NICE National Institute for Health and Care Excellence

NICE guidance

Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer)

Technology appraisal guidance
Published: 26 April 2001
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www.nice.org.uk/guidance/ta23

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Temozolomide is recommended as an option for treating malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy only if the person has a Karnofsky performance status score greater than or equal to 70 and a life expectancy of 12 weeks or more.

When using the Karnofsky performance status score, clinicians should be aware of the need to secure equality of access to treatment for people with disabilities. Clinicians should bear in mind that people with disabilities may have difficulties with activities of daily living that are unrelated to their prognosis for malignant glioma. For such people clinicians should make appropriate judgements about performance status, taking into account the person's usual functional capacity and need for assistance with activities of daily living.

1.2 This recommendation has been updated by recommendation 1.1 in NICE's technology appraisal guidance on carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma.

1.3 This recommendation has been updated by recommendation 1.1 in NICE's technology appraisal guidance on carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma.

1.4 People whose treatment with temozolomide is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 Clinical need and practice

2.1 Although brain tumours account for only 1.5% of all primary cancers and 2% of cancer deaths, they result in 7% of life-years lost before the age of 70. About 55% of primary brain cancers occur in males. Approximately 29% of adult patients survive 1 year after diagnosis and 13% survive 5 years.

2.2 Malignant glioma is the most common form of primary brain tumour. The incidence in England and Wales is 4 per 100,000 population. There are about 3,500 new cases in the UK each year. They represent 50% to 60% of all primary brain tumours, and about 0.8% of all malignant neoplasms in adults in England and Wales.

2.3 Anaplastic, or grade 3, astrocytomas (AA) comprise some 30% to 35% of malignant gliomas, glioblastoma multiforme (GBM), also known as grade 4 astrocytomas, 40% to 45% and anaplastic, or grade 3, oligodendrogliomas (AO) 5% to 15%. The average age of people with GBM is 10 years greater than that of people with AA. Median survival time from diagnosis for GBM is of the order of 5 to 12 months, but for AA is longer at 11 to 36 months. The WHO grading system for gliomas ranges from 1 (benign) to 4 (malignant and aggressive) and is detailed in section 11.

2.4 People with malignant glioma can suffer from a range of symptoms and impairments. Some symptoms may be general and others may be specific to the area of brain where the tumour is located. General symptoms include headache, anorexia, nausea, vomiting, seizures, drowsiness, personality changes, and cognitive slowing. More focal (specific) symptoms could include difficulties with hearing, speech, ambulation, dexterity, visual difficulties, and mood disturbances. These symptoms can have a profound effect on the quality of life of the patient as well as their ability to work and to care for themselves. A significant physical and emotional burden is often placed on carers, particularly as the disease progresses.

2.5 Treatment of malignant glioma varies from country to country. In the UK, about 30% of patients receive only supportive care with steroids, with or without anticonvulsants.

2.6 More intensive treatment is offered to patients with less severe disability, measured on the Karnofsky scale (Karnofsky performance status more than 60): see section 10 for details. The tumour is removed as far as possible, but can usually not be fully excised because of the infiltrative nature of these tumours. The remaining tumour tissue undergoes radical radiotherapy. The whole procedure adds some 4 to 5 months to median survival. In the USA, chemotherapy is routinely given 6 weeks after radiation (adjuvant chemotherapy), but this is not the practice in the UK or Europe.

2.7 The great majority (at least 70%) of malignant gliomas recur locally after initial treatment, usually with very disabling neurological deficit and poor and rapidly deteriorating quality of life. Options for further treatment at this stage are limited and palliative. In the UK and Europe, clinical or imaging evidence of tumour progression after radiation therapy is employed as indication for first line chemotherapy.

2.8 For a patient whose tumour recurs or progresses following surgery or radiotherapy, the chemotherapy treatment options are limited because the currently available agents have only a small chance of being effective. Although high dose oral procarbazine is used as a single agent in the USA, it is not usual in the UK except in combination with lomustine and vincristine (PCV) regimen. This currently constitutes standard first line chemotherapy. Lomustine alone is sometimes used as first line therapy. The likelihood of response depends on age, tumour type and Karnofsky performance status (see section 10). In general, anaplastic astrocytoma (AA) is more responsive to chemotherapy than glioblastoma multiforme (GBM).

2.9 Current UK practice is to give first line chemotherapy to less than one-third of patients whose tumour recurs after initial treatment, or about 15% of all diagnosed cases of brain tumour. This represents about 500 to 600 new cases per year.

2.10 Chemotherapy is given in cycles. PCV is given for 28 consecutive days in 56-day cycles, or for 21 consecutive days in 42-day cycles, usually for a maximum of 6 cycles. Therapy is usually stopped after 2 cycles in those who do not respond (based on both clinical and radiological monitoring) and in those who experience significant toxicity. Usual outcome measures include clinical response, imaging

parameters, side effect profile, progression free survival, overall survival and quality of life.

2.11 A meta-analysis of 10 randomised controlled trials (RCTs) of chemotherapy for glioma shows that mean survival time increases by 2 months (Confidence Interval 1 to 3 months) and that there are a number of other similarly small but significant improvements on other outcomes after chemotherapy.

3 The technology

3.1 Temozolomide (Temodal) is an alkylating agent derived from dacarbazine and first synthesised in 1984. It is indicated for the treatment of patients with malignant glioma showing recurrence or progression after standard therapy. It is easier to administer than other chemotherapeutic regimes for this indication and is given orally once a day for 5 days in a 28-day cycle. It has high bioavailability and crosses the blood-brain barrier where it is spontaneously hydrolysed to its active form. It is toxic to cancer cells due to inhibition of tumour cell DNA replication.

3.2 It exhibits a broad spectrum of anti-tumour activity in animals and man. Side effects are less than existing regimes and include nausea, vomiting, fatigue and headache. Haematological toxicity is mild and non-cumulative.

3.3 Dosage in chemotherapy-naïve patients is 200 mg per square metre of patient surface area per day (that is, generally averaging 340 mg per day). In patients previously treated with cytotoxic drugs, the dose is usually reduced by 25%.

3.4 The current UK price of this drug is £1,176 per 5-day cycle for a daily dose of 340 mg for those who have not had prior chemotherapy, and £934 for those who have.

4 Evidence

4.1 Clinical effectiveness

4.1.1 There has been only 1 randomised controlled trial (RCT) of 225 patients involving temozolomide versus procarbazine alone in patients with recurrent glioblastoma multiforme (GBM). There are no trials of temozolomide in anaplastic astrocytoma (AA). All patients in the GBM trial had received radiotherapy and two-thirds had also received first-line nitrosourea-based chemotherapy. Patients were required to have a histologically proven supratentorial GBM or gliosarcoma at first relapse, recurrence or progression (as assessed by imaging), Karnofsky performance status of 70 or more and a projected life expectancy of 12 weeks or more at entry.

4.1.2 Progression-free survival in the RCT at 6 months was 21% for those on temozolomide, compared with 8% for those on procarbazine (a statistically significant difference, p=0.008). The 6-month survival was 60% for temozolomide and 44% for procarbazine (also a significant difference, p=0.019), however the median survival advantage of 6 weeks in favour of temozolomide was not statistically significant.

4.1.3 Procarbazine alone is rarely if ever used in first line therapy in the UK and a more appropriate control arm for the UK might have been PCV (procarbazine with lomustine and vincristine) or lomustine alone. As this comparison has not been carried out, there is no direct evidence that temozolomide is more effective than a current UK standard treatment.

4.1.4 Six preliminary or phase 2 single-group studies each with over 40 patients, and several smaller such studies have been undertaken. The main results are that about 5% of GBM patients show a partial response to temozolomide (aggregate tumour volume halved) and for some 30% to 40% the disease exhibited no progression for a period of time. In other forms of malignant glioma about 10% show a complete response to temozolomide (disappearance of all enhancing tumours in neuroimaging), a further 25% a partial response and about 30% exhibit a period of no progression.

4.1.5 Importantly for an incurable condition such as GBM, the quality of life for patients on temozolomide improves significantly prior to the onset of further disease progression, though it deteriorates rapidly thereafter. A similar trend is apparent following recurrence of other malignant gliomas but the evidence is less robust.

4.2 Cost effectiveness

4.2.1 There is insufficient evidence to assess the clinical effectiveness of temozolomide as first-line chemotherapy. Therefore, its cost-effectiveness in this indication has not been considered any further.

4.2.2 Where first-line chemotherapy with PCV has failed, temozolomide should be compared with the only alternative, which is best supportive care. However, the only data compares the benefits of temozolomide with those of procarbazine alone. Costs per cycle of temozolomide are estimated to be £1,488 including hospital costs and medications for side effects.

4.2.3 Estimating cost per quality adjusted life year (QALY) is difficult because the extension of median survival time is not statistically significant, and the quality of life data are limited. The main benefit of temozolomide is that a proportion of patients benefit from a longer progression free survival time. Therefore the most useful measure of cost-effectiveness is cost per progression free week. Costs will continue to accrue if patients remain progression free, because further cycles of the drug will be given until progression occurs.

4.2.4 For glioblastoma multiforme (GBM), the median estimate of progression-free survival, using temozolomide was 12.4 weeks, and using procarbazine, 8.3 weeks (a difference of 4.1 weeks, p=0.006). The incremental cost of temozolomide against procarbazine was £4,044, giving an incremental cost per progression-free week of £1,000. The cost per progression-free week for temozolomide against placebo (assuming the placebo would have no cost and no effect) would have been £400.

4.2.5 For anaplastic astrocytoma (AA), the figures are more uncertain than for GBM, as there is no RCT on which to base estimates, only single group studies. On the basis that for temozolomide the median estimate of progression free survival is 11

weeks in AA, and that none of this is a placebo effect, the cost per progression-free week would be £410.

4.2.6 For GBM, the costs per life year gained are as follows. For an estimated gain in median progression free survival of 4.1 weeks associated with a gain in total survival of 6 weeks, and for no incremental gain in utility due to an improved quality of life, the incremental cost per life year gained of temozolomide against procarbazine for GBM is estimated to be £35,000. The cost per life year gained of temozolomide for GBM against PCV is not known.

4.2.7 For AA, assuming an estimated gain in progression free survival of 11 weeks and in total overall survival of 12 weeks, with no incremental gain in utility due to an improved quality of life, and assuming no placebo effect, the cost per life-year gained of temozolomide is estimated to be £35,000. The cost per life-year gained of temozolomide for AA against PCV is not known.

4.2.8 Whilst the indirect and informal costs of malignant glioma may be substantial, the change in these costs when temozolomide is introduced is unlikely to be large. Therefore the costs per unit of benefit will not alter to any extent from those reported above when these costs are included in the calculations.

5 Implications for the NHS

5.1 Currently, chemotherapy is used for about 500 to 600 people with recurrent malignant glioma per year. The number of patients for whom first line chemotherapy fails and whose condition will allow sufficient benefit from temozolomide as a second-line therapy is likely to be only a small proportion of these, perhaps 25%. It is therefore assumed that 150 patients per year would be eligible for temozolomide treatment under this guidance. If they were to receive an average of 4 cycles, the incremental cost would be about £6,400 per person. This would amount to about £1 million in aggregate, per year, for the NHS.

5.2 Other impacts on the NHS would be small. If total survival were to increase by the same amount as the progression-free period, then a small increase in total NHS costs could be expected.

6 Further research

6.1 A randomised controlled trial of temozolomide against PCV is needed (and planned by the Cancer Research Campaign) for those with relapsed glioblastoma multiforme (GBM), anaplastic astrocytoma (AA) and other malignant gliomas. It should have sufficient power to detect a 2-month difference in median survival time, and particular emphasis should be placed on quality of life measurement with sufficient detail on key symptoms (for example, headache, epileptic fits, rate of cognitive decline) for robust comparisons to be made.

6.2 Studies of temozolomide in combination chemotherapy (including at least 1 with an agent which diminishes the repair enzyme AGT O6-alkylguanine-DNA-alkyltransferase) against other classes of chemotherapy drugs would be valuable.

6.3 Research into the effect of the drug on children is required.

7 Implementation

7.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

7.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

7.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has recurrent malignant glioma and the healthcare professional responsible for their care thinks that temozolomide is the right treatment, it should be available for use, in line with NICE's recommendations.

8 Appraisal Committee members

The Appraisal Committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend 1 or the other. Declared interests may also exclude a member from individual technology appraisals. The committee are supplemented by technology specific experts as indicated in section 9.

Dr Jane Adam
Radiologist, St George's Hospital, London

Dr Sunil Angris
General Practitioner, Waterhouses Medical Practice

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Professor Carol Black
Consultant Physician, Royal Free Hospital and UCL, London

Professor John Brazier
Health Economist, University of Sheffield

Professor Bruce Campbell
Consultant Surgeon, Royal Devon and Exeter Hospital

Professor Mike Campbell
Statistician, Institute of General Practice and Primary Care, Sheffield

Dr Karl Claxton
Health Economist, University of York

Professor Jack Dowie
Health Economist, London School of Hygiene and Tropical Medicine, London

Dr Paul Ewings
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Sally Gooch
Director of Nursing, Mid-Essex Hospital Services Trust

Liz Heyer
Chief Executive, Barnet and Chase Farm Hospitals NHS Trust

Dr Diane Ketley
Research into Practice Programme Leader, NHS Modernisation Agency

Ruth Lesirge
Patient Representative; Director, Mental Health Foundation

Dr George Levvy
Patient Representative; Chief Executive, Motor Neurone Disease Association

Dr Gill Morgan
CEO, North and East Devon Health Authority

Professor Miranda Mugford
Health Economist, University of East Anglia

Siân Richards
General Manager, Cardiff Local Health Group

Professor Philip Routledge
Professor of Clinical Pharmacology, University of Wales

Dr Rhiannon Rowsell
Pharmaceutical Physician, AstraZeneca UK Ltd

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Professor Andrew Stevens
Professor of Public Health, University of Birmingham

Professor Ray Tallis
Consultant Physician, Hope Hospital, Salford

Professor Mary Watkins
Head of Institute of Health Studies, University of Plymouth

Dr Norman Waugh
Public Health Consultant, University of Southampton

Dr Fay Wilson
General Practitioner, Birmingham

9 Sources of evidence

The following documentation and opinion was made available to the Committee:

Assessment report:

- prepared by Wessex Institute for Health Research and Development, University of Southampton (The effectiveness and cost effectiveness of temozolomide for the treatment of recurrent malignant glioma, November 2000).

Manufacturer or sponsor submissions:

- Schering Plough UK Ltd

Professional or specialist group, patient or carer group and trade association submissions:

- Royal College of Physicians and the Royal College of Radiologists (joint)
- MRC Clinical Trials Unit
- Royal College of General Practitioners
- Royal College of Surgeons of England
- Association of British Neurologists and the Royal College of Physicians (joint)

External expert and patient advocate submissions:

- Dr Paul Symonds, Reader and Consultant in Clinical Oncology, University of Leicester
- Douglas Guerrero, Clinical Nurse Specialist, Neuro-Oncology, Royal Marsden Hospital
- Dr Mike Brada, Reader and Consultant in Clinical Oncology, Royal Marsden Hospital

10 Karnofsky performance score

100%: The patient has no complaints and is without evidence of disease

90%: The patient has minor signs or symptoms, but is able to carry out his or her normal activities

80%: The patient demonstrates some signs or symptoms and requires some effort to carry out normal activities

70%: The patient is able to care for self, but is unable to do his or her normal activities or active work

60%: The patient requires medical care and much assistance with self-care

50%: The patient is able to care for self, but requires occasional assistance

40%: The patient is disabled and requires special care and assistance

30%: The patient is severely disabled and hospitalisation is indicated; Death is not imminent

20%: The patient is very ill with hospitalisation and active life-support treatment necessary

10%: The patient is moribund with fatal process proceeding rapidly

0%: Dead

Table 1 ECOG, WHO, RTOG to KPS (Approximate Conversion System)

E, W, R	Karnofsky	Details
0	90% to 100%	Normal activity
1	70% to 80%	Symptoms demonstrated, but the patient remains ambulatory, and able to perform self-care
2	50% to 60%	Ambulatory more than 50% of the time and requires occasional assistance

E, W, R	Karnofsky	Details
3	30% to 40%	Ambulatory less than 50% of the time and requires nursing care
4	10% to 20%	Bedridden
5	0%	Death

11 The new WHO classification of tumours affecting the central nervous system

In 1993, the WHO ratified a new comprehensive classification of neoplasms affecting the central nervous system. The classification of brain tumours is based on the premise that each type of tumour results from the abnormal growth of a specific cell type. To the extent that the behaviour of a tumour correlates with basic cell type, tumour classification dictates the choice of therapy and predicts prognosis. The new WHO system is particularly useful in this regard with only a few notable exceptions (for example all or almost all gemistocytic astrocytomas are actually anaplastic and hence grade 3 or even 4 rather than grade 2 as designated by the WHO system). The WHO classification also provides a parallel grading system for each type of tumour. In this grading system most named tumours are of a single defined grade. The new WHO classification provides the standard for communication between different centres around the world. An outline of this classification is provided below.

11.1 Neuroepithelial tumours of the CNS (first 5 main types)

1.Astrocytic tumours (glial tumours categories 1 to 5 may also be subclassified as invasive or non-invasive, although this is not formally part of the WHO system, the non-invasive tumour types are indicated below. Categories in italics are also not recognized by the new WHO classification system, but are in common use.)

1. Astrocytoma (WHO grade 2)

a. variants: protoplasmic, gemistocytic, fibrillary, mixed

2. Anaplastic (malignant) astrocytoma (WHO grade 3)

a. hemispheric

b. diencephalic

c. optic

d. brain stem

e. cerebellar

3. Glioblastoma multiforme (WHO grade 4)

a. variants: giant cell glioblastoma, gliosarcoma

4. Pilocytic astrocytoma 9non-invasive, WHO grade 1)

a. hemispheric

b. diencephalic

c. optic

d. brain stem

e. cerebellar

5. Subependymal giant cell astrocytoma (non-invasive, WHO grade 1)

6. Pleomorphic xanthoastrocytoma (non-invasive, WHO grade 1)

2.Oligodendroglial tumours

1. Oligodendroglioma (WHO grade 2)

2. Anaplastic (malignant) oligodendroglioma (WHO grade 3)

3.Ependymal cell tumours

1. Ependymoma (WHO grade 2)

a. variants: cellular, papillary, epithelial, clear cell, mixed

2. Anaplastic ependymoma (WHO grade 3)

3. Myxopapillary ependymoma

4. Subependymoma (WHO grade 1)

4.Mixed gliomas

1. Mixed oligoastrocytoma (WHO grade 2)

2. Anaplastic (malignant) oligoastrocytoma (WHO grade 3)

3. Others (for example, ependymo-astrocytomas)

5.Neuroepithelial tumours of uncertain origin

1. Polar spongioblastoma (WHO grade 4)

2. Astroblastoma (WHO grade 4)

3. Gliomatosis cerebri (WHO grade 4)

A number of grading systems are in common use for tumours of astrocytic lineage (that is, astrocytomas, anaplastic astrocytomas and glioblastomas). Grades are assigned solely based on the microscopic appearance of the tumour. The numerical grade assigned for a given tumour, however, can vary depending on which grading system is used as illustrated by the following table. Thus, it is important to specify the grading system referred to when a grade is specified. The St. Anne-Mayo grade has proven to correlate better with survival than the previously common Kernohan grading system. It can only be applied to invasive tumours of astrocytic lineage; it is otherwise similar to the WHO grading system.

Table 2 Grading of astrocytic tumours

WHO designation	WHO grade	Kernohan grade	St. Anne-Mayo grade	St. Anne-Mayo criteria
pilocytic astrocytoma	1	1	excluded	-
astrocytoma	2	1, 2	1	no criteria fulfilled
-	-	-	2	1 criterion: usually nuclear atypia

WHO designation	WHO grade	Kernohan grade	St. Anne-Mayo grade	St. Anne-Mayo criteria
anaplastic (malignant) astrocytoma	3	2, 3	3	2 criteria: usually nuclear atypia and mitosis
glioblastoma	4	3, 4	4	3 or 4 criteria: usually the above and necrosis and/or endothelial proliferation

Note: The WHO and Kernohan systems are not criteria-based. Thus, a given tumour may not fall under the same designation in all 3 systems.

Update information

March 2016: The wording of recommendation 1.1 has been updated in line with NICE's wording conventions.

Recommendations 1.2 and 1.3 for temozolomide for the first-line chemotherapy treatment of malignant glioma when primary therapy (surgery and/or radiotherapy) has failed, have been updated recommendation 1.1 in NICE's technology appraisal guidance on carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma.

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