Scottish Medicines Consortium

temozolomide 5, 20, 100 and 250mg capsules (Temodal®)
Schering Plough UK Ltd No. (244/06)

New indication: for the treatment of newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as monotherapy treatment.

10 February 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

temozolomide (Temodal®) is not recommended for use within NHS Scotland for the treatment of newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and subsequently as monotherapy.

In the pivotal phase lll study, an increase in median survival was seen in patients with good performance status and favourable prognostic markers. The benefit seems to increase over time with 16% more patients surviving at 24 months in the temozolomide plus radiotherapy group rather than the radiotherapy alone. However, the economic case has not been demonstrated.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Temozolomide 5, 20, 100 and 250mg capsules (Temodal®)

Indication

For the treatment of newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and subsequently as monotherapy treatment.

Dosing information

In combination with focal radiotherapy, the concomitant phase, at a dose of 75mg/m^2 daily for 42 days followed four weeks after completing the concomitant phase by up to six cycles of temozolomide monotherapy of 150-200mg/m^2 once daily on days 1 to 5 of a 28 day cycle.

UK launch date

10 June 2005

Comparator medications

Surgery with or without radiotherapy; surgery with radiotherapy combined with antineoplastic agents such as a nitrosourea-based regimen eg. procarbazine, carmustine and vincristine (PVC); best supportive care plus steroids with or without anticonvulsants.

Cost of relevant comparators

Drug	Dose	Cost per course of treatment*
Temozolomide concomitant plus monotherapy	**75mg/m^2 daily for 42 days with focal radiotherapy plus 150mg/m^2 daily as monotherapy, days 1 - 5 of a 28 day cycle followed by 200mg/m^2 daily, days 1 - 5 of a 28 day cycle for five cycles or 150mg/m^2 daily, days 1-5 of a 28 day cycle for five cycles if dose escalation not achieved.**	**£9 530- £11 090**
Carmustine implant	Up to 8 implants	up to £5203
PCV	Procarbazine 100mg/m^2/day on days 1-10 Lomustine 100mg/m^2 on day 1 Vincristine 1.5mg/m^2 on day 1 (maximum 2mg) *Up to 12 cycles*	up to £1730 for 12 cycles
PCV	Procarbazine 60mg/m^2/day on days 8-21 Lomustine 110mg/m^2 on day 1 Vincristine 1.4mg/m^2 on day 8 and 29 (maximum 2mg) *Given every 6-8 weeks for up to 1 year.*	up to £1306 for 8 cycles

*Costs from BNF Edition 50 and based on body surface area of 1.8m^2, where applicable.

Summary of evidence on comparative efficacy

The majority of brain tumours are gliomas, which develop from the glial cells that support the nerve cells of the brain. Among high-grade gliomas, glioblastoma multiforme (GBM) is the most common primary brain tumour in adults and is highly malignant, infiltrating the brain extensively. The WHO grades GBM as a grade IV astrocytoma. Temozolomide is a prodrug which at physiological pH undergoes non-enzymatic hydrolysis, rapidly converting to the active metabolite. The cytotoxicity of temozolomide is due primarily to alkylation of DNA. It crosses the blood brain barrier, with the concentration in the cerebral spinal fluid 20-40% of that in plasma.

A preliminary open-label, phase ll study in 64 newly diagnosed GBM patients determined the tolerability and efficacy of concomitant temozolomide plus radiotherapy followed by temozolomide monotherapy. Temozolomide was well tolerated and the overall survival in the intention-to-treat-population was 16 months (95%CI, 11-21 months).

The pivotal, open-label, randomised, phase lll study was conducted under the auspices of the European Organisation for Research and Treatment of Cancer (EORTC) in 15 countries. A total of 573 patients with histologically confirmed GBM were randomised equally to either radiotherapy alone (fractionated focal irradiation in daily fractions of 2 Gy given for 5 days per week for 6 weeks [total 60 Gy]), or radiotherapy plus concomitant temozolomide (75 mg/m^2 per day for 42 days, from the first day of radiotherapy to the last day but no longer than 49 days), followed, after a break of 4 weeks by temozolomide monotherapy (150 to 200 mg /m^2 on days 1 to 5 of a 28 day cycle, for up to 6 cycles). Over 85% of patients had a WHO performance status of 0 (fully active, able to carry on all pre-disease performance without restriction) or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), and >80% had undergone de-bulking surgery within 6 weeks of study entry. Patients were randomised within 6 weeks of histological diagnosis and the assigned treatment had to begin within 1 week of randomisation. Salvage chemotherapy (including with temozolomide) was provided for both treatment arms upon disease progression. The primary endpoint for this trial was overall survival as measured from the date of randomisation until death in the intention-to-treat population. The secondary endpoints included progression-free survival (defined as the radiological, neurological or clinical progression whichever comes first, from day of randomisation to date of disease progression or death whichever comes first), safety and quality of life. The study had a power of 80% at a significance level of 0.05 to detect a 33% increase in median survival (hazard ratio (HR) for death, 0.75). At database closure, 480 (84%) of the 573 patients had died and the median follow-up was 28 months. The unadjusted HR for death in patients treated with radiotherapy plus temozolomide compared to radiotherapy alone was 0.63 (95%CI, 0.52–0.75; p<0.001), representing a 37% relative reduction in the risk of death. The adjusted HR was 0.62 (95%CI, 0.51-0.75). The median overall survival benefit was 2.5 months; the median survival in the temozolomide plus radiotherapy group was 14.6 months (95%CI, 13.2 -16.8) compared with 12.1 months (95%CI, 11.2-13.0) in the radiotherapy group (p<0.001). The magnitude of the survival benefit for radiotherapy plus temozolomide relative to radiotherapy alone increased steadily over time. At 12 months, 51% (95%CI, 44.7-56.4) of patients in the radiotherapy alone group had survived compared with 61% (95%CI, 55.4-66.7) of patients in the temozolomide plus radiotherapy group and at 24 months this was 10.4%(95%CI, 6.8-14.1) and 26.5% (95%CI, 21.2-31.7), respectively. Subgroup analysis found that overall survival in patients with poor performance status (WHO PS>2 i.e. patients who are ambulatory and capable of self-care but unable to carry out any work activities) and in patients who had undergone biopsy alone was not significantly different between the treatment groups. However, subgroup analyses were not prospectively powered to test for statistical significance. The benefit of

treatment with radiotherapy plus temozolomide in extending progression-free survival supported the results for overall survival. The HR for death or disease progression was 0.54 (95%CI, 0.45-0.64; p <0.001), representing a 46% decreased risk of death or disease progression favouring the radiotherapy plus temozolomide group compared to the radiotherapy only group. Quality of life was a secondary outcome measure in the study but was reported separately. It was assessed using the EORTC quality of life questionnaire core-30 (QLQ-C30) and the EORTC brain cancer module (EORTC BN-20). In total, 248 radiotherapy patients and 242 radiotherapy plus temozolomide patients qualified for the final health-related quality of life (HRQOL) analysis. Changes from baseline in seven pre-selected domains, fatigue, global health, social functioning, emotional functioning, future uncertainty, insomnia and communication deficit were calculated for both groups. At the first follow up during initial radiotherapy, there was a statistically and clinically significant difference between the groups in favour of radiotherapy alone for the domain of social functioning ($p<0.005$). No significant difference was noted in any other domain. The authors concluded that the addition of temozolomide to radiotherapy for newly diagnosed GBM had no long term negative impact on HRQOL and that the overall HRQOL did not deteriorate by a clinically significant amount in either treatment group over time and even improved for some assessments and scales. The European Product Assessment Report concluded that a small negative impact on quality of life was seen in patients treated with combined radiotherapy and chemotherapy and a positive influence on quality of life could not be proven.

Summary of evidence on comparative safety

No clinically important new safety concerns were reported in the EORTC study but post-marketing surveillance of patients receiving temozolomide is ongoing. Adverse events were analysed separately, during radiotherapy (with and without concomitant temozolomide), during temozolomide monotherapy, and for the entire study period. They were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0 (with 1= mild adverse effects, 2=moderate, 3=severe, 4=life threatening). Haematological adverse effects are the dose limiting toxicities for temozolomide; in patients treated with temozolomide, 46 patients (16%) had a documented Grade 3 or 4 haematological event during the study, 21 patients (7%) had a Grade 3 or 4 neutropenia and 33 (12%) patients had a Grade 3 or 4 thrombocytopenia. In six subjects treated with temozolomide, death was attributed by the investigators to, or temporally associated with, serious adverse events considered at least possibly related to temozolomide, and occurring within 30 days of stopping therapy.

Summary of clinical effectiveness issues

The EORTC study showed a significant improvement in median survival for patients treated with combined radiotherapy and temozolomide over radiotherapy alone. This survival benefit increased over time. It was noted in an accompanying editorial that the patient population included in the trial were relatively healthy, most patients were under 70 years of age (median age 57 years), had good performance status, and were eligible for de-bulking surgery - all of which are favourable prognostic factors. The patient population included in the EORTC study may therefore not be typical of the presenting Scottish patient population but may identify those patients who would benefit most from therapy.

To improve the cost effectiveness of temozolomide plus radiotherapy, the challenge is to identify those patients most likely to benefit from chemotherapy. A retrospective, post hoc study of a subset of 206 patients from the EORTC study whose histology was available for analysis, investigated whether O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation was associated with a survival benefit. Significantly improved survival time was

seen in patients with methylation. However, the numbers were small and the assessment of the methylation status of the promotor of MGMT is not widely available and is still in the very preliminary stages of validation.

Patients within the study began therapy within 6 weeks of diagnosis. To reproduce the study conditions this requirement for patients to receive radiotherapy within 6 weeks of diagnosis may present problems in the units where waiting lists for radiotherapy exceed this period of time.

Summary of comparative health economic evidence

The manufacturer submitted a cost-effectiveness analysis (incremental cost per life year gained) comparing temozolomide and radiotherapy with use of radiotherapy alone in patients with newly diagnosed glioblastoma multiforme (GBM).

The economic evaluation was trial based, using survival and resource use data from the 2 year phase III EORTC trial. All survival and resource use data were derived from the clinical trial. Mean survival was extrapolated beyond the trial period. Analysis was conducted for an economic sample of patients in the trial for whom resource use data were collected, and for the survival outcomes for the whole patient population in the trial. In the economic analysis once patients moved into a disease progression health state radiotherapy only patients were also eligible to receive temozolomide. The incremental cost per life year gained estimated by the manufacturer was between £11,000 and £33,000 but with high uncertainty.

An important limitation is that the manufacturers have attempted to apply a non-UK trial-based economic evaluation to a Scottish and UK context without adaptation or validation (except for use of UK unit costs). The main weaknesses were the lack of estimates of QALY outcomes despite quality of life data having been collected in clinical trials, and use of non-UK resource use estimates meaning that the incremental cost-effectiveness results produced are of low reliability for the Scotland NHS perspective.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturer estimated a gross budget impact of £281,000 in 2006 rising to £563,000 in 2010 based on an estimated 29 patients being treated in year 1 with 58 by year 5 as clinician experience of use of temozolomide increases. This is based on dose administered in the EORTC trial with an estimated acquisition cost per patient for temozolomide use of £9,700 (including allowance for less than 100% adherence).

Guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) have a health technology appraisal in development for *Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma*, with an expected date of issue of August 2006.

Additional information

The SMC accepted carmustine implants (Gliadel®) for use within NHS Scotland for the treatment of newly diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation in November 2005. In the pivotal study, the use of carmustine implants was associated with a 29% relative decrease in the risk of death, which equates to an increase in median survival time of 2.3 months.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 17 January 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration. The undernoted references were supplied with the submission.

References

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