Temozolomide for recurrent malignant glioma

Rapid review

The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review

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Executive summary

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Executive summary

Background

Brain tumours make up approximately 1.5% of all malignant neoplasms in adults in England and Wales. About 50–60% of brain tumours are malignant gliomas (approximate incidence rate 3–4 per 100,000 per year), most of which are anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM).

AA and GBM are the highest grades of astrocytoma and are not considered curable. Patients can suffer from a range of symptoms and impairments that can have a profound effect on quality of life (QoL), as well as their ability to work and to care for themselves.

Following diagnosis and primary treatment (usually with surgery, radiation and corticosteroids), most patients will experience a tumour recurrence. Subsequent treatment options are limited and palliative. In the UK, approximately 30% of people with GBM or AA currently receive chemotherapy on relapse. Median survival time from initial diagnosis is 27–36 months for AA and approximately 11–12 months for GBM. The average cost of treatment is approximately £11,900 per patient at a cost to the NHS in the region of £25 million per annum.

Aim of the review

To provide a rapid review of the effectiveness and cost-effectiveness of temozolomide (TMZ) in the treatment of primary malignant brain tumours (AA and GBM).

Methods

An extensive literature search was conducted using databases including the Cochrane Library, MEDLINE, EMBASE, CANCERLIT, Toxline, ISI Web of Science, BIOSIS, and PreMEDLINE. Searches were conducted using the generic and trade names for the drug to locate all available clinical trials involving the drug and its adverse effects. The primary inclusion criteria were that the study should evaluate TMZ in malignant glioma patients, be a randomised controlled trial (RCT) or include more than 45 patients, and include effectiveness and/or QoL outcome measures. The quality of included studies was assessed using two quality assessment tools: the scale developed by Jadad was used to assess RCTs, and all studies were also assessed using a shortened version of a check-list developed for an epidemiological review.

Two reviewers independently assessed studies for inclusion, extracted data from the studies and evaluated the quality of each included study. Disagreements were resolved through discussion.

Due to the paucity of data, a narrative rather than a statistical synthesis of the effectiveness data was undertaken.

A simple model was used to explore the cost-effectiveness of TMZ in comparison with best alternative care. Estimates of effectiveness and QoL (utilities) used in the model were obtained from the literature review. Direct costs relating to incremental cost of TMZ administration and follow-up were estimated. Both cost-effectiveness and cost–utility analyses were performed. All parameters used in the model (effectiveness, QoL and costs) were varied in a sensitivity analysis.

Results

Quantity and quality of available evidence

Nine full reports of seven effectiveness studies were identified for inclusion: one RCT and six uncontrolled studies (one of which was available only in abstract format). The RCT was a multicentre, open-label study of TMZ versus procarbazine, which did not report the method of randomisation used and was neither single- nor double-blinded. The comparator chosen is not commonly used in the UK, limiting the generalisability of the trial results. The remaining studies suffer from all of the biases inherent in non-comparative studies, further limiting the conclusions that can be drawn. Furthermore, most of the included studies applied performance status and life expectancy criteria such that they may have recruited somewhat

healthier patients than would be considered eligible in routine practice.

Effectiveness of TMZ

Although the quality of the available evidence is relatively poor, gliomas do appear to show some response to TMZ. The main benefit in patients with GBM, demonstrated in one RCT and one relatively large uncontrolled study, is an increase (13%) in the estimated proportion of patients remaining progression-free at 6 months and a significant increase in median progression-free survival (PFS) of approximately 4 weeks. No significant overall survival advantage was found in comparison with procarbazine.

For patients with AA, one large uncontrolled study suggests some improvement in both PFS and possibly in survival. The magnitude of any benefit in AA is difficult to quantify due to the lack of a within-study comparison of TMZ with an alternative treatment regimen.

Subgroup analyses provide some suggestion of better outcomes in patients who were chemotherapy-naïve, although patient numbers were small. As adjuvant chemotherapy is not commonly used in the UK, these results may be more applicable to the UK population, but require confirmation in large RCTs.

TMZ appears to cause few serious adverse effects, with vomiting usually well controlled by prophylactic anti-emetic regimens. Some clinicians believe that toxicity, particularly myelosuppression, is more predictable with TMZ and this has been noted as one of the advantages of this drug over others. Empirical evidence is, however, limited.

Quality of life

One of the major claims of benefit from TMZ is that conferred on health-related QoL. There is some evidence that QoL is improved from recurrence until the point of disease progression for patients with GBM or AA.

Cost-effectiveness and cost–utility

On the basis of current evidence, which suggests only an increase in PFS, the cost per progression-free week gained lies between £700 and £1000 for AA and GBM, respectively. If a moderate impact on QoL alongside a moderate increase in PFS is assumed, the cost per quality-adjusted life-year (QALY) gained for patients with either GBM or AA is around £40,000 (for a QALY gain of 0.09 and 0.20, respectively). These estimates are highly speculative and reflect the adoption of a 'best-case' outlook.

Limitations of the analyses

The weaknesses of the primary studies seriously affect the strength of the conclusions that can be drawn about the effectiveness and cost-effectiveness of TMZ. Only one RCT is available, the remainder of the evidence to date coming from relatively small uncontrolled studies. Most of the studies were conducted in patients with a relatively favourable prognosis compared with those who might be eligible to receive TMZ in routine care and the RCT did not use a comparator commonly used in the UK. These factors limit the generalisability of the results to UK practice.

These factors also impact on the reliability of the results of the economic analyses. First, the most appropriate analysis for a UK scenario would be to compare TMZ to a current standard treatment such as the chemotherapy combination of procarbazine, CCNU and vincristine (PCV). Although it was possible to obtain cost estimates for these two regimens, there are no effectiveness data available that directly compare these two treatment options. Therefore, alternative sources of data were used to estimate the results that might be seen with PCV.

Secondly, no reliable utility data were available. An estimate of the utility experienced at recurrence was provided by studies that used psychometric questionnaires to assess QoL. The accuracy of this estimate may be questioned, but it did at least allow some exploration of the effect of TMZ on QoL while progression-free, and the resulting impact on the cost–utility of the treatment.

Because there was a further lack of data on utilities experienced following progression of disease, the deterioration in QoL during this phase of disease was assumed to be linear. In practice, it may be more likely that the utility curve would dip sharply and then level off, in which case the assumptions made are likely to have over-estimated the value of life following progression and any hypothesised increase in survival.

Finally, only the direct costs of treatment at recurrence were considered. No data were available on the cost of treatment at the end of life, and any potential impact on such costs from the use of TMZ. It may be that TMZ introduces some cost

savings by shortening the period of time from progression to death, but this was not possible to evaluate.

Conclusions

It is the authors' opinion that the evidence is currently too weak for firm conclusions to be drawn. However, a speculative economic model suggests some indication of benefit from TMZ, at a cost per QALY gained of around £40,000. The incidence of malignant glioma is relatively low and the overall budgetary impact for the NHS as a whole is in the order of £4 million per annum.

The true effectiveness of TMZ for recurrent glioma will only be determined by large RCTs comparing TMZ with best alternative care in a wider population of patients (i.e. not limited to those with favourable prognosis), with separate pre-planned analyses for those who are chemotherapy-naïve.

Publication

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