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Title **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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Aim

To assess the clinical and cost effectiveness of adjuvant carmustine wafers (BCNU-W) and also of adjuvant and concomitant temozolomide (TMZ), compared to surgery with radiotherapy.

Conclusions and results

A large multicenter randomized controlled trial (RCT) suggested a possible survival advantage with BCNU-W among a cohort of patients with grade III and IV tumors, adding a median of 2.3 months. Analysis using per-protocol, unstratified methods shows this difference to be not statistically significant. Long-term followup suggests a significant survival advantage. The cost of surgery and radiotherapy, with followup, treatment of adverse effects, and end-of-life care is estimated to be around GBP 17 000 per patient. Treatment with BCNU-W adds GBP 6600. A modeled cohort of 1000 patients suggests BCNU-W costs an additional GBP 6.6 million and confers an additional 122 quality-adjusted life-years (QALYs). On average, that is GBP 6600 per patient for 0.122 QALYs. The base-case incremental cost-effectiveness ratio (ICER) is GBP 54 500/QALY. In probabilistic sensitivity analyses, BCNU-W was not cost effective in 89% of the simulations, assuming a willingness-to-pay threshold of GBP 30 000/QALY. It is unlikely to be the most cost-effective option at normal levels of willingness to pay.

TMZ provides a small but statistically significant median survival benefit of 2.5 months, giving a hazard ratio (HR) of 0.63. At 2 years, 26.5% of patients treated with TMZ were alive compared to 10.4% of those in the control arm. Median progression-free survival (PFS) is also enhanced with TMZ, giving a median 1.9 months' advantage. A median gain of 6.4 more life-months is seen with TMZ among those with reduced O6-methylguanine-DNA methyltransferase (MGMT), giving an HR of 0.51 ($p<0.007$). PFS is increased by a median of 4.4 months, giving an HR of 0.48 ($p=0.001$). The model shows a cost per patient treated with surgery, radiotherapy, and including adverse effects of treatment and end-of-life care of around GBP 17 000 per patient. TMZ in the adjuvant and concomitant phase adds around GBP 7800. Across the modeled cohort of 1000 patients, use of TMZ costs an additional GBP 7.8 million and confers an additional 217 QALYs. For the average patient this is GBP 7800 for an additional 0.217 QALY. The base-case ICER is GBP 36 000/QALY. Probabilistic sensitivity analysis shows that TMZ was not cost effective in 77% of the simulations. The cost-effectiveness acceptability curve (CEAC) suggests a 23% chance that TMZ is the most cost-effective option at a willingness-to-pay level of GBP 30 000/QALY, rising to be more cost effective than no TMZ at slightly higher levels (50% probability at GBP 35 000/QALY).

Recommendations

BCNU-W has not shown a significant advantage in survival for patients with grade III tumors when treated with the drug, compared to placebo, nor a survival advantage for patients with grade IV tumors. Limited evidence suggests a small (significant) advantage in both overall survival and PFS with TMZ in a mixed population with grade IV and III (7%–8%) tumors. There does appear to be a survival advantage for patients with grade IV tumors. Neither BCNU-W nor TMZ is likely to be considered cost effective by NHS decision makers (based on limited evidence of variable quality).

Methods

See Executive Summary link above.

Further research/reviews required

Future use of genetic and biomarkers may help identify subtypes that will respond, but current licensing indications do not specify these. Further research is suggested into the effectiveness of these drugs and other areas, eg, genetic markers, chemotherapy, and patient and carer quality of life.

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