Economic evaluation of temozolomide in the treatment of recurrent glioblastoma multiforme

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use temozolomide (TMZ), an oral alkylating agent, for the treatment of glioblastoma multiforme (GBM) and anaplastic astrocytoma. The treatment with TMZ was given during 5 days in 28-day cycles at oral dosages of 150 - 200 mg/m2 per day.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with malignant gliomas who had undergone primary treatments such as surgery and radiotherapy before first relapse.

Setting
The setting was a hospital. The economic study was carried out in Finland.

Dates to which data relate
The effectiveness data were derived from studies published between 2000 and 2003. The resource use data were gathered from 1998 to 2000. The price year was 2001.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and experts’ opinions.

Modelling
A Markov model was constructed to model the disease process of malignant gliomas. The model included three health states. These were "progression free" (time from the beginning of chemotherapy to the second relapse), "progression" (time from the second relapse to death) and "death. Transitions back to the progression-free state from the progression state were not considered possible. The length of a cycle was 1 month. The model was run until all patients were transferred to the "death" state. A simplified structure of the model was reported.

Outcomes assessed in the review
The outcomes assessed in the model were treatment efficacy, in terms of the probability of disease progression and the probability of death during 1 month. The probabilities of adverse events with TMZ and PCV were also reported.
Study designs and other criteria for inclusion in the review
A systematic review of the literature was undertaken to identify primary studies providing data on treatment efficacy. The following inclusion criteria were considered:

- disease and disease stage had to be GBM at first relapse;
- the results had to be presented as overall survival (OS) or 6-month OS rate, or progression-free survival (PFS) or 6-month PFS;
- chemotherapy had to involve either TMZ (≥ 100 mg/m² per day) or some part of PCV chemotherapy.

The included studies led to a total adjusted sample size of 111 individuals for TMZ and 113 for PCV.

Sources searched to identify primary studies
PubMed was searched in June 2003 for relevant articles. The keywords used were "(PCV OR temozolomide) AND (GBM OR glioblastoma)".

Criteria used to ensure the validity of primary studies
The quality of the primary estimates was assessed in terms of pertinence and validity, as described in an earlier study.

Methods used to judge relevance and validity, and for extracting data
Study researchers independently assigned scores of pertinence and validity. In unclear cases, a consensus decision was made.

Number of primary studies included
Of the 109 primary studies initially identified, 23 were considered relevant but only 5 met the inclusion criteria and were included in the review.

Methods of combining primary studies
A meta-analysis was used to combine primary estimates, weighting each study by its quality. The statistical approach was accurately described.

Investigation of differences between primary studies
Not stated.

Results of the review
The probability of disease progression during 1 month with TMZ and PCV were reported as beta distributions with the following parameters:

- for TMZ, alpha = 22.33 and beta = 89.00;
- for PCV, alpha = 27.93 and beta = 85.70.

The probability of death during 1 month with TMZ and PCV were reported as beta distributions with the following parameters:

- for TMZ, alpha = 95.63 and beta = 15.70;
for PCV, \( \alpha = 97.35 \) and \( \beta = 16.27 \).

TMZ was thus associated with a lower probability of progression and a slightly lower probability of death.

An average of 6.06\% of patients that received TMZ and 16.13\% of patients that received PCV experienced severe nausea or vomiting.

**Methods used to derive estimates of effectiveness**

Since there was no preference-based information directly available on the quality of life of patients with high-grade gliomas after the first and second relapse, quality of life estimates were derived from six leading neuro-oncologists using a visual analogue scale. The neuro-oncologists were not informed of the chemotherapies being compared. The utilities for health states were defined independently of the treatment.

**Estimates of effectiveness and key assumptions**

The mean utility values (standard deviation, SD) were:

- \( \text{Stage 1} (45\text{-year-old glioma patient who is having their first surgery}), \) 0.41 (SD=0.06)
- \( \text{Stage 2} (\text{same patient after surgery and radiotherapy (60 Gy) on the tumour area; the symptoms have recurred}), \) 0.43 (SD=0.10)
- \( \text{Stage 3} (\text{chemotherapy alternative TMZ}), \) 0.31 (SD=0.07)
- \( \text{Stage 4} (\text{chemotherapy alternative PCV}), \) 0.14 (SD=0.09)
- \( \text{Stage 5} (\text{progression}), \) 0.14 (SD=0.09)

**Measure of benefits used in the economic analysis**

The summary benefit measures used were the expected life-months, progression-free life-months and quality-adjusted life-years (QALYs). These were derived using a modelling approach. The benefits were discounted at an annual rate of 5%.

**Direct costs**

The cost analysis was performed from the perspective of the Finnish health care payer. It included oncologist visits, hospital stay, laboratory visits, magnetic resonance imaging scans, TMZ chemotherapy, anti emetics related to TMZ chemotherapy, PCV chemotherapy, anti emetics related to PCV chemotherapy and travel costs. Resource use associated with the post chemotherapy state was assumed to be equal in both groups and was not included in the analysis. The unit costs were presented separately from the quantities of resources used for most items. Resource use was derived from hospital databases. Data on TMZ came from a cohort of 16 high grade GBM patients treated with TMZ at Helsinki University Central Hospital and Turku University Hospital between 1998 and 2000. Resource consumption associated with PCV treatment was gathered from a cohort of 10 patients treated at Turku University Hospital between 1998 and 2000. The costs came from Finnish health service unit costs and official medicine prices. Only the cost of lomustine was derived from a hospital database. Costs occurring during a 1 year timeframe were discounted at an annual rate of 5%. The price year was 2001.

**Statistical analysis of costs**

The costs were assigned probabilistic distributions that were used in the sensitivity analysis. In particular, gamma distributions were assigned to oncologist visits, laboratory tests and hospital days.

**Indirect Costs**
The indirect costs were not taken into consideration because they were not relevant to the perspective adopted in the study.

**Currency**
Euros (Euro).

**Sensitivity analysis**
A Monte Carlo simulation was performed to address the issue of uncertainty in the model inputs. Beta distributions were assigned to transition probabilities and utility values. Cohorts of 1,000 patients were run through the model 1,000 times. The results were presented using cost effectiveness acceptability curves, which represent the probability of cost effectiveness as a function of willingness to pay per additional unit of effectiveness.

**Estimated benefits used in the economic analysis**
The mean OS was 12.07 (median 11.92) months with TMZ and 11.11 (median 10.96) months with PCV.

The mean PFS was 4.74 (median 4.61) months with TMZ and 3.69 (median 3.59) months with PCV.

The mean quality-adjusted life months were 2.98 with TMZ and 2.14 with PCV. This led to mean QALYs of 0.25 with TMZ and 0.18 with PCV.

**Cost results**
The mean costs were Euro35,380 with TMZ and Euro33,107 with PCV.

**Synthesis of costs and benefits**
The costs and benefits were combined by calculating cost-effectiveness and cost-utility ratios.

The incremental cost per life-year gained with TMZ in comparison with PCV was Euro28,404.

The incremental cost per progression-free life-year gained with TMZ in comparison with PCV was Euro25,980.

The incremental cost per QALY gained with TMZ in comparison with PCV was Euro32,471.

The acceptability curve showed that the probability of TMZ being more cost-effective than PCV was greater than 60% at all values of willingness to pay per life-month gained in excess of Euro5,000.

The probability of TMZ being more cost-effective than PCV was greater than 75% at all values of willingness to pay per progression-free life-month gained in excess of Euro10,000. It was about 85% at all values of willingness to pay per quality-adjusted life-month gained in excess of Euro20,000.

Using data relevant to the Finnish setting, it was estimated that the population expected value of prefect information (EVPI) was approximately Euro4.1 million, which represents the maximum value of acquiring information. If the fixed costs of proposed research are below this EVPI value, additional research is potentially cost-effective.

**Authors' conclusions**
Temozolomide (TMZ) was a cost-effective treatment for patients with glioblastoma multiforme (GBM).

**CRD COMMENTARY - Selection of comparators**
The authors justified the choice of the comparators, which appear to have been appropriate since PCV represented the standard treatment before the introduction of TMZ into the market. You should decide whether they are valid.
comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from a review of the literature, the methods and conduct of which were extensively described. For example, both the search strategy and inclusion criteria were reported. Some characteristics of the primary studies included in the review were reported. The methods used to pool the primary estimates and then address the issue of uncertainty were provided. Finally, the quality of each study was accurately assessed, and studies with higher validity contributed more to the final estimate of efficacy. The utility values were derived from a sample of experts, owing to the lack of published evidence, and the approach used to derive robust and unbiased estimates was reported. Utility weights, as well as treatment efficacy parameters, were extensively investigated in the sensitivity analysis. Uncertainty in clinical parameters and utility values was satisfactorily addressed in the probabilistic sensitivity analysis.

**Validity of estimate of measure of benefit**
Both disease-specific and more generalisable benefit measures were used in the economic analysis. While PFS is comparable only with the benefits of similar interventions, the use of survival and QALYs would enable comparisons with the benefits of other health care interventions. Extensive information on the methods used to elicit the utility values was provided. Discounting was applied.

**Validity of estimate of costs**
The cost analysis was consistent with the perspective adopted in the study. Extensive information on the unit costs, quantities of resources used, price year and source of the data was provided, thus enhancing the possibility of replicating the results of the analysis in other settings and facilitating reflation exercises in other settings and time periods. The costs reflected national tariffs, which were the costs relevant from the perspective of the national health care payer. The uncertainty surrounding the cost estimates was addressed in the probabilistic sensitivity analysis.

**Other issues**
The authors noted that, owing to the scarcity of published studies on GBM treatments, it was difficult to compare their results with those from other studies. However, the differences between the current study and a prior UK study were highlighted. The issue of the generalisability of the study results to other settings was not explicitly addressed, but the issue of uncertainty was extensively addressed in the probabilistic sensitivity analysis. The authors noted some limitations of their analysis. First, the resource use data were collected from only two university hospitals, which might reduce the generalisability of the cost results because of variability in cost estimates across centres. Second, the primary studies providing data on treatment efficacy included small samples of patients. Third, the utility values were elicited from a sample of experts who may be expected to assign ratings for health states lower than those usually assigned by patients. The same issue arises with the use of visual analogue scale scores, these usually being characterised by lower scores in comparison with standard questionnaires.

**Implications of the study**
The study results appear to support the use of TMZ for the treatment of high-grade glioma patients. The results of the EVPI could help prioritise further research.

**Source of funding**
Supported by Schering-Plough, Finland Oy.

**Bibliographic details**
PubMedID
16097842

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Antineoplastic Agents, Alkylating /economics /therapeutic use; Antineoplastic Combined Chemotherapy Protocols /economics /therapeutic use; Brain Neoplasms /drug therapy; Cost-Benefit Analysis; Dacarbazine /analogs & derivatives /economics /therapeutic use; Finland; Glioblastoma /drug therapy; Humans; Recurrence

AccessionNumber
22005008325

Date bibliographic record published
31/03/2006

Date abstract record published
31/03/2006