



Evidence, economics, and emotions: the case for temozolomide

David Hamilton

Abstract

Temozolomide, given as part of first line therapy in the treatment of grade IV astrocytoma, has been shown to improve survival in the short term. The financial cost of the treatment is considerable in New Zealand. This drug provides a good example in the field of oncology of a modern expensive pharmaceutical being a clear improvement over its cheaper predecessors, but it raises the question of what price should be paid to prolong survival in an incurable illness?

Drug	Temozolomide (Temodal®) oral capsule
Class	Cytotoxic imidazotetrazine alkylating agent
Indications	<p>Patients with newly diagnosed glioblastoma multiforme (grade IV astrocytoma) concomitantly with radiotherapy and then as adjuvant treatment.</p> <p>Patients with recurrent high-grade glioma, such as glioblastoma multiforme or anaplastic astrocytoma.</p> <p>First-line treatment for patients with advanced metastatic malignant melanoma.</p>
Costs*	<p>Average cost per patient for newly diagnosed regimen = NZ\$53,500 (Manufacturer price = \$31,000)</p> <p>Average cost per patient per monthly cycle for recurrent high grade glioma = \$6,100 (Manufacturer Price = \$3,500)</p> <p>(Costs to patient are estimated by applying MIMS' standard factor of 1.725 to the stated manufacturer price. This may vary between pharmaceutical outlets and the actual price charged may be less. Subsequent prices in this article are based on this standard mark up.)</p> <p>*MIMS online (November 2005.). URL: http://www.mimsonline.co.nz/DrugAlert/Interactions/Default.aspx</p>
Subsidy	None. Not currently included in Pharmaceutical Schedule.

Background

Primary brain tumours account for 3.1% of cancer deaths in New Zealand (NZ) males and 2.6% of cancer deaths in NZ females.

In 2001, 146 males and 108 females were registered as having a primary brain tumour and 130 males and 95 females died of brain tumour.**

The majority of primary brain tumours in adults are high-grade astrocytomas of which the great majority are glioblastoma multiforme (GBM) giving a figure of approximately 100–120 patients per annum in NZ with GBM.

GBM is a tumour with a very poor prognosis, with a median survival of 9–10 months and 1-year survival of around 40%. Figures quoted in the literature may vary depending on case selection, with older patients known to experience a poorer outcome. The standard therapy is maximal safe surgical debulking followed by high-dose radiotherapy.

The use of chemotherapy with nitrosoureas remains controversial. The majority of published trials of chemotherapy in high-grade glioma include a proportion of patients with grade III astrocytoma in whom the prognosis is better.

The most recent published meta-analysis*** of chemotherapy as part of initial combined modality management of high-grade glioma reported an increase in 1-year survival for GBM from 35% to 41%, and 2-year survival from 9% to 13% with the addition of nitrosourea-based chemotherapy.

The evidence behind the use of temozolomide in newly diagnosed GBM is the large randomised study published in the *New England Journal of Medicine***** in March 2005, which only included patients with GBM, aged ≤ 70 and in good general condition. This reported an improvement in 1-year survival from 50.6% to 61.1% and in 2-year survival from 10.4% to 26.5% with the addition of temozolomide to postoperative radiotherapy.

This increase in 2-year survival has been hailed as the greatest improvement in outcome for GBM patients in several decades and sets the new “gold standard” for therapy. This has led to the inclusion of temozolomide on the Australian Pharmaceutical Benefits Schedule (PBS) for this indication on 1 July 2005, and the inclusion of this indication by Medsafe on 1 September 2005 in NZ.

In the relapsed situation, 20% of patients with GBM would be expected to have progression-free survival at 6 months on

temozolomide therapy.

There is an increasing body of literature reporting encouraging results for the use of temozolomide in other primary brain tumour histologies, particularly oligodendroglial tumours.

**Cancer: New Registrations and Deaths 2001. Wellington: NZHIS; 2005.
URL: <http://www.nzhis.govt.nz/publications/Cancer.html>

***Stewart LA, Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet*. 2002;359:1011–8.

****Stupp R. Radiotherapy plus concurrent and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987–96. Abstract online at <http://content.nejm.org/cgi/content/abstract/352/10/987>

Discussion

At the time of writing, temozolomide remains unfunded in NZ for any indication. This led to the recent patient protest outside parliament on 15 November 2005 calling for an accelerated process to provide funding through PHARMAC and to bring NZ into alignment with Australia. The Pharmacology and Therapeutics Advisory Committee (PTAC) was considering the application for funding at a meeting on 17 November 2005.

The evidence for efficacy of first line temozolomide is strong, being based on a large randomised controlled phase III trial. The results reported are also similar to previously reported phase II data. The results available however extend only to 2 years from treatment. Although 26% of treated patients are alive at 2 years, only 10.7% are progression-free.

Unlike most cancers, brain tumours can affect patients of any age and are the second most common tumour in children after leukaemias. GBM however occurs in a minority of paediatric patients. It is, however, the commonest histology in adult brain tumours.

As a clinician treating patients with brain tumours I wish to be able to offer them the best standard treatment available. Aggressive treatment is not necessarily appropriate for all patients, but applying similar criteria to those used in the *New England Journal of Medicine* study, patients with a good functional status following surgery and a “good” quality of life are most likely to benefit from the addition of temozolomide to radiation therapy.

In discussing therapeutic options with patients, the Health & Disability Commissioner has ruled that this should include options not necessarily available in the treating centre, or even in NZ. “Standard” treatment therefore has to include world

standards. Patients confronted with this disease and its dreadful prognosis make extensive use of the Internet looking for treatments that offer hope of benefit.

In the absence of a validated, subsidised therapy, they may look at other more anecdotal and potentially harmful regimens.

This raises the economic question of what value does NZ society place on the prolongation of survival, probably of the order of magnitude of a few months for patients with an effectively incurable disease.

Assuming 100 patients diagnosed with GBM in NZ per annum, and that only 50 are fit enough to undergo combined modality therapy, the additional annual drug cost for temozolomide (not including the necessary anti-emetics and prophylactic antibiotics) would be \$2,675,000.00. In clinical outcomes, this would lead to an additional 8 patients alive at 2 years, at an effective cost of \$334,375 per patient.

In NZ, PHARMAC is charged with containing the cost of the pharmaceutical budget. Any new therapy has to “compete” with others for funding from a limited budget. Something else has to give to enable a new therapy to be subsidised. In the case of management of newly diagnosed GBM, this is effectively a new treatment, and does not replace any prior component of treatment. Without an increase in the overall pharmaceutical budget, it is difficult to see how temozolomide will secure funding.

Unfortunately, brain tumour therapy is only an example of a common issue in oncology practice where new drugs used in addition to existing regimens add to survival at defined time points in a statistically significant way at a cost commonly around \$60,000 to \$100,000 per patient treated. With absolute gains in survival of 3%–10% this may cost one million dollars per additional patient alive.

Statistics and health economics are however very difficult concepts for the individual wishing to have the best therapy possible.

Ultimately, politicians will decide where NZ stands in the world rankings of contemporary medicine, and what offers the best health return from a constrained budget.

Conflict of interest statement: I have not been the recipient of any funding from Schering-Plough, the manufacturer of Temodal®, and have not participated in any clinical trials of its use. I am the principal neuro-oncologist for the Wellington Region.

Author information: David Hamilton, Oncologist, Blood and Cancer Centre, Wellington Hospital, Riddiford St ,Wellington South

Correspondence: Dr David Hamilton, Blood and Cancer Centre, Wellington Hospital, Private Bag 7902, Wellington South. Fax (04) 385 5984; email: david.hamilton@ccdhb.org.nz

NZMJ Note: Refer to <http://www.nzma.org.nz/journal/118-1227/1806> in this issue of the *Journal* for PHARMAC's response.