

The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation

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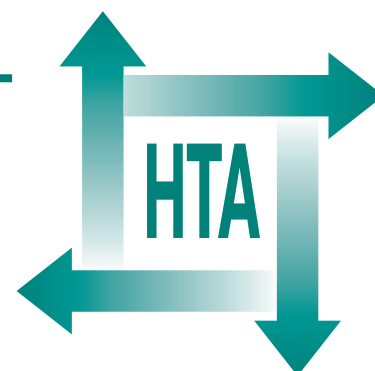
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Executive summary

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Executive summary

Background

High-grade (grade III and IV) gliomas are rare but very aggressive brain tumours. There are about 1700 new cases of high-grade glioma diagnosed annually in England (3.6/100,000). Incidence is highest among those in their early 70s and gliomas are slightly more common in men than women. High-grade gliomas are incurable and treatment aims to increase survival while maintaining quality of life. Median survival is around 1 year for those with grade IV tumours and 2–3 years for those with grade III tumours.

Current treatments include surgery, which may relieve symptoms through debulking and provides material for histological diagnosis. Radiotherapy in addition to surgery has been shown to improve survival over surgery alone. Hitherto, existing approaches to chemotherapy have not conclusively demonstrated a significant survival benefit and may be associated with considerable adverse effects.

Carmustine-impregnated wafers (BCNU-W) are used in newly diagnosed grade III and IV gliomas as adjuvant therapy to surgery and radiotherapy. BCNU-W are inserted into the tumour cavity at the time of operation.

Temozolomide (TMZ) is an oral preparation used in newly diagnosed grade IV gliomas as adjuvant and concomitant therapy to surgery and radiotherapy.

Objectives

This report assesses the clinical and cost-effectiveness of:

- adjuvant BCNU-W with surgery and radiotherapy, compared with surgery and radiotherapy alone
- adjuvant and concomitant TMZ with surgery and radiotherapy, compared with surgery and radiotherapy alone.

Methods

Electronic databases were searched for relevant published research on effectiveness and cost-effectiveness of BCNU-W or TMZ as treatments

for newly diagnosed high-grade glioma. Updated searches were undertaken on 25 August 2005. Included trials were critically appraised for key elements of internal and external validity. Relevant data were extracted and a narrative synthesis of the evidence was produced. Where possible, data on absolute survival at a fixed time point were meta-analysed using a random effects model.

A Markov (state transition) model was developed in Excel to assess the cost–utility of the two interventions. The model compared BCNU-W or TMZ separately with the current standard treatment of surgery and radiotherapy. The simulated cohort had a mean age of 55 years and was modelled over 5 years.

Results: carmustine wafers

Number and quality of studies

Two previous systematic reviews of BCNU-W were identified. One used patient-level data from two randomised controlled trials (RCTs) to assess the effectiveness of BCNU-W. However, few details of methods used to identify studies were given and there was no assessment of study quality. The other was not peer reviewed and gave few details about study quality. We therefore undertook our own systematic review.

Two randomised trials ($n = 32$, $n = 240$) and two observational studies of BCNU-W compared with placebo wafers as adjuvant therapy to surgery and radiotherapy for newly diagnosed high-grade glioma were identified. All the studies were in adults and provided data on 193 patients who had received BCNU-W.

The RCTs appear to use adequate randomisation and allocation concealment methods, although blinding was challenged by differences between the active and placebo wafers. Given the primary end-point of survival, this is unlikely to have an impact; however, it may have influenced identification of the point at which disease progressed, which allowed investigators discretion as to salvage therapy to be instigated. Choice of salvage therapy may also have been influenced by knowledge of first-line treatment. ►

Intention-to-treat analyses were used. However, the statistical analysis reported in the published paper for the main trial was not per protocol and enhances the apparent treatment effect.

There was a slight imbalance in tumour type between the two arms, with more chemosensitive types being seen in the group receiving BCNU-W. Further, although these were defined by a central pathologist, a different central pathologist's assessment suggested that there might be greater imbalance in grade III tumours between the arms.

The RCT findings may not be widely generalisable owing to the exclusion of under 65-year-olds and those with a Karnofsky Performance Status of less than 60.

Summary of risks and benefits

The previous meta-analysis used patient-level data from two RCTs and found a 32% reduction in the risk of death with BCNU-W compared with placebo wafer [unadjusted hazard ratio (HR) 0.68; 95% confidence interval (CI) 0.57 to 0.87; $p = 0.006$].

The largest multi-centre RCT suggested a possible survival advantage with BCNU-W among a cohort of patients with grade III and IV tumours, adding a median of 2.3 months (95% CI -0.5 to 5.1). However, analysis using per-protocol, unstratified methods shows this difference to be not statistically significant (HR 0.77, 95% CI 0.57 to 1.03, $p = 0.08$). Long-term follow-up suggests a significant survival advantage using unstratified analysis. However, this is based on a small number of the original cohort and may be influenced by tail effects. Furthermore, there is overlap in the CIs for median survival time reported for BCNU-W and placebo wafer.

No difference in progression-free survival (PFS) was demonstrated.

Subgroup analysis of those with grade IV tumours also showed no significant survival advantage with BCNU-W (HR 0.82, 95% CI 0.55 to 1.11, $p = 0.20$, unstratified analysis).

The only adverse effect reported in significantly more of those in the treatment arm was intracranial hypertension. However, the control arm used a placebo wafer implant and it is not clear if this wafer itself may lead to increased adverse effects.

Summary of costs

It is estimated that the cost of surgery and radiotherapy, with follow-up, treatment of adverse

effects and end of life care is around £17,000 per patient. Treatment with BCNU-W adds an additional £6600.

Summary of cost-effectiveness

Across the modelled cohort of 1000 patients, use of BCNU-W costs an additional £6.6 million and confers an additional 122 quality-adjusted life-years (QALYs). On average, that is £6600 per patient for 0.122 QALYs (6.3 quality-adjusted life-weeks). The base-case incremental cost-effectiveness ratio (ICER) is £54,500/QALY.

Sensitivity analyses

One-way sensitivity analysis showed that the model is particularly sensitive to:

- median overall survival benefit with treatment
- median PFS benefit with treatment
- quality of life (utility) for 'stable' disease
- quality of life (utility) for 'progressive' disease
- cost of BCNU-W.

These were investigated through one-way threshold analyses. In order for the ICER for BCNU-W to become £30,000/QALY, median survival benefit would need to increase to 18 weeks (from the 10 weeks modelled from trial data), or PFS to 8 weeks (from none in the modelled trial data). As utility values have an upper limit of one, it was not possible for the ICER to be estimated below £30,000. However, if utility values are lowered, which seems possible as the estimates obtained for the model are high, then the ICER rises, slightly for lower utility values in stable disease and dramatically for lower utility values in the progressive disease state.

In probabilistic sensitivity analyses, BCNU-W was not cost-effective in 89% of the simulations assuming a willingness to pay threshold of £30,000/QALY. In 15% of simulations, BCNU-W was dominated (i.e. did more harm than good, conferring fewer QALYs at greater cost). The cost-effectiveness acceptability curve (CEAC) suggests that it is unlikely to be the most cost-effective option at normal levels of willingness to pay (11% probability at £30,000/QALY), only becoming likely to be the most cost-effective option at much higher levels of willingness to pay (50% probability at £55,000/QALY).

Results: temozolomide

Number and quality of studies

No previous systematic reviews of TMZ in newly diagnosed high-grade glioma were identified. ►

Two RCTs ($n = 130$, $n = 573$) and two observational studies were included, giving evidence for 429 adult patients receiving TMZ. Patients in the RCTs were randomised up to 6 weeks post-surgery, which will have excluded patients with surgical complications and those who died soon after surgery. The trials were open label but the main outcome, survival, is unlikely to be affected by this. Detection bias in measuring PFS, however, is possible. Methods of randomisation were not detailed in either trial.

The trials were limited to those with grade IV tumours. However, 7–8% were re-categorised as having grade III tumours. No analysis restricted to confirmed grade IV tumours was undertaken. It is possible that small numbers of more chemosensitive tumours may have impacted on findings. Currently, TMZ is licensed for use in those with newly diagnosed grade IV gliomas only.

The RCTs may not be widely generalisable owing to the exclusion of those with lower performance status and, in the larger RCT, those older than 70 years.

Summary of risks and benefits

TMZ provides a small but statistically significant median survival benefit of 2.5 months (95% CI 2.0 to 3.8), giving an HR of 0.63 (95% CI 0.52 to 0.75, $p < 0.001$).

At 2 years, 26.5% of patients treated with TMZ were alive compared with 10.4% of those in the control arm.

Median PFS is also enhanced with TMZ, giving a median 1.9 months' advantage (95% CI 1.4 to 2.7, $p < 0.001$).

No analysis of the subgroup of patients with confirmed grade IV tumours was undertaken.

Subgroup analysis of patients by O^6 -methylguanine-DNA methyltransferase (MGMT) activity showed a significant treatment advantage for those with reduced MGMT activity but not for those with normal activity. However, it should be noted that this analysis was based on a selected sample of patients and that the test used has proved difficult to replicate. A median gain of 6.4 (95% CI 4.4 to 9.5) more life-months is seen with TMZ among those with reduced MGMT, giving an HR of 0.51 ($p < 0.007$). PFS is increased by a median of 4.4 months (95% CI 1.2 to 6.3), giving an HR of 0.48 ($p = 0.001$).

It is possible that the overall trial results are being driven by the chemosensitive tumours, as indicated

either by grade III tumour types or possibly those with reduced MGMT activity described above.

Summary of costs

The model shows a cost per patient for being treated with surgery, radiotherapy and including adverse effects of treatment and end of life care of around £17,000 per patient. TMZ in the adjuvant and concomitant phase adds an additional cost of around £7800.

Summary of cost-effectiveness

Across the modelled cohort of 1000 patients, use of TMZ costs an additional £7.8 million and confers an additional 217 QALYs. For the average patient this is £7800 for an additional 0.217 QALYs (11 quality-adjusted life-weeks). The base-case ICER is £36,000/QALY.

Sensitivity analyses

The model is particularly sensitive to:

- median overall survival benefit
- median PFS benefit
- quality of life (utility) with 'stable' disease
- quality of life (utility) with 'progressive' disease
- cost of TMZ.

These were investigated through one-way threshold analyses. In order for the ICER for TMZ to be £30,000/QALY, median survival benefit would need to increase to 22 weeks (from the 10.8 weeks modelled from trial data), or PFS to 14 weeks (from 8.2 weeks in the modelled trial data). As utility values have an upper limit of one, it was not possible to estimate an ICER of below £30,000/QALY. However, if utility values are lowered, which is possible as the estimates obtained for the model seem high, then the ICER rises slightly for utility in progressive disease and dramatically in the stable disease state.

Probabilistic sensitivity analyses shows that TMZ was not cost-effective in more than 77% of the simulations. The CEAC suggests that there is a small chance (23%) that TMZ is the most cost-effective option at a willingness to pay level of £30,000/QALY, only rising to be more cost-effective than no TMZ at higher levels (50% probability at £35,000/QALY).

Discussion

Strengths and weaknesses of analyses and uncertainties

The systematic review is based on few trials, which are variable in quality.

No studies in children were identified.

No previous cost–utility assessment relevant to the UK exists for either drug. Extensive sensitivity analyses were undertaken in the PenTAG model.

Utility values obtained using the Value of Health Panel are high. Sensitivity analysis showed that lower utilities increased the ICER.

The impact of specific tumour type needs to be further explored to identify which, if any, patients are likely to benefit from chemotherapy.

Generalisability of findings

The exclusion criteria of the included trials means that a younger, fitter population is studied than that found in normal clinical practice.

For both drugs, results may be driven by a small number of patients with chemosensitive tumours. The BCNU-W analysis shows no survival advantage for patients with grade IV tumours, and the TMZ trial does not provide subgroup analysis in patients with confirmed grade IV tumours.

It is not known how delays in receiving radiotherapy in the NHS impact on patient survival and what impact this has on the generalisability of these results.

Conclusions

BCNU-W has not been proven to confer a significant advantage in survival for patients with grade III tumours when treated with the drug, compared with placebo. There does not appear to be a survival advantage for patients with grade IV tumours. No increase in PFS has been shown.

Limited evidence suggests a small but significant advantage in both overall survival and PFS with TMZ among a mixed population with grade IV and grade III (7–8%) tumours. However, it remains unclear whether this is true in grade IV tumours alone.

On the basis of best available evidence, we consider that neither BCNU-W nor TMZ is likely to be considered cost-effective by NHS decision-makers. However, data for the model were drawn from limited evidence of variable quality.

Tumour type is clearly important in assessing patient prognosis with different treatments. Grade IV tumours are commonest and appear to have least chance of response. There were too few grade

III tumours included to carry out a formal assessment, but they appear to respond better and drive results for both drugs. Future use of genetic and biomarkers may help identify subtypes which will respond, but current licensing indications do not specify these.

Further research

Further research is suggested into the following areas:

- The effectiveness and cost-effectiveness of BCNU-W have not been proven. Further research is needed to investigate these in specific populations.
- Evidence for effectiveness of TMZ is limited. In particular, it is not known whether patients with confirmed grade IV tumours (the licensed indication) benefit from TMZ. Further research should investigate this.
- The emerging work on genetic markers suggests that grade III and IV tumours can also be classified according to genetic subtype with strong implications for their responsiveness to chemotherapy. Further research on refining these categories/subtypes, and their identification, is required, followed by studies that explore the feasibility of using these markers to inform treatment decisions for individual patients in standard clinical settings.
- Future trials should seek to compare different chemotherapy regimens directly rather than against placebo, and also seek to specify and evaluate sequences of treatment, including second- and third-line treatments, more closely.
- Future trials should also seek to clarify aspects of quality of life that matter most to patients and to characterise the changes in quality of life that occur during stable and progressive disease. More explicit consideration of carer views should also be sought.
- It is important to explore the value that patients put on small absolute survival advantages compared with the disadvantages of treatment requirements; these advantages may be valued differently by those with terminal illness than others in the population.

Publication

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NIHR Health Technology Assessment Programme

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