TEMODAL®
(temozolomide)

Temozolomide for the treatment of newly diagnosed high-grade glioma in England and Wales

A Submission to the National Institute for Health and Clinical Excellence

Schering-Plough Ltd

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EXECUTIVE SUMMARY

Background

High-grade gliomas are rare but devastating tumours of the brain that account for the majority of new cases of, and deaths from, brain cancer. Among high-grade gliomas, glioblastoma multiforme (GBM) is the most common primary brain tumour in adults. The incidence of high grade gliomas in England and Wales is approximately 3-4 cases/100,000 population, with GBM accounting for 40%-50% of these tumours. Despite their relatively low incidence, their economic impact is significant, predominantly because of indirect costs attributable to early mortality amongst the young and middle aged. Median survival for patients with GBM is less than one year, despite intensive, multimodality treatment.

The treatment options for high-grade gliomas are limited. Patients are usually treated with surgery, radiation, and corticosteroids, but there are few clear evidence-based treatment guidelines available in the literature. The standard of care for high-grade glioma in the UK has historically been surgery followed by radiotherapy (RT).

Clinical effectiveness of temozolomide

Temozolomide (TEMODAL®) is the only systemic chemotherapeutic agent to be licensed for brain tumours in the last 30 years. It was initially approved for the treatment of adult and paediatric patients with malignant glioma (such as GBM) showing recurrence or progression after standard first-line treatment. More recently, as of 03 June 2005, the European Commission granted approval for a new TEMODAL® indication, for treatment of adult patients with newly diagnosed GBM concomitantly with radiotherapy and subsequently as monotherapy treatment.

This decision was based upon data from a recently published randomised controlled Phase III study demonstrating the efficacy following surgery, of first line treatment of newly-diagnosed GBM with TMZ. The trial was conducted under the auspices of the EORTC in 85 institutions in 15 countries. In this trial, patients with newly diagnosed, histologically confirmed GBM were randomly assigned to receive RT alone (focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy) or RT plus continuous daily TMZ (75 mg/m^2 per day, 7 days per week from the first to the last day of RT), followed by six cycles of adjuvant TMZ (150 to 200 mg/m^2 for 5 days during each 28-day cycle). Data on the health related quality of life (HRQOL) of patients were collected using the EORTC quality of life questionnaire C30 (EORTC QLQ-C30) and the EORTC brain cancer module (EORTC-BN 20). The primary endpoint for the trial was overall survival, with secondary endpoints of progression-free survival, safety, and HRQOL.

A total of 573 patients underwent randomisation. The median age was 56 years, and 84% of patients had undergone debulking surgery. At a median follow-up of 28 months, the median survival was 14.6 months (95% CI: 13.2 to 16.8) in the RT plus TMZ arm and 12.1 months (95% CI: 11.2 to 13.0) with RT alone. The unadjusted hazard ratio for death in the RT plus TMZ arm was 0.63, or a 37% decreased risk of death favouring the RT plus TMZ group compared to the RT-only group (95% CI: 0.52 to 0.75; $p<0.001$ by the log-rank test). The 2-year survival rate was 26.5% (95% CI: 21.2 to 31.7 percent) with RT plus TMZ and 10.4% (95% CI: 6.8 to 14.1 percent) with RT alone. The median progression-free survival was 6.9

months (95% CI: 5.8 to 8.2) with RT plus TMZ and 5.0 months (95% CI: 4.2 to 5.5) with RT alone. The HR for death or disease progression was 0.54, or a 46% decreased risk of death or disease progression favouring the RT plus TMZ arm compared to the RT only group (95% CI: 0.45–0.64; p<0.001 by the log-rank test). Overall, 19 patients (7%) had any type of Grade 3 or 4 haematological toxic effect during concomitant TMZ therapy. During TMZ monotherapy, 32 patients (14%) had any Grade 3 or 4 haematological toxic effects. No Grade 3 or 4 haematological toxicities were observed in the RT group.

In subgroup analyses, treatment with RT plus TMZ extended both overall and progression-free survival benefits to patients compared to treatment with RT only, regardless of resection type (biopsy, partial resection, and complete resection).

For the first time in 30 years, a statistically significant and clinically relevant survival benefit has been demonstrated for patients early in the course of GBM as a result of first-line systemic chemotherapy, namely, the addition of TMZ to RT, followed by a course of TMZ monotherapy. These results are superior to any other chemotherapy currently available, and have demonstrated efficacy in all types of patients, regardless of preceding surgical intervention type.

Cost-effectiveness of temozolomide

An economic evaluation was conducted to estimate the incremental costs and consequences of combination TMZ plus RT, compared to RT alone for the first-line treatment of patients with GBM. The economic evaluation was a cost-effectiveness analysis comparing these two treatment approaches, and the perspective of the evaluation was that of the NHS. The source of clinical data for this evaluation was the EORTC trial, since it is the best available source of data demonstrating the efficacy of combination RT plus TMZ compared to RT alone. Economic data were collected prospectively in the trial and were obtained for a smaller subgroup of 224 patients from the larger centres in the trial. Economic analyses were performed on both the full cohort of 573 patients and on patients in the smaller subgroup for whom complete economic data were available.

The incremental cost-effectiveness ratio (ICER) for the full trial cohort was [redacted] per life-year gained, favouring the RT plus TMZ combination over RT alone, using a 2-year restricted mean survival (which assumes that all patients are censored at 2 years after randomisation). The ratios were [redacted] per life-year gained when an extrapolated mean survival estimate (which suggests that the differential survival observed extends longer than the 2-year time frame) was used in the calculation. These latter results are important because at 2 years, only 10.4% of patients in the RT arm were surviving, while 26.5% of those in the combination arm were surviving. This survival advantage would reasonably be expected to extend for some period of time after the 2-year timepoint since randomisation.

In the analysis of the 224-patient economic subgroup, the ICERs obtained were similar (for example, the ICER for the extrapolated mean calculation was [redacted] per life-year gained),

but higher than those of the full cohort due to subgroup selection factors that affected both the different survival benefits and costs.

NHS impact

Despite their low incidence rate, brain tumours such as GBM have a substantial economic impact on society. Most patients with GBM are likely to die within two years of diagnosis. Comparisons of survival from adult brain tumours in eight former NHS regions and Wales suggest regional differences in treatment outcome may still exist, despite the introduction of the NHS Cancer Plan in 2000. Inconsistencies across health authorities in the current provision of treatment with TMZ in malignant glioma should be addressed to ensure an equitable delivery of treatment and comparably optimised outcomes for newly diagnosed GBM. The overall incremental cost of using TMZ to treat patients with newly diagnosed GBM has been estimated to be in the region of £7,000 per patient. The expected incremental cost of treatment with TMZ for England and Wales is in the order of £4.3 million to £7.2 million in the first year. These costs are projected to rise to approximately £8.5 million in year 2 and £10 million in the third year as the policy is broadly adopted and long-term treatment costs are incorporated.