

Temozolomide for High Grade Glioma (Review)

Hart MG, Grant R, Garside R, Rogers G, Somerville M, Stein K



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[Intervention Review]

Temozolomide for High Grade Glioma

Michael G Hart¹, Robert Grant¹, Ruth Garside², Gabriel Rogers², Margaret Somerville³, Ken Stein²

¹Clinical Neurosciences, Bramwell Dott Building, Western General Hospital, Edinburgh, UK. ²PenTAG, Peninsular Medical School, Exeter, UK. ³Peninsula College of Medicine and Dentistry, Universities of Exeter and Plymouth, Plymouth, UK

Contact address: Michael G Hart, Clinical Neurosciences, Bramwell Dott Building, Western General Hospital, Crewe Road, Edinburgh, Midlothian, EH4 2XU, UK. m.g.hart@doctors.net.uk.

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ABSTRACT

Background

High grade glioma (HGG) is an aggressive form of brain tumour the treatment of which usually entails biopsy or resection where possible followed by radiotherapy. Temozolomide is a novel oral chemotherapeutic drug that penetrates into the brain and has a low incidence of adverse effects.

Objectives

To assess whether temozolomide holds any advantage over conventional therapy for HGG in either primary or recurrent disease settings.

Search strategy

The following databases were searched: the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 2, 2007. Medline, EMBASE, Science Citation Index, Physician Data Query and the Meta-Register of Controlled Trials. Reference lists of identified studies were searched. The Journal of Neuro-Oncology was hand searched from 1999 to 2007 including conference abstracts. Neuro-oncologists were contacted regarding ongoing and unpublished trials.

Selection criteria

Randomised controlled trials (RCTs). Interventions included the use of temozolomide during primary therapy or for recurrent disease. Patients included those of all ages with a proven pathological diagnosis of HGG.

Data collection and analysis

Quality assessment and data extraction were undertaken by two review authors. Outcome measures included survival, time to progression, quality of life (QOL) and adverse events.

Main results

In primary disease two RCTs were identified, enrolling a total of 703 patients, that investigated concomitant and adjuvant temozolomide in Glioblastoma Multiforme (GBM). Temozolomide increased survival (hazard ratio (HR) 0.84, confidence interval (CI) 0.50 to 0.68, $P < 0.001$) and an increase in time to progression (HR 0.52 CI 0.42 to 0.64 $P < 0.0001$). This was without having a statistically significant negative effect on QOL and with a low incidence of early adverse events. Grade 3/4 haematological toxicity was found in 5 to 14%. The long term effects of temozolomide are still to be assessed. In recurrent GBM a single trial enrolling 225 patients in total found that temozolomide did not increase overall survival but it did increase time to progression (HR 0.68 CI 0.51 to 0.90 $p0.008$). Severe adverse events were low in this setting.

Authors' conclusions

Temozolomide is an effective therapy in GBM for prolonging survival and delaying progression as part of primary therapy without impacting on QoL and with a low incidence of early adverse events. The frequency and severity of late adverse events is unknown. In recurrent GBM it improves time to progression but not overall survival. These findings are from three good quality but non-blinded RCTs of over 900 patients in total.

PLAIN LANGUAGE SUMMARY

High grade glioma is a rapidly progressive form of brain tumour: half of all patients will die within a year of diagnosis even after treatment with surgery and radiotherapy

High grade glioma (HGG) is a rapidly progressive form of brain tumour with a poor survival rate even after treatment with surgery and radiotherapy. We found two trials, enrolling 703 patients in total with a newly diagnosed glioblastoma multiforme (a form of HGG), that studied chemotherapy with temozolomide during and after radiotherapy. This was compared with radiotherapy only. Those who received temozolomide had an improved survival and delayed time to recurrence. The short term adverse events associated with temozolomide are low but can be severe, while the long term effects are unknown. In recurrent disease a single trial was identified that included 225 patients with glioblastoma multiforme at first relapse. In this instance temozolomide delayed progression but did not improve overall survival. No RCTs investigated the use of temozolomide in HGGs other than glioblastoma multiforme. All these trials enrolled highly selected patients with good prognostic features that are not entirely representative of all patients with glioblastoma multiforme limiting the general applicability of these results.

BACKGROUND

Description of the condition

Gliomas are tumours of the brain and spinal cord, so called because they develop from the glial cells which form structures that surround and support the nerve cells. Gliomas are graded by the World Health Organisation classification on a scale of I to IV, based on the histological appearance of the tumour (Kleihues 1993). HGGs belong to grades III or IV and have in common an aggressive and infiltrating nature. The majority of HGG are Glioblastoma Multiforme (GBM), Anaplastic Astrocytoma (AA) and Anaplastic Oligodendrocytoma (AO). The incidence of HGG is less than 8 per 100, 000 per year, resulting in around 4800 new cases in the UK each year (Counsell 1996). Overall, HGG make up about one percent of all new tumours types (SHS 2006).

Description of the intervention

In general, HGGs have a poor prognosis, are rapidly progressive and resistant to therapy. Their infiltrating nature means they cannot be completely excised and the majority will recur within 2cm

of their original location. Median survival is around one year for GBM, two years for AA and five years for AO (Winger 1989). Management is based around symptomatic relief and increasing survival. The first option is surgery, which is usually required in some form for histological diagnosis. This may entail a biopsy or more aggressive resection. Currently there is no good evidence from RCTs that either approach results in any difference in survival over best medical care although resection is commonly attempted where feasible (Hart 2000). Radiotherapy is the treatment with the greatest evidence base for effect and this is now part of standard management, resulting in an increase in median survival from three to four months to around nine to ten months (Walker 1978). The other principle therapy is glucocorticosteroids, which have an important role in the reduction of peri-tumoural oedema and can produce a marked improvement in neurological symptoms and survival by themselves (Kaal 2004).

Chemotherapy has been used as part of initial therapy as either single agent or multi-agent regimes to try and maximise penetration through the blood brain barrier and tumour responsiveness. The results have generally been conflicting, and there is a significant morbidity associated with chemotherapy (Rampling 2005).

Recently a meta-analysis of chemotherapy in HGG has demonstrated an improvement in survival with PCV chemotherapy (HR 0.85 CI 0.78 to 0.92 $P < 0.0001$) with an overall improvement of two months in median survival to around 12 months (GMT Group 2002). It is not clear whether the gain in survival reflects a useful period of good QOL. In grade III tumours two recent RCTs did not demonstrate an increase in survival with PCV (Cairncross 2006; van den Bent 2006).

Why it is important to do this review

Temozolomide is a chemotherapeutic drug which is administered orally that methylates DNA in a way which prevents tumour cell proliferation. Early case series have suggested temozolomide to be a safe therapy with haematological toxicity in five to ten per cent, as well as being associated with a good median survival of around 16 months (Lanzetta 2003; Stupp 2002). These survival figures compared favourably with expected prognosis in GBM, while toxicity was lower than with high dose procarbazine chemotherapy. Temozolomide is rapidly becoming standard therapy for GBM in the primary and recurrent disease settings, and has recently been licensed by the National Institute of Clinical Excellence in the UK in these disease settings. This practice has largely been based on a single high profile RCT although there is no full systematic review and meta-analysis in the field to fully assess the evidence basis for this trend in clinical practice.

OBJECTIVES

To assess the effectiveness of Temozolamide in HGG as part of:

- a) Initial therapy, or;
- b) Therapy for recurrent disease

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

- Primary therapy: Participants will be patients of any age with a histologically confirmed HGG. They may have

undergone any form of surgery to reach a histological diagnosis (biopsy or resection)

- Recurrent disease: participants will be patients of all ages with a previous histologically confirmed HGG and presumed recurrent disease. Recurrent disease must be confirmed by both clinical and radiological criteria (MacDonald 1990).
- HGG will include Glioblastoma Multiforme (GBM), Anaplastic Astrocytoma (AA), Anaplastic Oligodendrocytoma (AO) and mixed Anaplastic Oligoastrocytoma (AOA).

Types of interventions

The intervention under investigation will be the use of oral temozolomide. Different dosing regimes of temozolomide may be used. The control arm may or may not include systemic chemotherapy as this is not part of standard practice, at least within the UK. However, in light of Grade I evidence for the effectiveness of PCV chemotherapy in primary disease (GMT Group 2002), trials will be subject to subgroup analysis depending on the use of systemic chemotherapy in the control arm. The use of chemotherapeutic wafers may also be included as part of the comparison arm but will also be subjected to a subgroup analysis. Both arms of the trial will receive radiotherapy.

Intervention

- Radiotherapy + Temozolomide

Comparison

- Radiotherapy +/- Chemotherapy e.g. PCV, Gliadel, etc

We included trials which used other forms of supportive care e.g. steroids, anti-epileptics and other drugs depending on appropriate clinical need (Grant 2004) only if similar care was given to both the intervention and comparison group.

Types of outcome measures

Primary outcomes

- Survival: from time of randomisation to time of death

Secondary outcomes

- Time to Progression: from time of randomisation to time of confirmed disease progression or censoring. Recurrence should be defined using both clinical and radiological criteria (MacDonald 1990). This is assumed to be roughly synonymous with progression free survival.

- QOL: time to deterioration beyond a set point using the Linear Analogue Scale assessment, the Functional Assessment of Cancer Therapy - Brain, or other equivalent grading system
- Adverse events: nature (as defined using MedDRA® (Medical Dictionary for Regulatory Authorities) criteria and timing. Examples include nausea, vomiting, alopecia, rash, fatigue, constipation, convulsions, weakness, thrombocytopenia, leucopenia, anaemia, pancytopenia and abnormal liver function tests.

Search methods for identification of studies

Electronic searches

The same principle was used to search each database. Firstly the terms and phrases identifying randomised controlled trials were combined using the Boolean “OR”. Secondly, all the terms and phrases describing malignant glioma, were combined with “OR”. Thirdly, everything used to identify the interventions of interest i.e. temozolomide, was also combined with “OR”. These three initial search results were then grouped with the Boolean operator “AND” and the results displayed. Wild cards and truncation symbols were used to ensure terms with alternative spellings and/or endings were not missed. MeSH terms were exploded. The full search strategy is described in [Table 1](#). Foreign language journals were eligible for inclusion.

Table 1. Search Strategy

Database	Strategy
EMBASE (1980 to Apr 2007)	<p>The original search strategy has been adapted from Ovid version to SilverPlatter version, all “MESH” headings were checked in Thesaurus (as the vocabulary was updated in January 2003) and minor changes were made in “MESH” terms.</p> <ol style="list-style-type: none"> 1. explode “clinical-trial”/all subheadings 2. explode “controlled-study”/all subheadings 3. explode “meta-analysis”/all subheadings 4. explode “crossover-procedure”/all subheadings 5. explode “double-blind-procedure”/all subheadings 6. explode “single-blind-procedure”/all subheadings 7. explode “randomization”/all subheadings 8. explode “prospective-study”/all subheadings 9. clin* near trial* 10. singl* 11. double* 12. (singl* or double* or trebl* or tripl*) near (blind* or mask*) 13. random*

Table 1. Search Strategy (Continued)

	<p>14. control*</p> <p>15. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14</p> <p>16. EC = "HUMAN"</p> <p>17. #15 and (EC = "HUMAN")</p> <p>18. explode "brain-tumor"/all subheadings</p> <p>19. explode "central-nervous-system"/all subheadings</p> <p>20. explode "brain-cortex"/all subheadings</p> <p>21. malignant near glioma*</p> <p>22. glioblastoma multiforme*</p> <p>23. astrocytoma* or anaplastic astrocytoma*</p> <p>24. brain tumo?r*</p> <p>25. neuroectodermal tumo?r*</p> <p>26. ependymoma*</p> <p>27. oligodendroglioma*</p> <p>28. #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27</p> <p>29. temozolamide</p> <p>30. temodar</p> <p>31. temodal</p> <p>32. #29 or #30 or #31</p> <p>33. 15 and 28 and 32</p>
<p>SCIENCE CITATION INDEX (1981 to 2007)</p>	<p>A similar search strategy to the one for Biosis was used. Searches were made in the Title, Keyword or Abstract. Unlike Biosis, there was no "major concepts" search facility.</p> <p>The differences were as follows:</p> <ol style="list-style-type: none"> 1. "tumo*" was used in place of "tumo*r" 2. "central & nervous & system & tumo*" and "central & nervous & system & neoplasm" were two additional searches.
<p>CENTRAL on the Cochrane Library, Internet version, search strategy,</p>	<p>Capital letters are MESH terms, the rest are free text terms. The original search strategy was used.</p> <ol style="list-style-type: none"> 1. CENTRAL NERVOUS SYSTEM NEOPLASMS 2. BRAIN NEOPLASMS 3. GLIOMA 4. (malignant and glioma) 5. (glioblastoma and multiforme) 6. astrocytoma* 7. (anaplastic and astrocytoma*) 8. (brain and tumor*) 9. (neuroectodermal and tumor*) 10. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) 11. Temozolamide

Table 1. Search Strategy (Continued)

	<p>12. Temodar 13. Temodal 14. (#11 or #12 or #13)</p> <p>15. #10 and #14</p>
Physician Data Query (PDQ): http://www.nci.nih.gov/cancer-topics/pdq	<p>The search followed the prescribed searching forms specific for the database, using terms from the above searches.</p> <p>Search form - all types of brain tumours - adults, children Treatment Active and closed Phase III and IV Temozolamide</p>
meta-Register of Controlled Trials (mRCT): http://www.controlled-trials.com/mrct	Keywords: brain, glioma, temozolamide
Medline	<p>The original search strategy has been adapted from the Ovid version to the Silver Platter version. Terms 1 to 37, used to identify all randomized and clinical controlled trials were taken from the first two parts of the Highly Sensitive Search Strategy (HSSS) devised by Carol Lefebvre.</p> <p>38. explode "Brain-Neoplasms"/all subheadings 39. explode "Central-Nervous-System-Neoplasms"/all subheadings 40. explode "Cerebral-Cortex"/all subheadings 41. explode "Glioma"/ all subheadings 42. malignant near glioma* 43. glioblastoma* or "glioblastoma multiforme" 44. astrocytoma* or "anaplastic astrocytoma" 45. brain tumo?r* 46. neuroectodermal tumo?r* 47. ependymoma* 48. oligodendroglioma* 49. or/38-48</p> <p>50. temozolamide 51. temodar 52. temodal 53. or/50-52</p> <p>54. 37 and 49 and 53</p>

Searching other resources

The references of all identified studies were searched to identify more trials.

Hand search

A hand search of the Journal of Neuro-Oncology from 1991 to Jan 2007 was undertaken in order to identify trials that may not have been present in the electronic databases. This included searching all conference abstracts published in the journal.

Personal communication

The manufacturer of Temozolomide (Schering-Plough) was contacted for information regarding any further RCTs using their product. As they are the sole manufacturer of Temozolomide they would be aware of all research using their product.

Data collection and analysis

Selection of studies

Identification of studies was made in two stages. Abstracts returned by the original search were examined independently by two review authors. Those studies that clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. Next, full texts of the selected references were obtained and further examined independently by two authors for inclusion or exclusion criteria. At all times any disagreements were resolved through discussion. If sufficient data was not available for assessment then the relevant authors of the trials were contacted.

Data extraction and management

For included studies, two review authors independently abstracted data on characteristics of patients and interventions, study quality, endpoints and deviations from protocol using a pre-specified form designed to complete the information required for the table of Characteristics of included studies, [Table 2](#) and [Table 3](#). Differences were reconciled by discussion or by consultation with a third review author.

Table 2. Internal Validity

Measure	Stupp 2005	Athanassiou 2005	Yung 2000
Power calculation?	Yes. Adequate power.	No. Probably under powered.	Yes. Adequate power (for PFS).
Proper randomisation?	Yes	Methods not reported	Not clear
Groups similar at baseline?	Yes	Yes	No
Investigators blinded?	No	No	No

Table 2. Internal Validity (Continued)

Outcome assessors blinded?	No	No	No
Patients blinded?	No	No	No
Eligibility criteria stated?	Yes	Inclusion: yes. Exclusion: no.	Yes
Objective outcome measures?	Predominantly	Predominantly	Predominantly
Analysis on ITT basis?	Yes	No	Yes
All patients accounted for?	Yes	Yes	Yes
Withdrawals specified?	Yes	Yes	Yes
Withdrawal reasons given?	Yes	No	Yes
Inter-centre consistency?	Not reported	Not reported	Not reported
Conflicts of interest?	Yes	No	Yes

Table 3. External Validity

Measure	Stupp 2005	Athassiou 2005	Jung 2000
Age (mean and range)	TMZ: 56 (19-70). Control: 57 (23-71)	Not reported	TMZ: 52 (21-76). PRO: 51 (21-74)
Sex (M:F)	TMZ 63:37 Control 64:36	TMZ 64:36 Control 61:39	TMZ 69:31 PCB 63:36
Histology	Confirmed GBM: TMZ 92% Control 93%	Not examined	Confirmed GBM: TMZ 91% PCB 96%
Performance Status (mean and range)	TMZ: WHO 0 39%, WHO 1 47%, WHO 2 13%. Control: WHO 0 38% WHO 1 49% WHO 2 12%	KPS over 80: TMZ 47% Control 32%. KPS 80 or less: TMZ 53% Control 68%	KPS 70 or more: TMZ 100% PCB 99%
Extent of Surgery	TMZ: Total 44%, Partial 39%, Biopsy 17%. Control: Total 45%, Partial 40%, Biopsy 16%	TMZ: Total 18%, Partial 40%, Biopsy 42%. Control: Total 15%, Partial 43%, Biopsy 42%	Previous resection: TMZ 87% PCB 91% Previous Chemotherapy: TMZ 65% PCB 68%
Follow up	median 28 months	median 11 months	not stated

- For time to event data (survival and time to progression) we abstracted the HR and its variance from trial reports; if these were not presented, we attempted to abstract the data required to estimate them (Parmar 1998). If it was not possible to estimate the HR (HR), we planned to abstract the number of patients in each treatment arm who experienced the outcome of interest and the number of participants assessed, in order to estimate a relative risk (RR).

- For dichotomous outcomes (e.g. adverse events) we abstracted the number of patients in each treatment arm who experienced the outcome of interest, in order to estimate a RR. For continuous outcomes (e.g. QOL) the final value and standard deviation of the outcome of interest in each treatment arm at the end of follow-up was abstracted for each study. For dichotomous and continuous data, we abstracted the number of patients assessed at endpoint.

- For continuous outcomes (e.g. QOL) the final value and standard deviation of the outcome of interest in each treatment arm at the end of the follow-up was abstracted for each study. For dichotomous and continuous data, we abstracted the number of patients assessed at endpoint.

Where possible, all data abstracted were those relevant to an intention to treat analysis.

In the case of missing data required for the review outcomes, the study authors were contacted.

Data extraction was performed by two authors and integration to RevMan (the Cochrane Collaborations software for preparing and maintaining Cochrane reviews) by a single author.

Assessment of risk of bias in included studies

Appraisal

Any trial deemed relevant was critically appraised using and were allocated to one of three groups, described in section 6 of the Cochrane Handbook, according to the risk of bias:

Group A - Low risk of bias

Group B - Moderate risk of bias

Group C - High risk of bias

Trials meeting the quality criteria for group A only were included.

Methodological quality of the included trials

Randomisation:

- adequate e.g. a computer-generated random sequence or a table of random numbers (A)

- inadequate e.g. date of birth, clinic ID number or surname (B)

- unclear e.g. not reported (C)

Allocation concealment:

- adequate e.g. where allocation concealments could not be foretold (A)

- unclear e.g. not reported (B)

- inadequate e.g. the computer generated allocation sequence was displayed so treatment providers could see which arm of the trial the next participant was assigned to, or kept in a sealed opaque envelope (C)

not used (D)

Blinding of participants, treatment providers and outcome assessors

- Yes

- No

- Unclear

Loss to follow-up: the number of participants lost to follow up in each intervention arms whose outcomes were not reported at the end of the study was recorded; we also noted if loss to follow-up was not reported.

Any trials meeting the inclusion criteria were critically appraised with tables constructed to summarise internal and external validity (Juni 2001)

Data synthesis

We pooled the results of trials of primary therapy and therapy for recurrent disease in separate meta-analyses.

- For time to event data, HRs were pooled using the generic inverse variance facility of RevMan 4.2.

- For dichotomous outcomes we calculated the RR for each study and then pooled the RRs.

- For continuous outcomes we pooled the weighted mean differences between the treatment arms at the end of follow-up using the mean difference method if all trials have measured the outcome on the same scale, or using the standardised mean difference method otherwise.

Fixed effects models were used for all meta-analyses.

In light of the known benefits of chemotherapy in primary disease, we planned to assign trials including systemic chemotherapy in the control arm to a separate sub-group and pool results of sub-groups if they showed consistent findings.

If sufficient studies were available, we planned to construct a funnel plot of treatment effect versus precision with the data from all studies included in order to investigate the likelihood of publication bias.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

From the literature search we found a total 351 potentially relevant references for which we screened the abstracts.

Included studies

Primary therapy

Two RCTs (presented in three articles) met the inclusion criteria (see table of included studies).

The first trial was run by the EORTC involving 85 centres in 15 countries from August 2000 to March 2002 (Stupp 2005). It assessed concomitant and adjuvant temozolomide with radiotherapy in comparison with radiotherapy alone in primary therapy for

histologically confirmed GBM only. Randomisation was adequate but the trial was not blinded and did not include a placebo. A total of 573 patients with newly histologically diagnosed GBM (at biopsy or resection) were included with inclusion criteria specifying age between 18 to 70 and a WHO performance score of 2 or less (Table 4). Standard radiotherapy schedules of 60Gy for 6 weeks was given to both arms. The temozolomide schedule was 75mg/m² daily during radiotherapy then up to 6 adjuvant cycles of 150 to 200mg/m² for 5 out of 28 days for a total of 6 cycles. No routine chemotherapy was given to the control arm. Subsequent management was given according to need with no pre-specified protocol mentioned. The primary end point was overall survival; secondary endpoints included progression free survival and safety. A follow up article was published describing only the QOL results from the initial trial run by the EORTC (Taphoorn 2005). This used the EORTC QLQ-C30 and QLQ-BCM20 as combined outcome measures which were then converted to a score of 0 to 100. The difference between groups and from baseline was recorded for seven groups (overall, fatigue, social function, emotional function, future uncertainty, insomnia and communication deficit). Compliance with questionnaires was also recorded.

Table 4. WHO Performance Status

Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work
2	Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any selfcare. Totally confined to bed or chair.
5	Dead

The second trial was also published in 2005 and was set in Greece (Athanassiou 2005). It used a dose intensification schedule of temozolomide in the adjuvant phase involving 150mg/m² of temozolomide on days 1 to 5 and 15 to 19. In the concomitant phase temozolomide was administered using a standard 75mg/m². Radiotherapy was administered to both arms in a dose of 60Gy over 6 weeks. Randomisation was adequate but the trial was not blinded and did not include a placebo. A total of 130 patients were randomised, with inclusion criteria specifying GBM on histology, KPS of 60 or more (Table 5), and age over 18 (but with no upper age limit specified). Poor medical condition was an exclusion factor. Primary outcome measures were overall survival and TTP; secondary outcome measures included toxicity.

Table 5. Karnofsky Performance Scale

Score	Definition
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity: minor symptoms of disease
80	Normal activity with effort: some symptoms of disease
70	Cares for self: unable to carry on normal activity or active work
60	Requires occasional assistance but is able to care for needs
50	Requires considerable assistance and frequent medical care
40	Disabled: requires special care and assistance
30	Severely disabled: hospitalisation is indicated, death not imminent
20	Very sick, hospitalisation necessary: active treatment necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

Recurrent disease

The single trial for recurrent disease was a randomised, multicentre, open-label phase II study comparing temozolomide with procarbazine for first relapse of GBM (Yung 2000). A total of 225 patients were randomised between January 1995 and October 1997 and subject to an intention to treat analysis. Randomisation was deemed to be adequate but was not blinded. Temozolomide was administered on days 1 to 5 out of 28 and procarbazine administered for 28 days out of every 56. No radiotherapy was administered to either arm. Primary outcome measures were progres-

sion free survival and overall survival. Secondary outcome measures were health related QOL (measured by EORTC QLQ-C30 and QLQ-BCM20), objective responsiveness and toxicity/adverse events.

Finally, one on-going RCT was identified being run by the EORTC comparing radiotherapy alone with radiotherapy and concomitant and/or adjuvant temozolomide in primary grade III gliomas without 1p19q loss.

Excluded studies

We excluded 339 references and retrieved 12 for detailed evaluation. Of these we excluded 8 for the following reasons (see table of excluded studies):

- Two phase II studies of temozolomide for primary therapy in GBM (Stupp 2002; Lanzetta 2003)
- Two phase II studies of temozolomide in therapy for recurrence of GBM (Bower 1997; Yung 1999a)
- One phase II study of temozolomide for anaplastic astrocytoma or oligoastrocytoma at first relapse (Yung 1999b)
- Two QoL reviews of an included RCT (Osoba 2000a; Osoba 2000b)
- One single centre retrospective series of temozolomide for both primary and recurrent therapy (Newlands 1996)

Risk of bias in included studies

A full analysis of the internal validity of the included studies is described in Table 2. The salient points are outlined below.

Primary therapy

The first trial by the EORTC (Stupp 2005) was of adequate power, included a rigorous ITT analysis and was thorough in reporting of all patients. Although randomisation methods were not specified randomisation by the EORTC is believed to be of high quality. The groups were similar at baseline but formal stratification for prognostic factors was not performed; age and performance status are known to be more significant predictors of survival than treatment. Pathological verification was not completed centrally in 15%, which may have covered up a bias in tumour histology between the arms; a disproportionate number of grade II tumours would increase survival in that arm. Finally, the trial was supported by an unlimited educational grant by Schering-Plough, although it is emphasised that the company had no control in the design or running of the trial.

The most serious concerns relate to the lack of blinding or use of placebo, which raises concerns of bias in outcome assessment and in post-treatment therapy. Un-blinded studies are known to over-estimate treatment effects such as disease progression (Juni 2001). Definition of disease progression was subjective, and therapy post-recurrence was unevenly balanced, with more chemotherapy used in the control arm. Many patients in the control arms also received temozolomide at this point which may have confounded the findings.

The follow on article describing QOL data (Taphoorn 2005) is subject to many of the same comments as the parent trial (Stupp 2005). The issue of blinding and recording of QOL outcomes is of particular concern given the subjective nature of recording such data. The intervals between recordings of data (three monthly) were long enough to introduce some lag time bias i.e. a lack of sensitivity in detecting actual times of events. Outcome data was included in a descriptive manner as it was the only trial including QOL data but not able to be converted into RevMan charts.

Athanassiou 2005

The second trial had broader entry criteria than the EORTC trial including older and less fit patients. Randomisation methods were not clearly specified and participants were not stratified for prognostic factors. Study groups had similar characteristics at baseline and although all patients were accounted for and withdrawals specified there was no intention to treat analysis. There was no clear conflict of interest. Short-comings include a lack of adequate power and no clear definition of disease progression. Again the lack of blinding or use of placebo was a major concern. The necessary statistics were not reported for survival or time to progression which necessitated their calculation from kaplan-meier plots (Parmar 1998).

The two RCTs were suitable for meta-analysis. The differences in entry criteria and dosing schedules was not of sufficient clinical significance to justify exclusion from meta-analysis.

Therapy for recurrent disease

The single trial in recurrent disease had broad entry criteria and few exclusion criteria. The definition for recurrence included only radiological criteria; this is known to be inadequate and will include some who do not have recurrence but changes due to treatment (MacDonald 1990). It was adequately powered but randomisation methods were not stated and stratification criteria were not used. The study groups were not similar at baseline with a greater time to relapse from initial diagnosis or radiotherapy for the procarbazine arm. It is not clear however if this is a marker for prognosis or different disease characteristics. The outcome measures for QOL were excellent although unfortunately there was no clear statistical analysis allowing inclusion in this review. There was good use of HRs with confidence intervals in reporting outcomes, although these required some conversion to be included in RevMan.

The main concern with this trial is again its non-blinded nature. This may lead to bias in reporting all non-objective outcome measures including time to progression, QOL and adverse events.

Effects of interventions

Primary therapy

Temozolomide resulted in an increase in survival (HR 0.58, 95% CI 0.50 to 0.68, $P < 0.001$) compared with the control arm. Fixed effects models were used as the entry criteria for each study were broadly inclusive. As only two trials were included and both demonstrated a survival benefit individually it was apparent that there was no gross heterogeneity between the trials and a formal statistical test of heterogeneity was deemed unnecessary. There was also an increase in time to progression with temozolomide (HR 0.52, 0.42 to 0.64, $P < 0.001$). For QOL there was no difference between the two arms for any of the seven outcome measures

(overall, fatigue, social function, emotional function, future uncertainty, insomnia and communication deficit). Due to the low level of adverse events these are presented in a descriptive manner. In the trial [Stupp 2005](#) grade 3/4 haematologic toxicity occurred in 7% during concomitant therapy and 14% in the adjuvant phase. Events lead to treatment discontinuation in 8%. No haematologic toxicity was noted in the control arm. No statistical difference in severe infections, fatigue or thromboembolic events was reported between either arm. In the trial [Athanasios 2005](#) grade 3/4 haematologica toxicity was reported in the concomitant phase as leucopaenia in 3.5% and thrombocytopenia in 5.2%. In the adjuvant phase the results were leucopaenia in 2% and thrombocytopenia in 5%. Non-haematological side effects were rash 5%, constipation 3.5%, arthralgia 1.5%.

Therapy for recurrent disease

Temozolomide was effective in increasing time to progression (HR 0.68, CI 0.51 to 0.90, $P = 0.008$) but not in increasing survival (HR 0.87, CI 0.65 to 1.16, $P = 0.34$). No appropriate data was available for calculation of QOL outcomes. Adverse events were noted in 77% of the temozolomide group and 76% of the procarbazine group. Grade 3/4 adverse events were found in 18% of the temozolomide group and 25% of the procarbazine group. Haematological adverse events were low at under 7% in both groups but were not cumulatively compared; there did not appear to be a difference in the individual subgroups of haematological adverse events. Drop outs due to adverse events were: temozolomide 3% versus procarbazine 11%. The most common side effects of all grades were: nausea (temozolomide 38% versus procarbazine 34%), vomiting (temozolomide 32% versus procarbazine 27%) and fatigue (temozolomide 27% and procarbazine 15%).

DISCUSSION

This study indicates that temozolomide increases survival when used as part of concomitant and adjuvant primary therapy for GBM. Median survival is estimated to be around 14 months with temozolomide, with a 2 month increase over therapy without chemotherapy. Analysis of the individual kaplan-meier plots suggests this benefit is mostly after 6 months. It is important to remember that patients were randomised after surgery and only included if their disease was stable and WHO/KPS post-surgery appropriate. The median survival times seen are likely to be higher than expected due to the exclusion of aggressive disease and post-operative deaths.

The median survival is similar to that seen with Gliadel® ([Hart 2008](#)) and in a meta-analysis of PCV chemotherapy ([GMT Group 2002](#)). There is a RCT currently being run by Cancer Research UK comparing PCV with concomitant and adjuvant temozolomide in primary disease (BR12). Implantation of wafers coated

with carmustine (Gliadel®) onto the resection cavity at the time of surgery is another means of delivering chemotherapy. Gliadel® also increases survival with a low incidence of adverse effects, although data on time to progression and QoL is more limited than with temozolomide. It is expensive and not all patients will be suitable due to anatomic and other surgical considerations. Decisions over which therapy is to be recommended in an individual patient are best taken in an multidisciplinary setting (www.nice.org.uk/cs-gbraincns and www.nice.org.uk and <http://guidance.nice.org.uk/TA121/?c=91498>).

There is also an increase in the secondary outcome measures of time to progression, which was not demonstrated in the Gliadel or PCV trials. Data on QoL was presented in a complicated and unclear manner in the included trial and was not suitable for inclusion in this analysis. Complex and detailed assessment of QOL data is hindered by drop outs and incomplete data with very few RCTs having provided satisfactorily data ([Walker 2003](#)). There is a low incidence of early severe adverse events from the included studies but less severe adverse events were fairly frequent. Drop outs due to adverse events were low. Long term data is minimal and there is some concern that combination treatment of chemoradiotherapy may result in significant long term toxicity, as has been seen in other brain tumours. This however is unlikely to be of major significance to the majority with GBM as the median survival is still only around one year.

In recurrent disease, temozolomide is also an effective therapy in prolonging survival and delaying time to progression without an increase in adverse events, although data on QOL is more limited. Many of the criticisms of these findings are similar to those for primary therapy, although in this case the evidence is taken from only a single RCT. Despite the broad entry criteria fewer patients will be suitable for chemotherapy in the recurrent disease setting due to general fitness and short survival times.

Although these findings are generally positive, there are reservations. The major concern is the lack of blinding or placebo control in all three trials, which significantly impairs the robustness of many of the findings. Lack of blinding could lead to detection bias with QOL, progression free survival and adverse event reporting. There could also be a bias with post-intervention therapy between arms.

When considering the applicability of these findings to patients in real clinical practice it is important to remember that the patients enrolled were highly selected, with mainly young and fit patients included. A proportion will also be excluded after surgery due to post-operative complications or aggressive disease. It is not clear how effective temozolomide is in those who present with GBM that did not meet the entry criteria, and who will constitute a large proportion of those presenting in clinical practice. Subgroup analysis from the individual trials suggests that young and fit patients undergoing resection rather than biopsy benefit the most. Addi-

tionally none of the trials included patients with HGG other than GBM. Therapy after recurrence was also aggressive, with a high proportion undergoing further surgery or chemotherapy. Therapy post-recurrence varies between units and this needs to be born in mind when considering the applicability of these results in day to day clinical practice (see table of external validity Table 3).

AUTHORS' CONCLUSIONS

Implications for practice

This study indicates that temozolomide is effective as primary therapy for GBM. It prolongs survival and time to progression without a significant risk of early adverse events. It appears to be most effective in young and fit patients with GBM who have had debulking surgery. These results are based on two RCTs of 703 patients in total. Temozolomide is also effective as therapy for recurrent disease, where it increases time to progression without an increase in adverse events. There are still some reservations with this data as the trials were not blinded or placebo controlled, whilst quality of life data could be further expanded upon. In a well selected subgroup of patients with GBM, temozolomide warrant consideration for use as in either primary or recurrent disease settings, but decisions need to be made on an individual patient basis as part of a multi-disciplinary meeting discussion.

Implications for research

Further trials are needed with improved methodology, including placebo control, blinding, and the use of clear statistical reporting of outcome measures in particular for recurrence and QoL. Entry criteria could be broadened to include older and less fit patients in order to increase the applicability of the results to the broader population of those with HGG. All the current studies only included GBM and further studies are needed investigate the potential of temozolomide in grade III tumours, and indeed there is an RCT currently on-going in this tumour group being run by the EORTC. Dose intensification schedules or combination therapies present room for exploration as a means of decreasing resistance to therapy. A trial comparing Gliadel with Temozolomide is warranted in light of the similar survival benefits in a similar patient population. Finally, the use of molecular markers to predict tumour response to chemotherapy is an active area of research which should prioritise treatment to those who are expected to benefit.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Athanassiou 2005

Methods	RCT
Participants	130 patients from multiple Greek oncology departments from 01/00 until 12/02. Inclusion criteria: age over 18, Grade IV tumour and KPS >60. Exclusion criteria: "poor medical condition because of non-malignant systemic disease or acute infection"; any medical condition that could interfere with oral administration of TMZ.
Interventions	Concomitant TMZ daily with RT for 6 weeks. Adjuvant TMZ on days 1-5 and 15-19 for less than 6 cycles.
Outcomes	Primary: Survival; PFS. Secondary: Safety
Notes	Survival: median TMZ 13.41 months (95% CI 9.53-17.13) versus control 7.7 months (95% CI 5.32 versus 9.2 months), log rank P<0.0001. Survival percentages at 6, 12 and 18 months. Time to progression: TMZ 10.8 months (95% CI 8.08-14.69), log rank P<0.0001. TTP survival percentages at 6, 12 and 18 months. Cox proportional hazards model (including age, extent of surgery, KPS and treatment group) for overall survival and TTP. Administration of TMZ and KPS were significant prognostic factors. Subgroup analysis for poor performance status group: non-significant for overall survival or TTP. Toxicity: concomitant TMZ Grade 3/4 leucopaenia 3.5% and thrombocytopenia 5.2%, adjuvant TMZ leucopaenia 2% and thrombocytopenia 5%. Non-haematological side effects: rash 5%, constipation 3.5%, arthralgia 1.5%.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Stupp 2005

Methods	RCT
Participants	573 patients enrolled from 85 centres in 15 countries. Inclusion criteria: Age 18-70, Grade IV tumour, WHO PS <2, adequate haematological and renal function. Exclusion criteria: Unstable or increasing dose of corticosteroids <14 days before randomisation.
Interventions	Concomitant daily TMZ (75mg/m ² /day) during RT (<7weeks). Adjuvant TMZ for first 5 days out of 28 for 6 or fewer cycles. RT was 60Gy focally to the tumour and a 2-3cm margin over 30 sessions and 6 weeks.

Stupp 2005 (Continued)

Outcomes	Primary: Survival. Secondary: PFS, Safety, QoL	
Notes	<p>Survival: median TMZ 14.6 months (95% CI 13.2-16.8) versus Control 12.1 months (CI 11.2-13), HR 0.63 (95% CI 0.52-0.75) P<0.001 log rank test. Also survival at 6 monthly intervals up to 24 months.</p> <p>Progression free survival: TMZ 6.9 months (95% CI 5.8-8.2) versus Control 5.0 months (4.2-5.5), HR 0.54 (95% CI 0.45-0.64) P<0.001 log rank test. Also progression free survival at 6 monthly intervals up to 24 months.</p> <p>Cox proportional hazards model (including age, corticosteroid use, sex, MMSE score and tumour location) : HR 0.62 (95% CI 0.51-0.75).</p> <p>Subgroup analyses: survival advantage maintained in all subgroups analysed except those undergoing biopsy and those with poor performance score</p> <p>Safety: TMZ Grade 3/4 haematologic toxicity in concomitant phase 7%, adjuvant phase 14%, leading to treatment discontinuation in 5%. No haematologic toxicity in control arm. No difference in severe infections, fatigue or thromboembolic events.</p>	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Taphoorn 2005

Methods	RCT	
Participants	As Stupp 2005	
Interventions	As Stupp 2005	
Outcomes	Quality of Life analysis of trial by Stupp 2005	
Notes	<p>Follow on paper describing only the quality of life results from the initial trial run by the EORTC.</p> <p>No significant difference in health related quality of life (HRQOL) between TMZ and control arms</p> <p>Used EORTC QLQ-C30 and QLQ-BN20 in combination converted to a score of 0-100.</p>	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Yung 2000

Methods	RCT	
Participants	225 patients from multiple international centres. Inclusion criteria: known GBM at first relapse, age of 18 or more, KPS of 70 or more, life expectancy of 12 weeks or more	

Yung 2000 (Continued)

Interventions	<p>Temozolomide: 200mg/m²/day (if chemotherapy naive) or 150mg/m²/day (if prior chemotherapy)for 5 days out of a 28 day cycle. Procarbazine 150mg/m²/day (chemotherapy naive) or 125mg/m²/day (if prior chemotherapy)for 28 consecutive days in a 56 day cycle. Exclusion criteria: more than one prior chemotherapy; previous chemotherapy with single agent PRO or dacarbazine; vincristine within 2 weeks prior to study drug; nitrosurea or mitomycin C within 6 weeks prior to study drug; chemotherapy (excluding vincristine, nitrosurea or mitomycin C) within 4 weeks prior to study drug; history of PRO-induced rash; pervious interstitial radiotherapy or stereotactic radiotherapy; pregnancy; breastfeeding; toxicity from prior radiotherapy; HIV positive; previous or concurrent solid tumour at other sites (excluding basal cell carcinoma). Treatment until unacceptable toxicity, disease progression or 2 years treatment completed.</p>
Outcomes	Objective response, six month PFS, median PFS, survival, adverse events, HRQL (QLQ-C30 and BCM20)
Notes	<p>Objective response: TMZ 45.6% versus PRO 32.7%, P=0.049 PFS: median TMZ 12.4 weeks versus PRO 8.32 weeks, HR 1.47 (95% CI 1.11-1.95)P=0.0063. PFS percentages at 6 months. Survival: HR 1.11, P=0.019. Survival percentages at 6 months. Adverse events. Drop outs due to adverse events, TMZ 3 versus PRO 11. No other adverse events at greater than 5% in either arm.</p>

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

RCT = Randomised Controlled Trial. TMZ = Temozolomide. RT = Radiotherapy. PFS = Progression Free Survival. QoL =Quality of Life.

Characteristics of excluded studies [ordered by study ID]

Bower 1997	Phase II study. Non-randomised participants.
Lanzetta 2003	A review on the experiences of temozolomide at a single institution between. No prospective data collection or randomisation of participants.
Newlands 1996	A single centre experience at the Charing Cross Hospital in London on the use of temozolomide. No prospective data collection or randomisation of participants.
Osoba 2000a	Quality of life data on glioblastoma multiforme from an earlier phase II study. Non-randomised trial.
Osoba 2000b	Quality of life data on anaplastic astrocytoma from an earlier phase II study. Non-randomised trial.

(Continued)

Stupp 2002	A phase II study. Participants were not randomised. Primary outcomes were safety and toxicity.
Yung 1999a	Phase II study. Participants were not randomised.
Yung 1999b	Phase II study. Participants were not randomised/single arm study..

DATA AND ANALYSES

Comparison 1. Primary Therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival for Primary Therapy	2	683	HR (Fixed, 95% CI)	0.58 [0.50, 0.68]
2 Progression Free Survival	2	683	Hazard Ratio (Random, 95% CI)	0.56 [0.48, 0.67]

Comparison 2. Recurrence Therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	1	225	Hazard Ratio (Random, 95% CI)	0.87 [0.65, 1.16]
2 Progression Free Survival	1	225	Hazard Ratio (Random, 95% CI)	0.68 [0.51, 0.90]

Analysis 1.1. Comparison 1 Primary Therapy, Outcome 1 Survival for Primary Therapy.

Review: Temozolomide for High Grade Glioma

Comparison: 1 Primary Therapy

Outcome: 1 Survival for Primary Therapy

Study or subgroup	TMZ and RT	RT alone	log [HR] (SE)	HR IV,Fixed,95% CI	Weight	HR IV,Fixed,95% CI
	N	N				
Athanassiou 2005	57	53	-0.7571 (0.1565)		27.1 %	0.47 [0.35, 0.64]
Stupp 2005	287	286	-0.462 (0.0953)		72.9 %	0.63 [0.52, 0.76]
Total (95% CI)					100.0 %	0.58 [0.50, 0.68]

Heterogeneity: Chi² = 2.59, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 6.66 (P < 0.00001)

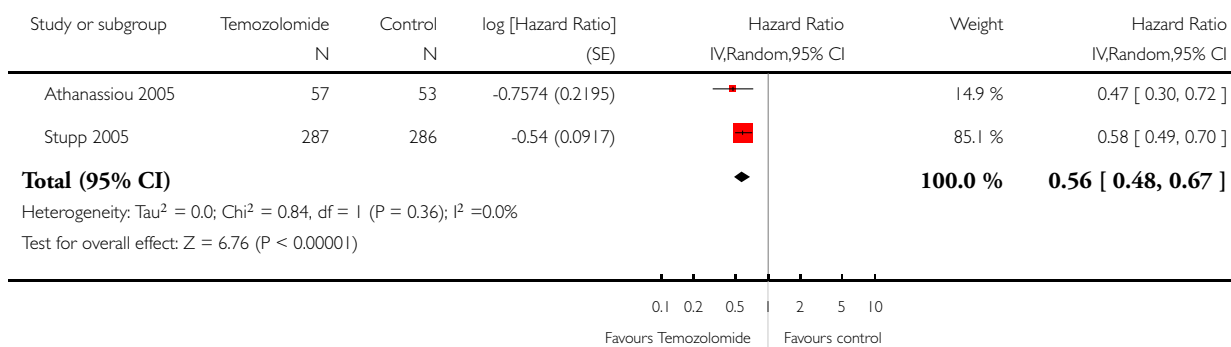
0.1 0.2 0.5 2 5 10
Favours TMZ and RT Favours RT alone

Analysis 1.2. Comparison 1 Primary Therapy, Outcome 2 Progression Free Survival.

Review: Temozolomide for High Grade Glioma

Comparison: 1 Primary Therapy

Outcome: 2 Progression Free Survival

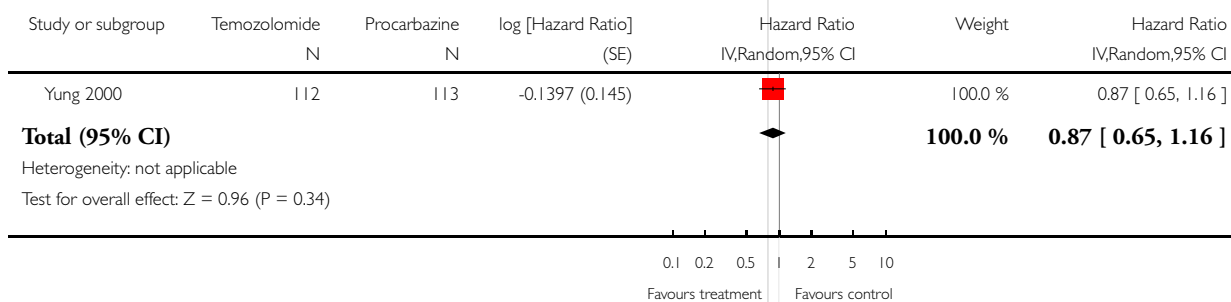


Analysis 2.1. Comparison 2 Recurrence Therapy, Outcome 1 Survival.

Review: Temozolomide for High Grade Glioma

Comparison: 2 Recurrence Therapy

Outcome: 1 Survival

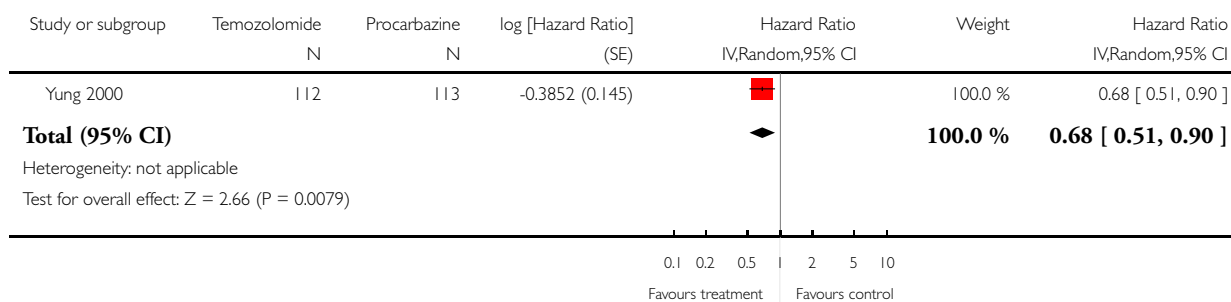


Analysis 2.2. Comparison 2 Recurrence Therapy, Outcome 2 Progression Free Survival.

Review: Temozolomide for High Grade Glioma

Comparison: 2 Recurrence Therapy

Outcome: 2 Progression Free Survival



WHAT'S NEW

Last assessed as up-to-date: 26 May 2008.

3 November 2009	Amended	Minor amendment made to typographically error in results section after being drawn to our attention by Feedback received. Temozolomide resulted in an increase in survival (HR 0.84 , 95% CI 0.50 to 0.68, P < 0.001) compared with the control arm now reads Temozolomide resulted in an increase in survival (HR 0.58 , 95% CI 0.50 to 0.68, P < 0.001) compared with the control arm.
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HISTORY

Review first published: Issue 4, 2008

3 June 2008	Amended	Converted to new review format.
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CONTRIBUTIONS OF AUTHORS

Michael Hart led and wrote the review. Ruth Garside ran the original report and was assisted by Gabriel Rogers, Margaret Somerville and Ken Stein. Robin Grant supervised the review and was involved with the final editing process.

DECLARATIONS OF INTEREST

All authors report no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Dr Michael Hart was a recipient of a Cochrane Review Grant, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents, Alkylating [* therapeutic use]; Brain Neoplasms [* drug therapy]; Dacarbazine [* analogs & derivatives; therapeutic use]; Glioblastoma [* drug therapy]; Neoplasm Recurrence, Local [drug therapy]

MeSH check words

Humans