoTTF-100A device was identified.

2012 Ethical, Cultural or Religious Considerations

No issues were identified from the retrieved material.
2012 OTHER ISSUES

The NovoTTF-100A device was approved by the FDA in April 2011 for the treatment of adult patients (>22 years) with histologically or radiologically confirmed recurrent GBM in the supratentorial region of the brain after receiving chemotherapy (FDA 2011b). This device is not currently listed on the Australian Register of Therapeutic Goods (ARTG).

Searches of clinical trial registers identified one trial involving TTF which is currently recruiting patients (Table 7).

Table 7 Ongoing and currently recruiting clinical trials involving TTF

<table>
<thead>
<tr>
<th>ClinicalTrials.gov id</th>
<th>Country</th>
<th>Description</th>
<th>Estimated date of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00916409 (currently recruiting, updated March 2012)</td>
<td>32 locations (USA, Austria, Czech republic, France, Germany, Israel, Italy, Switzerland)</td>
<td>A company sponsored RCT comparing NovoTTF-100A plus Temozolomide versus Temozolomide alone in patients with newly diagnosed glioblastoma multiforme. Patients: n=700; Follow-up: 5 years</td>
<td>April 2015</td>
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</table>

This technology is also being used to treat cancers other than GBM, as highlighted in an abstract by Kirson et al (2009), in which TTF was used as an adjunct to pemetrexed to treat 14 patients with non-small cell lung cancer. This study reported an absence of treatment-related serious AEs, a low rate of progressive disease at 12 weeks (3/14, 23%) and a high six-month survival rate (89%); however, the absence of a control in this study did limit the utility of the results.

2012 SUMMARY OF FINDINGS

Based on data provided in the EF-11 pivotal study (FDA 2011a) TTF appears to be non-inferior to BSC for the treatment of recurrent GBM. The treatment is associated with a higher rate of procedure-related AEs in the form of rashes due to electrodes; however, it is associated with a reduced rate of gastrointestinal AEs compared with BSC. In addition, TTF may confer a slight increase in overall survival, progression free survival at six months and time to progression. Importantly however, the mean duration of treatment was higher for the TTF group than the BSC group (4.2 months vs 2.6 months), and the study was sponsored by the manufacturer of the NovoTTF-100A device (NovoCure), thus caution should be taken when interpreting these results. As no data were presented comparing TTF to a no-treatment control group, it is difficult to ascertain what effect the toxicity of chemotherapy played with regards to outcomes of effectiveness. Additional comparative data is required before any definitive conclusions regarding the safety and effectiveness of TTF compared with BSC can be drawn.
2012 HEALTHPACT ASSESSMENT

It is noted that the toxicity associated with chemotherapy may have contributed to the increased incidence of adverse events within the control group. It is recommended that no further research on behalf of HealthPACT be conducted at this time, however, with the publication of further evidence available or if the indications for TTF expand in the future (particularly to non-small cell lung cancer) an update may be commissioned.

2012 INCLUDED STUDIES

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the following link on the HealthPACT website.

Total number of included studies 1
Total number of level II intervention evidence studies 1

2012 REFERENCES


PRIORITISING SUMMARY 2009

REGISTER ID S000096

NAME OF TECHNOLOGY TUMOUR TREATING FIELDS (TTF)

PURPOSE AND TARGET GROUP PATIENTS WITH GLIOBLASTOMA MULTIFORME (GBM)

STAGE OF DEVELOPMENT (IN AUSTRALIA)

- ✓ Yet to emerge
- □ Experimental
- □ Investigational
- □ Nearly established

- □ Established
- □ Established but changed indication or modification of technique
- □ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- □ Yes
- ✓ No
- □ Not applicable

INTERNATIONAL UTILISATION

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<th>COUNTRY</th>
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<td>Limited Use</td>
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2009 IMPACT SUMMARY

The Tumour Treating Fields (TTF) device (NovoCure Ltd., Haifa, Israel) delivers low-intensity, intermediate-frequency, alternating electric fields to treat cancer. The

Tumour treating fields for glioblastoma multiforme: June 2009
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).

**2009 BACKGROUND**

The World Health Organisation (WHO) categorises primary brain tumours based on their origin and histologic appearance. Meningiomas, derived from meningotheelial 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).

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).

2009 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; Salzburg 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.

2009 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.

2009 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 who 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±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.

**2009 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.

**2009 Ethical, Cultural or Religious Considerations**

No issues were identified from the retrieved material.

**2009 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.

**2009 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.

**2009 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.

**2009 Number of studies included**

<table>
<thead>
<tr>
<th>Total number of studies</th>
<th>3</th>
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<tbody>
<tr>
<td>Level IV intervention evidence</td>
<td>3</td>
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**2009 References**


**2009 Search Criteria to be used**

TTF
Tumour Treating Fields
Tumor Treating Fields