Cochrane Library

Cochrane Database of Systematic Reviews

Procarbazine, lomustine and vincristine for recurrent high-grade glioma (Review)

Parasramka S, Talari G, Rosenfeld M, Guo J, Villano JL

Parasramka S, Talari G, Rosenfeld M, Guo J, Villano JL.
Procarbazine, lomustine and vincristine for recurrent high-grade glioma.
Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD011773.
DOI: 10.1002/14651858.CD011773.pub2.

www.cochranelibrary.com

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 3
BACKGROUND 6
OBJECTIVES 7
METHODS 7
Figure 1. 8
Figure 2. 9
Figure 3. 10
RESULTS 11
DISCUSSION 13
AUTHORS' CONCLUSIONS 14
ACKNOWLEDGEMENTS 14
REFERENCES 16
CHARACTERISTICS OF STUDIES 18
ADDITIONAL TABLES 23
APPENDICES 24
WHAT'S NEW 28
CONTRIBUTIONS OF AUTHORS 28
DECLARATIONS OF INTEREST 28
SOURCES OF SUPPORT 28
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 28
INDEX TERMS 29

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Procarbazine, lomustine and vincristine for recurrent high-grade glioma

Saurabh Parasramka[1], Goutham Talari[1], Myrna Rosenfeld[2], Jing Guo[3], John L Villano[1]

[1]Department of Internal Medicine, University of Kentucky College of Medicine, Lexington, Kentucky, USA. [2]Department of Neurology, Hospital Clinic /IDIBAPS, Barcelona, Spain. [3]Center for Health Services Research, Kentucky Clinic, Lexington, USA

Contact address: John L Villano, Department of Internal Medicine, University of Kentucky College of Medicine, 800 Rose Street, CC447, Lexington, Kentucky, 40536, USA. jlvillano@uky.edu.

Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: Edited (no change to conclusions), published in Issue 7, 2017.

Citation: Parasramka S, Talari G, Rosenfeld M, Guo J, Villano JL. Procarbazine, lomustine and vincristine for recurrent high-grade glioma. *Cochrane Database of Systematic Reviews* 2017, Issue 7. Art. No.: CD011773. DOI: 10.1002/14651858.CD011773.pub2.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Recurrent high-grade glioma (HGG) carries an extremely poor prognosis. There is no current standard of care or guideline-based recommendations. Nitrosourea-based multidrug chemotherapy or PCV — procarbazine, lomustine (CCNU) and vincristine — is one of the treatment options at recurrence. There has been no meta-analysis which looks at the benefits and harms of PCV chemotherapy in adults with recurrent HGG.

Objectives

To assess the effectiveness and safety of procarbazine, lomustine, and vincristine (PCV) chemotherapy with other interventions in adults with recurrent high-grade glioma. To investigate whether predefined subgroups of people benefit more or less from chemotherapy.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL Issue 4, 2017), MEDLINE (1946 to 22 May 2017), and Embase (1980 to 22 May 2017). We searched trial registries including the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch) and the National Institutes of Health (NIH; ClinicalTrials.gov). We searched the reference lists of all identified studies; the electronic table of contents of the *Journal of Neuro-Oncology* (1983 to 2016) and *Neuro-Oncology* (1999 to 2016); and conference abstracts from the Society for Neuro-Oncology (SNO) and the American Society of Clinical Oncology (ASCO 2004 to 2016). We also searched unpublished grey literature and other regional databases. There were no language restrictions.

Selection criteria

Randomised controlled trials (RCTs), quasi-randomised trials (QRCTs), or controlled clinical trials (CCTs) where PCV was used to treat adults with recurrent HGG. Comparison arm included no chemotherapy, other second line chemotherapy or best supportive care.

Data collection and analysis

Two review authors extracted the data and undertook a 'Risk of bias' assessment and critical appraisal of the studies.

Main results

We identified two RCTs meeting our inclusion criteria. The two trials tested different comparisons.

One RCT included 35 participants and compared PCV with 'eight drugs in one day' multidrug chemotherapy, which is a combination of drugs with different mechanisms of action. Median survival was 6 months for the PCV group and 6.5 months for the 'eight drugs in one day' group. Adverse event outcomes were not graded or quantified. Progression-free survival (PFS) and quality of life (QoL) were not described in the methods and were not an outcome of interest. The sample size in this study was small, which lead to insufficient statistical power

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

to detect clinical differences. According to the GRADE approach we judged the quality of evidence to be low for survival outcome and very low for chemotherapy toxicity

The second multi-institutional RCT included 447 participants and compared PCV with Temozolomide (TMZ). Participants were randomised into three arms to receive PCV, and two different regimens of TMZ in a 2:1:1 ratio at first recurrence. The trial reported a median overall survival of 6.7 months and 7.2 months for the PCV and TMZ group respectively. It reported a PFS of 3.6 months for the PCV group and 4.7 months for the TMZ group. There was no observed difference of effect on overall survival (hazard ratio (HR) 0.91, 95% CI 0.74 to 1.11; P = 0.35) or PFS (HR 0.89, 95% CI 0.73 to 1.08; P = 0.23) in participants receiving PCV or TMZ chemotherapy. The proportion of people with at least one grade 3 or 4 adverse event was not clinically important at 9.2% versus 12.2% in PCV and TMZ arms respectively. Mean QoL scores calculated at baseline, 12 weeks and 24 weeks was 51.9 versus 59.8 favouring TMZ (P = 0.04) which is statistically but not clinically significant and was less than the pre-defined 10 point change for moderate improvement. We judged the GRADE quality of evidence to be moderate for overall survival, PFS, and chemotherapy toxicity and low for QoL.

Authors' conclusions

Evidence is based on a single large trial analysis as the other trial was small, with inadequate power to detect survival difference. Chemotherapy-naive patients with HGG at first recurrence when treated with PCV or TMZ have similar survival and time-to-progression outcomes. Adverse events are similar and QoL scores are statistically but not clinically significant between TMZ and PCV. Further RCTs should be conducted with adequate power following CONSORT guidelines with emphasis on QoL outcomes.

PLAIN LANGUAGE SUMMARY

PCV chemotherapy for recurrent high grade glioma

The issue
Gliomas are primary brain tumours arising from supporting cells of the brain or spinal cord. The World Health Organization (WHO) classifies the condition into low-grade and high-grade glioma (HGG) depending on their appearance under the microscope. Higher grade correlates with worse outcomes. One of the outcomes is recurrence of glioma.

The aim of the review
Recurrent high-grade glioma carries a very poor prognosis. Treatment options are limited at recurrence. PCV is a nitrosourea-based multi-drug chemotherapy which can be used at recurrence. A multidrug regimen kills the cancer cells in more than one way and is therefore assumed to be more effective. There is lack of knowledge about the efficacy and adverse effects of PCV when used for treating recurrent HGG.

What are the main findings?
In this review we found two randomised controlled trials which studied PCV in recurrent HGG patients. The comparator was Temozolomide (TMZ) in one and 'eight drugs in one day' multidrug chemotherapy in another. Results of the two trials were not combined because they compared PCV with different treatments.

What is the quality of evidence?
Conclusions should be drawn with caution as they are based on a single trial analysis as the other trial was too small and underpowered to detect significant difference. Adverse effects and QoL results are based on a single trial analysis. The proportion of participants experiencing severe adverse events with PCV was similar to TMZ. QoL scores were higher with TMZ but not clinically significant. We attributed moderate-grade quality of evidence for overall survival, progression-free survival, chemotherapy toxicity and low-grade evidence for QoL.

What are the conclusions?

Chemotherapy-naive patients with HGG at first recurrence when treated with PCV or TMZ have similar survival and time-to-progression outcomes. Adverse events are similar and QoL scores are statistically but not clinically important between TMZ and PCV. The results do not apply to our contemporary patients with recurrent HGG as most of them would receive chemotherapy after original diagnosis as standard care. Participants in this trial received only radiotherapy prior to recurrence. Molecular markers were not used in decision making, which is the standard of care now.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

'Eight drugs in one day' compared with PCV for recurrent GBM in adults

Patient or population: Adults with recurrent GBM

Settings: Hospital setting in Milan, Italy

Intervention: 'Eight drugs in one day' multi-drug chemotherapy

Comparison: PCV

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	PCV	"eight in one"				
Overall Survival	See comments	See comments	Not provided	35 (1 study)	⊕⊕⊝⊝ **low** [1]	Small sample size, exclusion criteria not explicit, baseline characteristic and statistical tests reporting inadequate. HR and survival data not provided
Chemotherapy toxicity	See comments	See comments	Not provided	35 (1 study)	⊕⊝⊝⊝ **very low** [2]	Unblinded for detection and performance. Toxicity not graded.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio;

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] OS was downgraded from high to low because of limitation in design due to inadequate reporting of allocation concealment leading to selection bias. Even though CI was not calculated it was at high risk of imprecision because of small sample size.
[2] Chemotherapy toxicity was downgraded from moderate to very low because of limitations in design leading to selection bias, due to lack of allocation concealment and imprecision because of small sample size. Toxicity was not measured on a graded scale.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Summary of findings 2.

PCV compared with TMZ for recurrent HGG in adults

Patient or population: Adults with recurrent HGG

Settings: Mutiple hospitals and centres in United Kingdom

Intervention: PCV

Comparison: TMZ

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TMZ	PCV				
Overall survival median follow-up 12 months	See comments	See comments	HR 0.91 (0.74 to 1.11); P = 0.35	447 (1 study)	⊕⊕⊕⊖ **moderate** [1]	Due to the way HR are estimated the assumed and corresponding risks would not take into account the outcome.
PFS Median follow-up 12 months	See comments	See comments	HR 0.89 (0.73 to 1.08); P = 0.23	447 (1 study)	⊕⊕⊕⊖ **moderate** [2]	Good concordance between independent and local assessor. Risk of inaccurate assessment because of limitation of diagnosis method. No assumed risk could be calculated
QoL EORTC QoL questionnaire C30; at baseline, 12 weeks and 24 weeks	See comments	See comments	51.9 for PCV versus 59.8 for TMZ arm (P = 0.04)	415 (1 study)	⊕⊕⊖⊖ **low** [3]	Unblinded study at risk for performance and detection bias. Measured at fixed intervals and thus at risk of survival bias. No assumed risk could be calculated
Chemotherapy toxicity During 1st 12 weeks of treatment	See comments	See comments	Not estimable	441 (1 study)	⊕⊕⊕⊖ **moderate** [4]	At risk of performance and detection bias because of unblinding. No assumed risk could be calculated

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; HR: Hazard Ratio

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] OS quality of evidence was downgraded from high to moderate because of indirectness of population, as the trial population had not received chemotherapy at original diagnosis which will be standard of care now.
[2] PFS evidence was downgraded from high to moderate level because of lack of blinding of participants and outcome assessors. It was assessed at fixed time period which may have missed interim changes and effected estimate of the outcome.
[3] QoL evidence was double downgraded from high to low because of the large effect of unblinding in a subjective outcome like this.
[4] Chemotherapy toxicity evidence was downgraded from high to moderate because of bias introduced by unblinding.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BACKGROUND

Description of the condition

Gliomas are primary brain tumours arising from supporting cells of the brain or spinal cord. The World Health Organization (WHO) separates gliomas into low-grade (I or II) and high-grade gliomas (grade III or IV) based on features reflecting aggressiveness and infiltration. Higher grade correlates with poorer clinical outcome. Grade III gliomas include anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO) and anaplastic oligoastrocytoma (AOA or mixed glioma). Grade IV gliomas are glioblastomas (GBM) (Louis 2007). In a recent update of WHO classification of central nervous system (CNS) tumours there has been a major restructuring of diffuse gliomas, with incorporation of genetically defined entities (Louis 2016).

The overall incidence rate for primary malignant brain and CNS tumours is estimated to be 7.27/100,000 per year for all age groups with peak incidence in the fifth and sixth decades. Astrocytoma and GBM combined account for about three-quarters of gliomas (Ostrom 2013). Data from the International Agency for Research on Cancer (IARC) estimates 256,213 worldwide cases of brain and CNS tumour, which is 1.8% of all estimated cancers, and 189,394 deaths, which is 2.3% of all cancer-related deaths (Ferlay 2015). An estimated 13,700 deaths were attributed to HGG in the brain and CNS in the USA in 2012 (Siegel 2012).

Initial presentation for people with glioma reflects the fast-growing nature of HGG and includes intractable headaches, cognitive changes such as generalised slowing or personality changes, memory and language difficulty, neurologic deficits such as weakness or numbness of extremity, and seizures (Hildebrand 2005). People suspected to have a CNS tumour are evaluated preferably by magnetic resonance imaging (MRI) of the brain or spinal cord, or both. HGG commonly demonstrates enhancement of margins with contrast. Surgery to remove as much tumour as possible safely and obtain a histologic diagnosis is optimal, as this can influence management and prognosis.

For GBM (grade IV), one RCT reported a survival benefit of 2.5 months in the group receiving concomitant chemo-radiation therapy followed by adjuvant chemotherapy with oral Temozolomide (TMZ) compared with the group treated only with radiation therapy (Stupp 2005). Anaplastic gliomas (grade III) are a heterogeneous group of tumours resulting in varied clinical course and survival influenced by type. AA fares worse than AO. These tumours tend to occur in a younger age group than GBM and response to chemotherapy is more likely. In one RCT on AA, there was delay in progression in people receiving chemotherapy compared to radiation therapy alone (Wick 2009). A Cochrane Review of trials comparing treatment interventions in AO or AOA demonstrated people receiving procarbazine, lomustine plus vincristine chemotherapy (PCV) and radiation therapy living longer (Abdulkarim 2014).

These trials discovered certain molecular bio-markers and genetic mutations with predictive and prognostic value. AO and AOA tumours with chromosomal abnormality 1p/19q co-deletions had superior survival. Isocitrate dehydrogenase (IDH-1 and 2) gene mutations are important markers for glial tumours. The O^6 methylguanine DNA-methyltransferase (MGMT) gene encodes for a protein responsible for deoxyribonucleic acid (DNA) repair and MGMT promoter methylation disables it from making that protein. It has prognostic value in HGG and is a predictor of response to treatment in GBM.

Description of the intervention

Although adjuvant radiation therapy plus chemotherapy improves survival, death is inevitable from recurrence (Eisele 2013). The management of recurrent disease is challenging as there is no widely agreed standard of care. The current treatment options include re-irradiation or surgery or both for localised recurrence with or without placing carmustine (bis-chloroethylnitrosourea (BCNU)) chemotherapy-containing wafers within the tumour cavity; or second-line chemotherapy, i.e. TMZ or nitrosourea as a single agent or in a combination PCV regimen; or anti-angiogenics (medicines that inhibit formation of new blood vessels within tumours); or both BCNU and second-line chemotherapy (Wang 2013).

At first recurrence, some benefit of chemotherapy has been shown for people with a good performance status (a measure of a person's functional capacity) who have not received prior adjuvant chemotherapy. There is evidence of activity of nitrosourea as a single agent or in a combination PCV regimen in recurrent disease. There are subtle differences in the doses of these chemotherapy agents used in different countries. In practice, single-agent TMZ is widely used at recurrence of HGG as it delays progression and has better QoL (Hart 2013). In a Cochrane Review on anti-angiogenic therapy, it appeared to delay progression without prolonging life and with unclear QoL benefit (Khasraw 2014).

A PCV regimen is associated with systemic toxicities. The main concern regards the haematological adverse effects. One study had a 64% frequency of serious (grade III to IV) haematological toxicities (Cairncross 2012); and 46% in another with no treatment-associated deaths (Van den Bent 2012). Alternative single-agent chemotherapy using TMZ would also have significant haematological adverse effects in recurrent HGG (Villano 2012).

How the intervention might work

For recurrent HGG, systemic therapy with PCV has been used in people who have not previously received chemotherapy or following failure of radiation therapy and concomitant and adjuvant chemotherapy such as TMZ. Single-agent nitrosourea therapy, such as lomustine, achieves tumour control in some people with recurrent glioma (Buckner 1995; Rajan 1994).

Two separate studies evaluating response to PCV in people with recurrent GBM demonstrated a similar trend and improvement in PFS and overall survival (Kappelle 2001; Schmidt 2006).

Procarbazine and nitrosoureas (BCNU, lomustine, and semustine) achieve good concentrations in the brain and cerebrospinal fluid (CSF; fluid around the brain and spinal cord). They mainly work by altering the structure and function of DNA, ribonucleic acid (RNA), and certain proteins. Vincristine is a vesicant (can cause tissue injury) and needs to be administered in large veins close to the heart (central vein). It works by inhibiting cell division. It has been argued that it does not cross the blood-brain barrier (BBB) (Boyle 2004); however, the BBB is not intact in people with AO and hence there is delivery of medicine across the BBB (Arismendi-Morillo 2005; Brooks 1984).

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

The combination of PCV may provide the most potent activity for people who have not responded to traditional therapy with radiation or TMZ chemotherapy, where treatment options are limited. Its use in recurrent disease may also be affected by prior usage.

Why it is important to do this review

We found no systematic reviews on the value of PCV chemotherapy in recurrent HGG. Trials are usually performed with a small subset of participants and only a meta-analysis might demonstrate significant activity associated with PCV use in recurrent HGG. The adverse effect profile of PCV is not well established in the treatment of recurrent disease and may vary based on the prior dosage and regimen of chemotherapy received. Our analysis will guide clinicians on the benefit or not of prescribing this combination chemotherapy.

Administering and monitoring PCV is cumbersome, which is one of the reasons physicians have historically been hesitant in prescribing it. However modern high-quality evidence that chemotherapy is advantageous as part of first-line therapy has encouraged re-appraisal of therapy at recurrence.

OBJECTIVES

To assess the effectiveness and safety of procarbazine, lomustine, and vincristine (PCV) chemotherapy with other interventions in adults with recurrent high-grade glioma. To investigate whether predefined subgroups of people benefit more or less from chemotherapy.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs meeting the inclusion criteria were evaluated.

Types of participants

We included adults (aged 18 years or older) with previously treated and histologically confirmed grade III or IV glioma based on WHO criteria at the time of original diagnosis.

Types of interventions

Studies where all variations of PCV chemotherapy in either arm have been evaluated with respect to dosage, intensity, median number of cycles received, and duration of treatment, were eligible. Other salvage therapy could have included corticosteroids, re-irradiations with different dosages, and re-surgeries with or without BCNU chemotherapy-containing wafers within the tumour cavity (as long as it is similar in both arms).

The control arm could receive any of the following: placebo; best supportive care; an active intervention with second-line chemotherapy or re-challenge with TMZ; anti-angiogenics (medicines that inhibit formation of new blood vessels within tumours); novel therapy such as electrical stimulation; or combination drug regimens that may include one or two of procarbazine, lomustine, or vincristine.

Types of outcome measures

Primary outcomes

- Overall survival defined as time from randomisation to death from any cause.

Secondary outcomes

- Progression-free survival (PFS), defined as time from randomisation to progression of disease. Criteria for recurrence was based on McDonald criteria extrapolated to MRI (Macdonald 1990) (Table 1); or Response Assessment in Neuro-Oncology (RANO) criteria (Wen 2010) (Table 2).
- Quality of life (QoL), measured using the European Organisation for Research and Treatment of Cancer (EORTC) Core QoL Questionnaire (QLQ-C30) or Brain Cancer Module (BCM) scale, or both; Functional Assessment of Cancer Therapy – General (FACT-G) or Functional Assessment of Cancer Therapy – Brain (FACT-Br) scale (Mauer 2008).
- The proportion of participants experiencing chemotherapy toxicity. Grades of toxicity were grouped according to Common Terminology Criteria for Adverse Events (CTCAE 2010).
    - Haematologic (leukopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage).
    - Gastrointestinal (nausea, vomiting, anorexia, diarrhoea, hepatobiliary, proctitis).
    - Genitourinary.
    - Skin (stomatitis, mucositis, alopecia, allergy).
    - Neurologic (peripheral and central).
    - Pulmonary.

Search methods for identification of studies

Electronic searches

The following large databases were searched. Foreign language journals were eligible for inclusion.

Appendix 1 lists the CENTRAL search strategy; Appendix 2 lists the MEDLINE search strategy; and Appendix 3 lists the Embase search strategy.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 4).
- MEDLINE (1946 to 22 May 2017 May).
- Embase (1980 to 22 May 2017).
- International Clinical Trials Register (ICTRP) Search Portal (apps.who.int/trialsearch/AdvSearch.aspx).
- ClinicalTrials.gov.

Searching other resources

- We searched the reference lists of all identified studies.
- We handsearched and also searched the electronic table of contents of the Journal of Neuro-Oncology and Neuro-Oncology to identify trials. We searched the conference reports of the Society for Neuro-Oncology (SNO) and the American Society of Clinical Oncology (ASCO 2004 to 2015).
- We searched the reference lists of neuro-oncology textbooks, review articles, and relevant studies.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

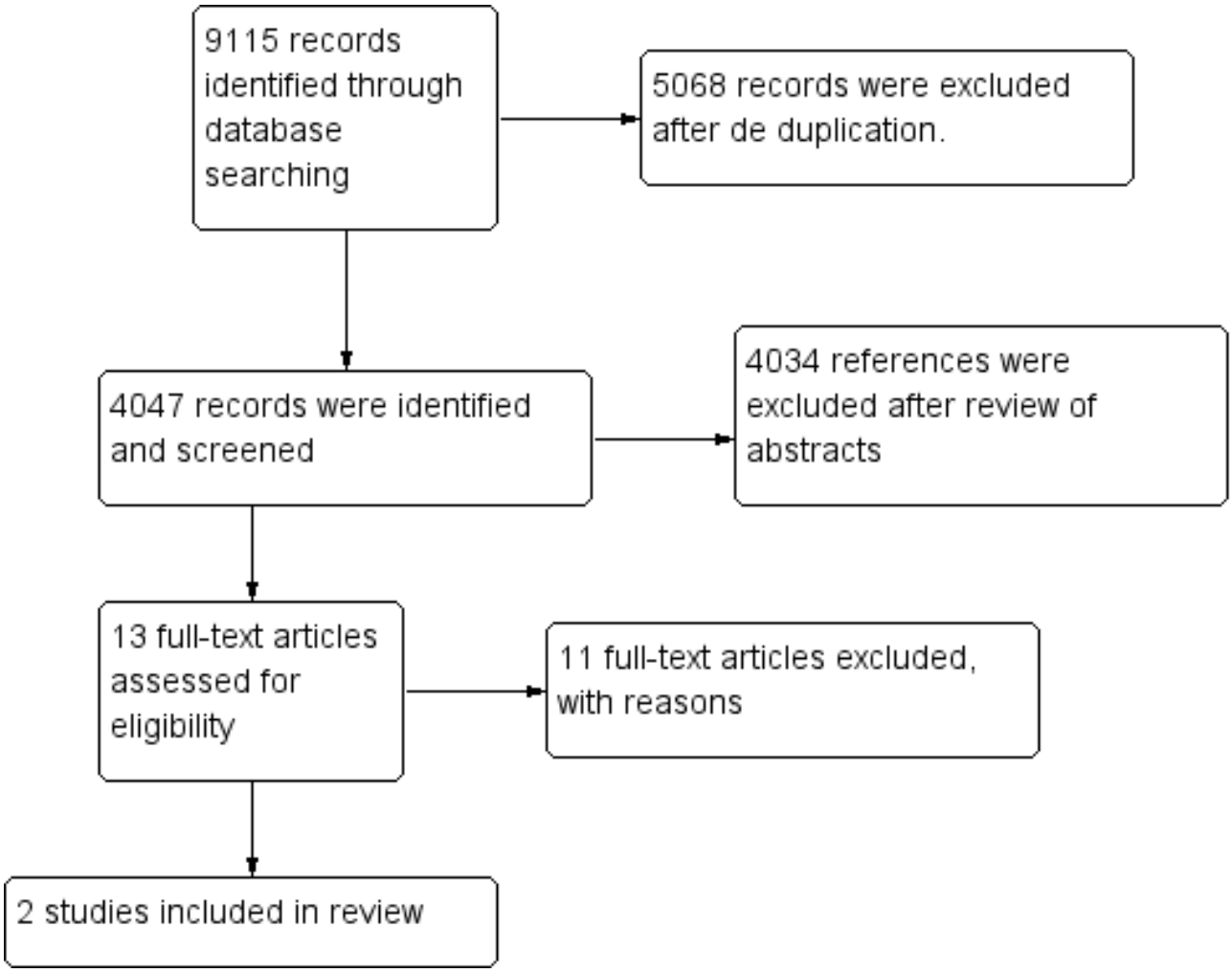
- We contacted investigators known to be involved in previous studies to seek information about unpublished data.
- We searched for unpublished grey literature on www.OpenGrey.eu.
- We searched other regional databases as given in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions*.

Data collection and analysis

Selection of studies

We used EndNote to download all studies identified by search methods and removed duplicates. Two review authors (SP and GT) independently screened all titles and abstracts of remaining references. We discarded records that were not applicable and retrieved the full-text reports of potentially relevant studies and reviews. Two review authors (SP and GT) independently assessed the reports to identify studies satisfying the inclusion criteria (Figure 1).

Figure 1. Study flow diagram.



We resolved disagreements at all stages by discussion. When disagreement was due to a difference in interpretation, a third review author (JV) resolved the deadlock by arbitration.

Data extraction and management

For included studies, two review authors (SP and GT) extracted data on characteristics of participants and interventions, outcomes, study quality and deviation from protocol. Studies with intention-to-treat analyses were used. A prespecified form in an Excel spreadsheet was used to collect data and complete the Characteristics of included studies (Appendix 4).

We extracted outcome data as follows.

- For time-to-event data (overall survival and PFS), we extracted the log of the hazard ratio (log (HR)) and its standard error from trial reports. If studies did not report these, we attempted to estimate the log (HR) and its standard error using the methods of Parmar 1998. If these variables could not be estimated, we reported available proportions with corresponding P values.
- For dichotomous outcomes (adverse events or deaths), if it was not possible to use HRs we extracted the number of participants in each treatment arm who experienced the outcome of interest

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR).

- For continuous outcomes, we extracted the final value and standard deviation (SD) of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (MD) (if trials measured outcomes on the same scale), or standardised MDs (if trials measured outcomes on different scales) between treatment arms and its standard error.

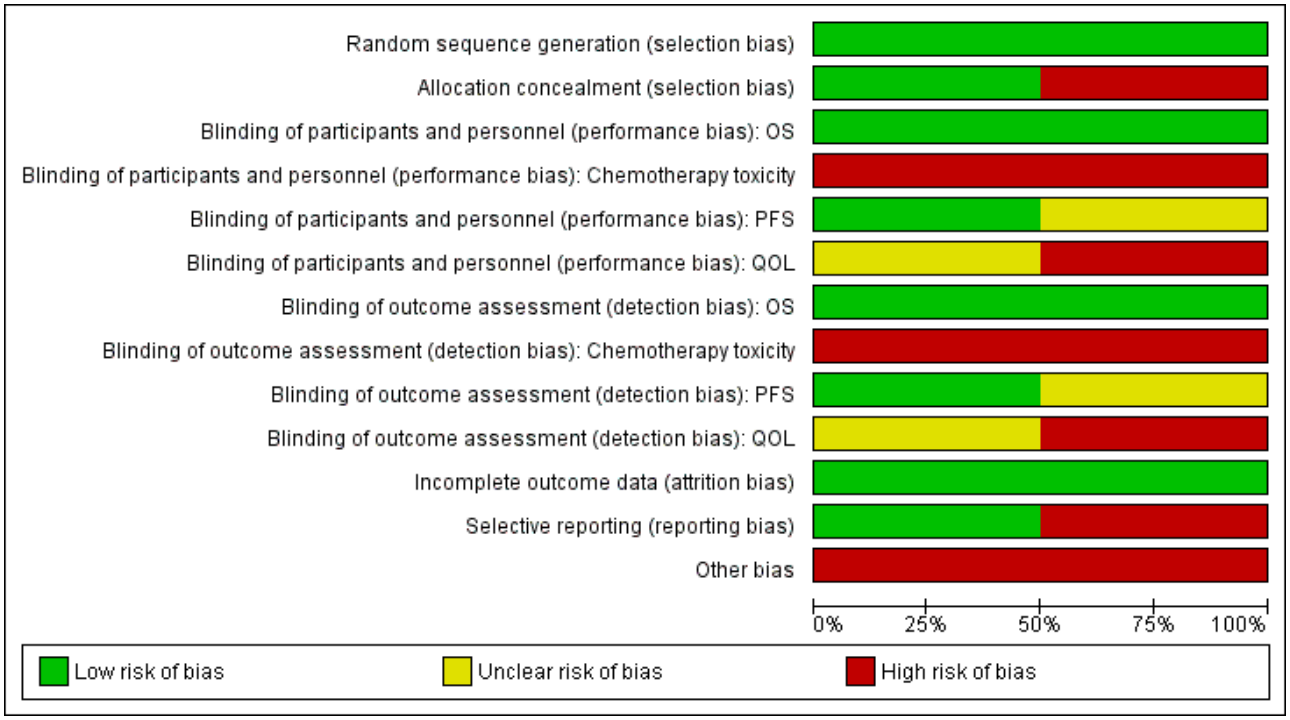
Where possible, we extracted all data relevant to an intention-to-treat analysis, analysing participants in the groups to which they were assigned. We noted the time points at which trials collected and reported outcomes.

Differences were reconciled by discussion or by consultation with third review author (JV). Data integration into Review Manager 5 (RevMan 5) was performed by single author (SP) (Review Manager 2014).

Assessment of risk of bias in included studies

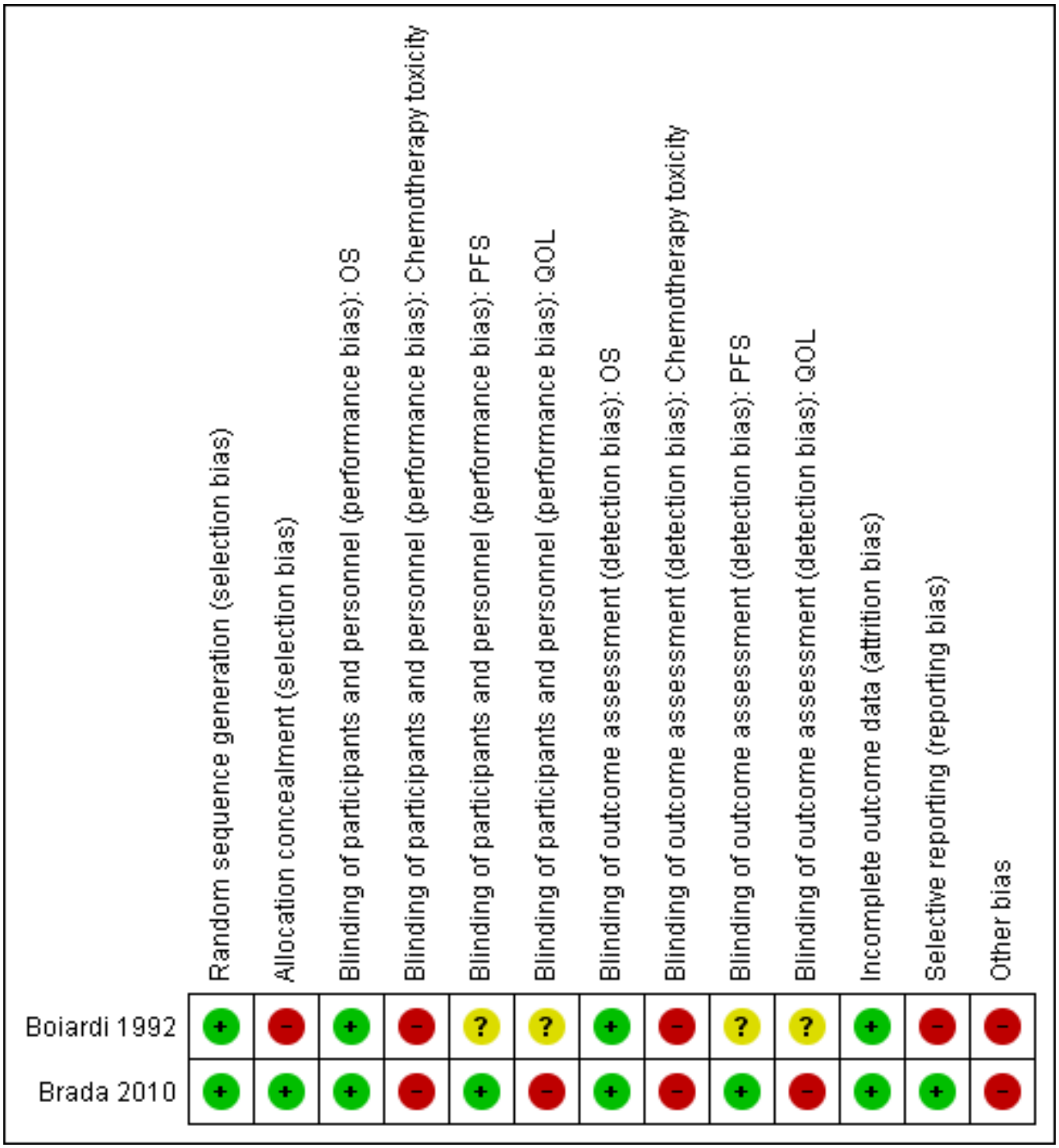
Two review authors (SP and JG) assessed the risk of bias and critically appraised the included studies as described in the Cochrane 'Risk of bias' assessment tool (Higgins 2011). Risk of bias was classified as high, low, or unclear as per the *Cochrane H andbook for Systematic Reviews of Interventions*. We resolved any disputes through discussion. Results are presented as a 'Risk of bias' graph (Figure 2); and a 'Risk of bias' summary (Figure 3). The seven domains assessed were:

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item for each included study.



Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



- sequence generation (selection bias);
- allocation concealment (selection bias);
- masking of participants and personnel (performance bias);
- masking of outcome assessors (detection bias);
- selective outcome reporting (reporting bias);
- incomplete outcome data (attrition bias);
- other sources of bias (e.g. funding source).

Measures of treatment effect

- For time-to-event data (overall survival and PFS), we used hazard ratio (HR) with 95% confidence intervals (CIs) where possible.
- For dichotomous outcomes (adverse events), we presented results as RR with 95% CIs.
- For continuous outcomes (QoL), we used MD or standardised mean difference (SMD) where possible.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Dealing with missing data

We did not impute missing data for any of the outcomes (Higgins 2011).

Data synthesis

We carried out data synthesis and analyses using RevMan 5 (Review Manager 2014).

- For time to event data we planned to pool the HR and its variance using the generic inverse variance facility of RevMan 5 (Review Manager 2014).
- For continuous outcomes, we planned to pool the MDs between the treatment arms at the end of follow-up using the MD method if all trials had measured the outcome on the same scale, or the SMD method if different scales had been used.
- For dichotomous outcomes, we planned to calculate the RR for each study and then pool all studies.

Summary of findings

For each comparison, we prepared Summary of findings for the main comparison and Summary of findings 2. Two review authors (SP and GT) independently assessed the quality of the evidence using the five GRADE considerations: study limitations; inconsistency; indirectness; imprecision; and publication bias.

Assessment of heterogeneity and reporting biases was planned but not carried out because the two studies tested different comparisons. Results are based on single trial analysis.

RESULTS

Description of studies

See Characteristics of included studies , Characteristics of excluded studies , Characteristics of ongoing studies

Results of the search

A directed search on large databases yielded 1336 results with 279 references from the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 4) in the Cochrane Library (searched 22 May 2017); 296 from MEDLINE (1946 to 22 May 2017); and 761 references from Embase (1980 to 22 May 2017). Other regional databases, as per Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions*, did not yield any results. A very broad search of the National Institutes of Health, ClinicalTrials.gov, yielded 6902 studies. The search on ICTRP, apps.who.int/trialsearch/AdvSearch.aspx, yielded 877 results. A total of 9115 references were identified. We download all studies into EndNote and deleted 5068 duplicates. We screened all titles and abstracts of remaining references, discarding 4034 records that were not applicable and retaining records of 13 references as being potentially relevant. We retrieved the full-text reports of records classified as being potentially relevant and identified two studies meeting the inclusion criteria for the review (Boiardi 1992; Brada 2010).

Please refer to Figure 1 for the PRISMA flow diagram process.

Included studies

See Characteristics of included studies table.

Two trials were eligible for inclusion and analysis (Boiardi 1992; Brada 2010).

Brada 2010

This was a multi-centred randomised controlled trial (RCT) conducted in the United Kingdom and enrolling 447 adult participants between 2003 and 2007 at first recurrence of HGG. All had histologically verified WHO grade 3 or 4 at original diagnosis and underwent primary treatment including radiotherapy. Diagnosis of recurrence was based on contrast-enhanced imaging. Participants with life expectancy of more than a month, World Health Organization (WHO) performance status (PS) of 0,1, 2 or 3, and adequate renal, hepatic and haematologic reserve were randomised to three arms to receive PCV and two different regimens of TMZ, in a ratio of 2:1:1. Primary analysis and outcomes of interest were overall survival, PFS, quality of life and adverse events. Would-be participants were excluded if they were pregnant, had oligodendroglial pathology, had WHO PS of 4 or had received chemotherapy, radiosurgery or brachytherapy for HGG.

PCV was administered in the control arm every six weeks for up to six cycles or until progression, and it comprised of procarbazine (100 mg/m^2) on days 1 through 10, lomustine (100 mg/m^2) and intravenous vincristine (1.5 mg/m^2 capped at 2 mg) on day 1. TMZ was administered orally. The TMZ-5 group received 200 mg/m^2 for 5 days repeated every 28 days for up to nine cycles or until progression. The TMZ-21 (dose dense) group received 100 mg/m^2 for 21 days repeated every 28 days for up to nine cycles or until progression.

PFS was measured both on a clinical and radiological basis and formal assessment was performed every 12 weeks. For QoL, mean score was measured using the European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30 with brain tumour module at baseline and at 12 and 24 week, along with the proportion of patients reporting a moderate improvement (defined as a 10-point change) from baseline to 12 weeks and baseline to 24 weeks. All patients were included in the analysis.

Boiardi 1992

This was a RCT conducted in hospitals in Milan, Italy enrolling 35 adult participants with recurrent GBM between 1988 and 1990. All participants had prior treatment with surgery and radiotherapy; and about 60% with chemotherapy. Diagnosis of recurrence was based on computed tomography (CT) imaging. Participants with Karnofsky performance scale (KPS) greater than 60%, life expectancy more than two months, no significant toxicity after prior chemotherapy, with normal renal, hepatic and haematological functions were randomised to two arms to receive 'eight drugs in one day' multidrug chemotherapy (n = 19, mean age = 56) and PCV (n = 16, mean age = 61). Primary outcomes of interest were adjunctive disease-free survival time (ADFS) in patients with objective response, median adjunctive survival time of the whole group, 18-month survival time, and adverse events.

The 'eight drugs in one day' multidrug chemotherapy protocol was given every 4 to 5 weeks and included drugs with different actions: vincristine 2 mg; lomustine (CCNU) 75 mg/m^2; procarbazine 75 mg/m^2; hydroxyurea 1500 mg/m^2; cisplatin 90 mg/m^2; cytosine arabinoside 300 mg/m^2; Dacarbazine (DTIC) 150 mg/m^2; and methylprednisolone 300 mg/m^2. This cocktail was administered three times each day at 6-hourly intervals. PCV was given in standard dose: CCNU 110 mg/m^2 on day 1, procarbazine 60 mg/m^2

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

daily for 14 days from day 8, and vincristine 1.4 mg/m² on day 8 and 29 of each 6-week treatment period. Response to therapy was evaluated by monthly neurological examination and every other month by contrast-enhanced CT scan. The response definition used were similar to McDonald's criteria (Table 1). Toxicity was monitored after each successive cycle.

Excluded studies

We excluded 11 studies after full-text review. Please refer to the Characteristics of excluded studies for reasons for exclusions.

Risk of bias in included studies

Risk of bias was assessed as per the Cochrane tool for assessing risk of bias (Higgins 2011). It is summarised in Figure 2 and Figure 3.

Allocation

In Boiardi 1992 random number generation was performed by drawing lots. Brada 2010 used minimisation with stratification factors of centre, tumour grade (3 or 4 or high grade unspecified), and PS (0 or 1 vs 2 or 3) across all three groups for randomizations and was performed by telephone call to the trials unit. Both studies were at low risk. There was no statement of an effort to conceal allocation in Boiardi 1992, giving high risk of selection bias.

Blinding

Both studies were unblinded. It was not possible to blind the participants or providers to the treatment, given the nature of interventions. Both studies were at high risk of performance bias.

For detection bias we assessed the effect of blinding on each outcome. For overall survival and median survival time, both the studies were at low risk. Boiardi 1992 was at high risk of detection bias for adverse event outcomes. Brada 2010 was at high risk of bias for QoL and adverse event outcomes. Radiological assessment of PFS was verified by an independent central review with high degree of concordance thus reducing detection bias between independent and local assessors.

Incomplete outcome data

There was no missing data in either of the studies. Brada 2010 had complete data for overall survival and PFS. For toxicity outcomes a total of six patients were not included in analysis as they died or did not receive the intended treatment prior to initiation of the study. There was overall low risk of bias on this account.

There are no missing data for survival outcomes in Boiardi 1992, giving low risk of bias. For toxicity outcomes there is unknown risk of bias as there is no reported loss to follow-up.

Selective reporting

Boiardi 1992 did not have a pre-published protocol hence is at high risk of selective reporting bias. Brada 2010 had a registered protocol and reported all pre-planned outcomes and has low risk of bias.

Other potential sources of bias

Boiardi 1992 had small sample size, introducing high likelihood of baseline imbalance. It was likely inadequately powered to detect differences in the stated outcomes.

In Brada 2010 radiological measurement of PFS was done at fixed time points of 12 and 24 weeks and may have missed interim changes. In patients without symptoms, radiological changes could also represent treatment effect rather than true progression. This may lead to inaccurate assessment of PFS.

There was survivor bias introduced in the measurement of QoL outcomes as it was done at fixed time points and excluded participants who died. Even though studies were not combined there was high likelihood of unequal treatment effect as these studies were done more than a decade apart.

Some authors had a financial relationship with pharmaceutical companies. The relationships were clearly disclosed and pharmaceutical companies had no role in the design and analysis of the study.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

See Summary of findings for the main comparison and Summary of findings 2 of the two studies. We did not combine the data of these two RCTs as they tested different comparisons.

Overall survival

Boiardi 1992 included 35 patients with recurrent GBM in the analysis of median survival time. Hazard ratio (HR) was not performed and it was not possible to report risk ratio (RR). Median survival time for the PCV group and the 'eight drugs in one day" chemotherapy group was 6 months and 6.5 months respectively (low-quality evidence).

Brada 2010 included 447 patients in the analysis, 223 in the TMZ arm and 224 in the PCV arm. There was no significant difference between the groups (HR 0.91, 95% CI 0.74 to 1.11; P = 0.35). Overall survival was 6.7 months and 7.2 months for the PCV and TMZ arms respectively (moderate-quality evidence).

Progression-free survival

It is not possible to comment on this as it was not an outcome of interest in Boiardi 1992.

Brada 2010 analysed 447 patients in the PCV and TMZ arms. There was no significant difference between the groups (HR 0.89, 95% CI 0.73 to 1.08; P = 0.23). PFS was 3.6 months and 4.7 months for the PCV and TMZ arms respectively (moderate-quality evidence).

Quality of life

It is not possible to comment on this as it was not an outcome of interest in Boiardi 1992.

Brada 2010 reported QoL data using the EORTC QOL-30 questionnaire. Increase in 10 points on the scale defined moderate improvement. Scores were calculated at baseline, 12 weeks and 24 weeks. At 24 weeks the mean score for the PCV group was 51.9 versus 59.8 for the TMZ arm (P = 0.04) favouring TMZ. Results were statistically but not clinically significant (low-quality evidence).

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Chemotherapy toxicity

The adverse event reporting does not appear to be of the required quality in Boiardi 1992. In general, adverse events were more common in patients pre-treated with chemotherapy. Five patients experienced haematological toxicity in the 'eight drugs in one day' arm and none were recorded in the PCV arm. Nausea and vomiting were not evaluated quantitatively, but generally were moderate and less than expected: one patient had seizure and four patients had polyneuropathy in each arm (very low quality evidence).

Brada 2010 reported grade 3 and 4 toxicities only. For the purpose of evaluation, adverse events were combined according to system organ class as per CTCAE 2010. The total proportion of patients with at least one grade 3 or 4 adverse event was not statistically significant at 9.2% versus 12.2% in the PCV and TMZ arms respectively. The total number of adverse events was less in the PCV arm, mainly driven by fewer neurological adverse events. Other organ system adverse events involving the haematological, gastrointestinal, and integumentary systems were similar in both arms. Genitourinary and pulmonary adverse events were not reported (moderate-quality evidence).

Subgroup analysis

Subgroups were analysed in Brada 2010. Amongst various pre-specified subgroups there was improved survival seen in patients within age group 51 to 60 (HR 0.67, 95% CI 0.47 to 0.95) and in patients with PS-3 (HR 0.37, 95% CI 0.18 to 0.79) in favour of TMZ. Between-study subgroup analyses was not performed as data were not pooled.

DISCUSSION

Summary of main results

This systematic review identified two studies that investigated the benefits and harms of PCV with two different chemotherapy regimens in adults with recurrent HGG. Conclusions are derived from a single trial analysis as the other trial was small and therefore underpowered.

Brada 2010 included 447 participants and compared PCV to Temozolomide (TMZ). We found no difference in overall survival or progression-free survival (PFS) between PCV and TMZ. The proportion of participants experiencing grade 3 or 4 adverse events was similar in both groups. When combined into organ classes, there were fewer neurological events in the PCV arm compared to TMZ. In other organ classes, i.e. haematological, gastrointestinal and integumentary, there were similar numbers of events. Quality of life (QoL) scores were statistically but not clinically significant in the TMZ group. There was statistically significant overall survival in favour of TMZ on subgroup analyses in the 51 to 60 age group and in participants with WHO PS 3 (Summary of findings 2).

The second trial, Boiardi 1992, enrolled 35 patients and compared 'eight drugs in one day' chemotherapy to PCV. It reported median survival time which was similar in both groups. Hazard ratio was not reported. PFS and QoL were not outcomes of interest. Adverse events were not graded according to CTCAE and occurred in more than half the patients in both arms. They were more common in patients pre-treated with chemotherapy (Summary of findings for the main comparison).

Overall completeness and applicability of evidence

We analysed two studies that evaluated PCV with different regimens of chemotherapy. These studies were done in different time periods when the use of chemotherapy for HGG in an adjuvant setting was not the standard of care.

Boiardi 1992 was a small study and was underpowered to detect clinical difference. Exclusion criteria were not explicit, with inadequate reporting of baseline characteristics and statistical methods. Hazard ratio and survival curve were not calculated. Adverse event outcomes were not graded. It was at high risk of selection bias and selective reporting bias. A typical contemporary patient with recurrent GBM would be treated differently at initial diagnosis than in the study. Due to lack of internal validity and other insufficiencies its results are not applicable to our current patient population.

The second study, Brada 2010, was a large and well-designed study. Participants with recurrence of HGG were treated only with radiotherapy at initial diagnosis. Baseline characteristics were similar in all the groups after randomization. Radiological assessment of PFS was based on increased enhancement on CT or MRI and was done at fixed intervals which may have led to inaccurate assessment. The study was unblinded and at risk of performance and detection bias for subjective outcomes such as QoL. There was risk of bias because of the industry association of the authors. On subgroup analysis there was a survival advantage favouring TMZ for patients aged between 51 and 60, and WHO PS of 0,1, 2, or 3.

This study grouped together grade 3 and 4 gliomas, which we know have different natural histories. Molecular markers were not used in decision making. These results are not applicable to our current patients as chemotherapy in adjuvant setting has become the standard of care at original diagnosis. Incidence of adverse effects and QoL scores were similar in both studies; however these could be more pronounced because of cumulative toxicity in contemporary patients already treated with chemotherapy at initial diagnosis. The evidence on QoL can be cautiously and very selectively applied in patients while formulating a treatment plan. Dose and timing of the multidrug PCV chemotherapy regimen was different compared to the standard recommended protocol today.

Quality of the evidence

There were two studies identified for the systematic review, one with 35 and the other with 447 participants. Boiardi 1992 was done in a earlier time period with different standards of care. It was inadequately powered to detect differences in survival outcomes. It was an unblinded study at risk of selection bias and selective reporting bias. There was sub-optimal reporting of methodology, exclusion criteria, baseline characteristics and outcomes. The study was unblinded and at high risk of bias for assessment of adverse effects. Boiardi 1992 had low GRADE quality of evidence for median survival and very low certainty for chemotherapy toxicity (Summary of findings for the main comparison).

Brada 2010 was a large well-designed RCT study. It included patients with recurrent HGG treated with prior radiation therapy only. Patients were randomised with explicit methods. A power calculation to reject the null hypothesis was done. Baseline characteristics were similar. It was at low risk of selection bias with

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

complete reporting, as per protocol. It was an unblinded study with risk of performance and detection bias for QoL data. QoL data were also at risk of survival bias because they were measured at fixed intervals. PFS outcome was at risk of inaccurate assessment because of a potential false reading of treatment-related changes at progression. Another risk of bias was because of an industry association of authors to manufacturers of one of the study drugs (Summary of findings 2).

We rated Brada 2010 as moderate GRADE certainty of evidence for overall survival because it was adequately powered to detect survival difference, had robust methodology with a published protocol and explicit criteria for randomisation. Unblinding of participants does not have impact on mortality outcomes. Additional trials may produce different results and would increase the power of meta-analysis.

Quality of evidence for PFS was moderate as it was adequately powered with robust methodology. There was very good concordance between the local and the independent radiological assessor thus removing inter-observer variability. Radiological assessment at fixed intervals may have missed interim changes and inaccurately assessed pseudo progression as true progression; however it accounted only for a total of 10% of participants. The questionnaire used to determine clinical progression in Brada 2010 was not available. There was risk of bias on account of unblinding, which was minimised by having objective criteria for assessing progression. Overall we feel with reasonable certainty that the evidence presented is of moderate quality.

Chemotherapy toxicity was assessed as moderate certainty of evidence because of methodological robustness: objective CTCAE criteria were used to measure the outcome. Risk of performance bias and detection bias was introduced because of unblinding but we thought the effect to be small.

Evidence for QoL outcome was low mainly because it introduced survival bias, as it was done at fixed intervals and excluded deceased patients from analysis.

Potential biases in the review process

We performed a thorough and comprehensive search, including grey literature. We screened all identified studies and two review authors independently extracted data. We restricted the included studies to RCTs as these provide the strongest level of evidence available. There were only two studies with one being very small and imprecise hence this is essentially a single-trial analysis.

Agreements and disagreements with other studies or reviews

Currently we are not aware of any other systematic review of RCTs studying efficacy of PCV in recurrent HGG. Nitrosourea- and/or Procarbazine-based single and/or multidrug chemotherapy has been studied in retrospective or prospective non-randomised settings. Buckner 1995 and Rajan 1994 showed efficacy of a nitrosourea-based regimen in recurrent HGG patients in a prospective single arm study. Brandes 2002 studied PCV in recurrent GBM patients in a prospective setting, and reported benefit. Triebels 2004 studied PCV in patients with recurrent AOD. Yung 2000's RCT studied TMZ against Procarbazine in participants with recurrent GBM and reported 6-month improvement in PFS and QoL with TMZ. Wick 2009 studied sequential radiochemotherapy in primary anaplastic glioma. Participants in the radiation therapy arm were randomised to PCV or TMZ at recurrence. Results of the subset randomised to chemotherapy PCV and TMZ after recurrence are not available.

These studies demonstrated benefit with PCV or TMZ independently in recurrent HGG patients.

AUTHORS' CONCLUSIONS

Implications for practice

These findings are based on a single trial analysis. For treatment of recurrent HGG, PCV and TMZ have similar survival outcomes in patients who are treated only with radiation therapy at original diagnosis of HGG. It is not applicable to our contemporary patients with a new diagnosis of GBM and non-co-deleted 1p19q grade 3 glioma, who will have received TMZ at initial diagnosis (Van den Bent 2016); and those with 1p19q co-deleted grade 3 tumours, who will receive PCV as initial plan.

These results should be applied with caution to a highly selected group of elderly patients with good WHO PS of 0,1, 2 or 3 who did not receive chemotherapy as part of their initial treatment plan. Even though TMZ is favoured over PCV in recurrent patients, in practice QoL as measured by EORTC QoL-30 questionnaire and grade 3 and 4 adverse events were similar with both regimens (Summary of findings 2).

The other trial was small and likely underpowered to detect clinically significant differences. Adverse events were not graded and PFS and QoL were not outcomes of interest (Summary of findings for the main comparison).

Implications for research

Further research is needed to establish the role of multi-drug chemotherapy in the management of recurrent GBM and grade 3 tumours separately. With increasing use of molecular markers for guiding treatment and prognostication, this should become an important part of patient selection. Future trials should be conducted with adequate power, include placebo control and study all relevant outcomes. Anaplastic gliomas or grade 3 tumours are heterogenous conditions with different natural histories. They should be studied separately at recurrence, with different interventions.

Good data is lacking with regards to QoL. This is an important patient-oriented outcome and needs clear statistical reporting. QoL data lends itself to survival bias as deceased patients are not accounted for when it is measured at fixed intervals. Improved measurement and analysis of QoL needs to be established.

ACKNOWLEDGEMENTS

We would like to thank and acknowledge the Cochrane Gynaecological, Neuro-oncology and Orphan Cancers Group for their support. We would also like to acknowledge funding support from the Society for Neuro-Oncology (SNO).

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancers Group. The views and opinions expressed herein are those of the

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service, or the Department of Health.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

REFERENCES

References to studies included in this review

Boiardi 1992 *{published data only}*

Boiardi A, Silvani A, Milanesi I, Broggi G, Fariselli L. Efficacy of '8-drugs-in-one-day' combination in treatment of recurrent GBM patients. Journal of Neuro-Oncology 1992; Vol. 12, issue 2:153-8.

Brada 2010 *{published data only}*

Brada M, Stenning S, Gabe R, Thompson LC, Levy D, Rampling R, et al. Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. Journal of Clinical Oncology 2010; Vol. 28, issue 30:4601-8.

References to studies excluded from this review

Bogdahn 2010 *{published data only}*

Bogdahn U, Stockhammer G, Mahapatra AK, Venkataramana NK, Oliushine VE, Parfenov VE, et al. Pseudoprogression after treatment with the TGF-beta 2 inhibitor trabedersen in high-grade glioma patients. *Journal of Clinical Oncology* 2010;**28**:abstr 2054.

Boiardi 2001 *{published data only}*

Boiardi A, Eoli M, Salmaggi A, Zappacosta B, Fariselli L, Milanesi I, et al. Efficacy of intratumoral delivery of mitoxantrone in recurrent malignant glial tumours. *Journal of Neuro-Oncology* 2001;**54**(1):39-47.

Bower 1997 *{published data only}*

Bower M, Newlands ES, Bleehen NM, Brada M, Begent RJ, Calvert H, et al. Multicentre CRC phase II trial of temozolomide in recurrent or progressive high-grade glioma. *Cancer Chemotherapy and Pharmacology* 1997;**40**(6):484-8.

Galanis 1998 *{published data only}*

Galanis E, Buckner JC, Burch PA, Schaefer PL, Dinapoli RP, Novotny PJ, et al. Phase II trial of nitrogen mustard, vincristine, and procarbazine in patients with recurrent glioma: North Central Cancer Treatment Group results. *Journal of Clinical Oncology* 1998;**16**(9):2953-8.

Gilbert 2005 *{published data only}*

Gilbert M, Campone M, Brandes AA, Gertler S, Green S, Fowst C, et al. Phase II/III randomized study of edotecarin vs. temozolomide or nitrosourea in patients with recurrent glioblastoma (GBM): Phase II results. *EJC Supplements* 2005;**3**(2):136.

Gutin 1975 *{published data only}*

Gutin PH, Wilson CB, Kumar ARV, Boldrey E, Levin V, Powell M, et al. Phase II study if procabazine, and vincristine combination chemotheraoy in the treatment of malignant brain tumors. *Cancer* 1975;**35**(5):1398-404.

Levin 1980 *{published data only}*

Levin VA, Edwards MS, Wright DC, Seager ML, Schimberg TP, Townsend JJ, et al. Modified procarbazine, CCNU, and vincristine (PCV 3) combination chemotherapy in the treatment of malignant brain tumors. *Cancer Treatment Reports* 1980;**64**(2-3):237-41.

Shapiro 1976 *{published data only}*

Shapiro WR, Young DF. Chemotherapy of malignant glioma with CCNU alone and CCNU combined with vincristine sulfate and procarbazine hydrochloride. *Transactions of the American Neurological Association* 1976;**101**:217-20.

Van den Bent 2003a *{published data only}*

Van den Bent MJ, Chinot O, Boogerd W, Bravo Marques J, Taphoorn MJ, Kros JM, et al. Second-line chemotherapy with temozolomide in recurrent oligodendroglioma after PCV (procarbazine, lomustine and vincristine) chemotherapy: EORTC Brain Tumor Group phase II study 26972. *Annals of Oncology* 2003;**14**(4):599-602.

Wick 2009 *{published data only}*

Wick W, Hartmann C, Engel C, Stoffels M, Felsberg J, Stockhammer F, et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide.. *Journal of Clinical Oncology* 2009;**27**(35):5874-80.

Yung 2000 *{published data only}*

Yung WK, Albright RE, Olson J, Fredericks R, Fink K, Prados MD, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *British Journal of Cancer* 2000;**83**(5):588-93.

References to ongoing studies

ChiCTR-OOC-15005759 2015 *{published data only}*

ChiCTR-OOC-15005759. A study to evaluate the safety and effectiveness of PCV chemotherapy in patients with recurrent high-grade glioma with IDH1/2 mutation. ClinicalTrials.gov 2015.

Additional references

Abdulkarim 2014

Abdulkarim B, Lecavalier-Barsoum M, Quon H. Adjuvant treatment of anaplastic oligodendrogliomas and oligoastrocytomas. *Cochrane Database of Systematic Reviews* 2014, Issue 5. [DOI: 10.1002/14651858.CD007104.pub2]

Arismendi-Morillo 2005

Arismendi-Morillo G, Castellano A. Tumoral micro-blood vessels and vascular microenvironment in human astrocytic tumors. A transmission electron microscopy study. *Journal of Neuro-Oncology* 2005;**73**(3):211-7.

Boyle 2004

Boyle FM, Eller SL, Grossman SA. Penetration of intra-arterially administered vincristine in experimental brain tumor. *Journal of Neuro-Oncology* 2004;**6**(4):300-6.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Brandes 2002

Brandes AA, Turazzi S, Basso U, Pasetto LM, Guglielmi B, Volpin L, et al. A multidrug combination designed for reversing resistance to BCNU in glioblastoma multiforme. *Neurology* 2002;**58**(12):1759-64.

Brooks 1984

Brooks DJ, Beaney RP, Lammertsma AA, Leenders KL, Horlock PL, Kensett MJ, et al. Quantitative measurement of blood-brain barrier permeability using rubidium-82 and positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism* 1984;**4**(4):535-45.

Buckner 1995

Buckner JC, Brown LD, Kugler JW, Cascino TL, Krook JE, Mailliard JA, et al. Phase II evaluation of recombinant interferon alpha and BCNU in recurrent glioma. *Journal of Neurosurgery* 1995;**82**(3):430-5.

Cairncross 2012

Cairncross G, Wang M, Shaw E, Jenkins R, Brachman D, Buckner J, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *Journal of Clinical Oncology* 2012;**31**(3):337-43.

CTCAE 2010

The Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, version 4.0, 2010. evs.nci.nih.gov/ftp1/CTCAE/About.html (accessed 13 June 2015).

Eisele 2013

Eisele G, Weller M. Targeting apoptosis pathways in glioblastoma. *Cancer Letters* 2013;**332**(2):335-45.

Ferlay 2015

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer* 2015;**136**(5):E359-86.

Hart 2013

Hart M, Garside R, Rogers G, Stein K, Grant R. Temozolomide for high grade glioma. *Cochrane Database of Systematic Reviews* 2013, Issue 4. [DOI: 10.1002/14651858.CD007415.pub2]

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook of Systematic Reviews of Interventions* 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hildebrand 2005

Hildebrand J, Lecaille C, Perennes J, Delattre J. Epileptic seizures during follow-up of patients treated for primary brain tumors. *Neurology* 2005;**65**(2):212-5.

Kappelle 2001

Kappelle AC, Postma TJ, Taphoorn MJ, Groeneveld GJ, van den Bent MJ, van Groeningen CJ, et al. PCV chemotherapy for recurrent glioblastoma multiforme. *Neurology* 2001;**56**(1):118-20.

Khasraw 2014

Khasraw M, Ameratunga MS, Grant R, Wheeler H, Pavlakis N. Antiangiogenic therapy for high-grade glioma. *Cochrane Database of Systematic Reviews* 2014, Issue 9. [DOI: 10.1002/14651858.CD008218.pub3]

Louis 2007

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathologica* 2007;**114**(2):97-109.

Louis 2016

Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathologica* 2016;**131**(6):803-20.

Macdonald 1990

Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *Journal of Clinical Oncology* 1990;**8**(7):1277-80.

Mauer 2008

Mauer ME, Bottomley A, Taphoorn MJB. Evaluating health-related quality of life and symptom burden in brain tumour patients: instruments for use in experimental trials and clinical practice. *Current Opinion in Neurology* 2008;**21**(6):745-53.

Ostrom 2013

Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro-oncology* 2013;**15 Suppl 2**:ii1-56.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34.

Rajan 1994

Rajan B, Ross G, Lim CC, Ashley S, Goode D, Traish D, et al. Survival in patients with recurrent glioma as a measure of treatment efficacy: prognostic factors following nitrosourea chemotherapy. *European Journal of Cancer (Oxford, England : 1990)* 1994;**30A**(12):1809-15.

Review Manager 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schmidt 2006

Schmidt F, Fischer J, Herrlinger U, Dietz K, Dichgans J, Weller M. PCV chemotherapy for recurrent glioblastoma. *Neurology* 2006;**66**(4):587-9.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Siegel 2012

Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA: a Cancer Journal for Clinicians* 2012;**62**(1):10-29.

Stupp 2005

Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *New England Journal of Medicine* 2005;**352**(10):987-96.

Triebels 2004

Triebels VH, Taphoorn MJ, Brandes AA, Menten J, Frenay M, Tosoni A, et al. Salvage PCV chemotherapy for temozolomide-resistant oligodendrogliomas. *Neurology* 2004;**63**(5):904-6.

Van den Bent 2012

Van den Bent M, Brandes A, Taphoorn M, Kros J, Kouwenhoven M, Delattre J, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC Brain Tumor Group Study 26951. *Journal of Clinical Oncology* 2012;**31**(3):344-50.

Van den Bent 2016

van den Bent MJ, Erridge S, Vogelbaum MA, Nowak AK, Sanson M, Brandes AA. Results of the interim analysis of the EORTC randomized phase III CATNON trial on concurrent and adjuvant temozolomide in anaplastic glioma without 1p/19q co-deletion: An Intergroup trial. *Journal of Clinical Oncology* 2016;**34**(suppl):abstr-LBA2000.

Villano 2012

Villano J, Letarte N, Yu J, Abdur S, Bressler L. Hematologic adverse events associated with temozolomide. *Cancer Chemotherapy and Pharmacology* 2012;**69**(1):107-13.

Wang 2013

Wang Y, Jiang T. Understanding high grade glioma: molecular mechanism, therapy and comprehensive management. *Cancer Letters* 2013;**331**(2):139-46.

Wen 2010

Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria for high-grade gliomas: response assessment in Neuro-Oncology Working Group. Journal of Clinical Oncology 2010; Vol. 28, issue 11:1963-72.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Boiardi 1992

Methods	RCT conducted in hospitals in Milan, Italy.
Participants	35 adult participants with recurrent GBM based on CT scan after standard treatment with surgery, radiotherapy and chemotherapy (60%) were enrolled between 1988 and 1990. Mean age in Group A ('8 drugs in 1 day' chemotherapy) was 56 (21 to 72) and in Group B (PCV) was 61 (26 to 79). All had adequate haematological, renal and hepatic reserves and KPS > 60%. There were no explicit exclusion criteria mentioned.
Interventions	Group A received '8 drugs in 1 day' multidrug chemotherapy protocol every 4 to 5 weeks which included drugs with different actions — vincristine 2 mg; CCNU 75 mg/m^2; procarbazine 75 mg/m^2; hydroxyurea 1500 mg/m^2; cisplatin 90 mg/m^2; cytosine arabinoside 300 mg/m^2; DTIC 150 mg/m^2; and methylprednisolone 300 mg/m^2 q6h — for 3 doses per day. Group B was given CCNU 110 mg/m^2 on day 1, procarbazine 60 mg/m^2 was administered daily for 14 days beginning on day 8, and vincristine 1.4 mg/m^2 was administered on day 8 and 29 of each 6-week cycle of therapy. Treatment was given as long as the chemotherapy was tolerated without irreversible sequelae or until the CT scan showed tumour progression.
Outcomes	ADFS was calculated as median PFS in participants with objective response after first 2 cycles. Median adjunctive survival time was calculated for the two groups and was defined as the median time of the survival. 18-month survival time was calculated, which is proportion of participants who survived at 18 months' follow-up. Toxicity was monitored carefully after each successive cycle in both the groups.
Notes	PFS for the two groups as a whole was not an outcome of interest. Toxicities were not graded and did not allow for statistical comparison. QoL was not an outcome of interest. There was no HR or standard error given for OS outcome.
Risk of bias	

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Boiardi 1992 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The chemotherapy was randomly chosen, that is by chance, drawing lots for treatment, every patient was assigned to one of the two protocols".
Allocation concealment (selection bias)	High risk	No statement to the effect reported.
Blinding of participants and personnel (performance bias) OS	Low risk	There was no blinding because of the nature of intervention however OS outcome is unlikely to be influenced as it is an objective event.
Blinding of participants and personnel (performance bias) Chemotherapy toxicity	High risk	There was no blinding and highly likely that the knowledge of treatment will have affected the behaviour and influenced the outcome
Blinding of participants and personnel (performance bias) PFS	Unclear risk	This was not an outcome of interest.
Blinding of participants and personnel (performance bias) QOL	Unclear risk	This was not an outcome of interest.
Blinding of outcome assessment (detection bias) OS	Low risk	There was no blinding because of the nature of intervention; however OS outcome is unlikely to be influenced as it is an objective event.
Blinding of outcome assessment (detection bias) Chemotherapy toxicity	High risk	There was no blinding and highly likely that the knowledge of treatment will have effected the behaviour and influenced the outcome.
Blinding of outcome assessment (detection bias) PFS	Unclear risk	This was not an outcome of interest.
Blinding of outcome assessment (detection bias) QOL	Unclear risk	This was not an outcome of interest.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were analyzed for survival outcomes. For toxicity outcome loss of follow-up was not reported. Toxicity outcomes were not graded according to CTCAE, hence not used for synthesis.
Selective reporting (reporting bias)	High risk	There is no study protocol available. Study at high risk of reporting bias.
Other bias	High risk	Unequal treatment bias and comparison as the study was done in early 1990s with different standard of care. Baseline imbalance because of small sample size.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Brada 2010

Methods	Multicentre RCT based in UK. Random assignment was performed to 3 arms by telephone call to the Medical Research Council Clinical Trials Unit. Treatment allocation used minimisation with stratification factors of centre, tumour grade (3 or 4 or high grade unspecified), and PS (0 or 1 vs 2 or 3) across all three groups. Primary comparison was between PCV and TMZ. With 380 deaths in 500 participants, study had 80% power to detect a 2-month increase in median survival (HR 0.75) and 90% power to detect a 3-month increase (HR 0.67), with a 2-sided significance level of P = 0.05. There was no post-randomisation exclusion. There were no losses to follow-up. Independent central reviews of pathology (eligibility and tumour grade) and radiology (evidence of progression at 12 and 24 weeks) were conducted.
Participants	447 participants with recurrent HGG from 36 centres in the UK were enrolled between June 2003 and January 2008. All had histologically verified AA, GBM, gemistocytic astrocytoma, oligoastrocytoma, or gliosarcomas (WHO grade 3 or 4 at diagnosis, relapse, or transformation) which were independently verified and had undergone primary treatment including radiotherapy completed more than 2 months before random assignment. Diagnosis of recurrence was confirmed by contrast-enhanced magnetic resonance imaging/computed tomography within 2 weeks before start of treatment. All had a life expectancy of 1 month, and were fit for chemotherapy with adequate hepatic, renal, and hematologic function and WHO PS of 1, 2 or 3. Baseline characteristics were similar across all 3 groups. There were 65% males in PCV and 63% males in TMZ arm with median age of 53 in both groups. Potential participants who had received chemotherapy, radiosurgery, or brachytherapy for glioma were excluded, but debulking at relapse was permissible. Potential participants with WHO performance status (PS) of 4, active pregnancy, or oligodendroglioma histology were excluded.
Interventions	Participants were randomly assigned to 3 groups: PCV = 224, TMZ-5 = 112, TMZ-21 = 111 in 2:1:1. PCV was administered every 6 weeks for up to six cycles or until progression, and it comprised: procarbazine (100 mg/m^2) on days 1 through 10; lomustine (100 mg/m^2) and intravenous vincristine (1.5 mg/m^2 capped at 2 mg) on day 1; and TMZ administered orally (TMZ-5 200 mg/m^2 and TMZ-21 100 mg/m^2) repeated every 28 days for up to nine cycles or until progression. Dose modifications for all treatments were specified in the protocol according to clinical evidence of grade 3 toxicity in the previous cycle and blood counts.
Outcomes	Primary outcome was OS. Secondary outcomes were PFS, QoL and adverse events. Formal assessment of clinical and radiologic progression, neurologic status, and PS was performed every 12 weeks. Criteria for clinical progression included the presence of any one of the following: neurologic deterioration (based on 12-point neurologic assessment), decline of 1 point in PS, increased corticosteroid requirements for more than 2 weeks where causes other than progression had been ruled out, or increased symptoms of raised intracranial pressure. Imaging was repeated on clinical progression wherever possible; scans were also performed at baseline and at 12 and 24 weeks, with progressive disease defined as 25% increase in two-dimensional tumour size. QoL mean score was measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (version 3.0) with brain tumour module at baseline and at 12 and 24 weeks, along with the proportion of participants reporting a moderate improvement (defined as a 10-point change) from baseline to 12 weeks and baseline to 24 weeks.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random assignment was performed by telephone call to the Medical Research Council Clinical Trials Unit".
Allocation concealment (selection bias)	Low risk	Quote: "Random assignment was performed by telephone call to the Medical Research Council Clinical Trials Unit".

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Brada 2010 *(Continued)*

Blinding of participants and personnel (performance bias) OS	Low risk	There was no blinding because of the nature of intervention; however overall survival outcome is unlikely to be influenced as it is an objective event.
Blinding of participants and personnel (performance bias) Chemotherapy toxicity	High risk	Unblinded and likely influenced by lack of blinding.
Blinding of participants and personnel (performance bias) PFS	Low risk	Unblinded and unlikely influenced by lack of blinding as it was a combination of objective radiological parameters and/or score-based clinical parameters.
Blinding of participants and personnel (performance bias) QOL	High risk	Unblinded and likely influenced by lack of blinding as knowledge of intervention may have led to change in behaviour.
Blinding of outcome assessment (detection bias) OS	Low risk	There was no blinding because of the nature of intervention; however OS outcome is unlikely to be influenced as it is an objective event.
Blinding of outcome assessment (detection bias) Chemotherapy toxicity	High risk	Unblinded and likely influenced by lack of blinding.
Blinding of outcome assessment (detection bias) PFS	Low risk	There was no blinding because of the nature of intervention; however there were objective measures of determining PFS.
Blinding of outcome assessment (detection bias) QOL	High risk	Unblinded and likely influenced by lack of blinding,
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data or loss to follow-up,
Selective reporting (reporting bias)	Low risk	All the outcomes mentioned in the protocol have been reported in the published study except for cost effectiveness.
Other bias	High risk	Survivor bias introduced in the measurement of QoL outcomes as it was done at fixed time points and excluded participants who died. Toxicity outcome was measured only during the first 12 weeks of treatment, hence missing late adverse effects

AA = anaplastic astrocytoma
ADFS = adjunctive disease free survival time
CT = computed tomography
GBM = glioblastomas
HR = hazard ratio
KPS = Karnofsky performance scale
OS = overall survival
PFS = progression-free survival
QoL = quality of life

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

TMZ = Temozolomide

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bogdahn 2010	RCT studying patients with recurrent HGG comparing intervention drug to standard chemotherapy including PCV and TMZ combined.
Boiardi 2001	Prospective non-randomised multi-arm study of participants with recurrent HGG comparing PCV to intratumoural study drug with and without repeat surgery.
Bower 1997	Prospective non-randomised single arm study of participants with recurrent HGG treated with TMZ.
Galanis 1998	Prospective non-randomised single arm study of participants with recurrent glioma treated with procarbazine, vincristine and nitrogen mustard.
Gilbert 2005	RCT in participants with recurrent GBM comparing study drug with standard chemotherapy in control arm which included TMZ, BCNU or CCNU.
Gutin 1975	Prospective non-randomised single arm study of participants with primary, recurrent and metastatic CNS tumours treated with PCV.
Levin 1980	Prospective non-randomised single arm study of participants with recurrent malignant brain tumours treated with PCV.
Shapiro 1976	Prospective non-randomised single arm study of participants with primary and recurrent malignant glioma treated with PCV.
Van den Bent 2003a	Combined prospective non-randomised single arm study of participants with primary HGG and recurrent OD and AOA treated with TMZ.
Wick 2009	RCT studying participants with primary anaplastic glioma (grade 3) treated with radiotherapy or chemotherapy.
Yung 2000	RCT studying participants with recurrent GBM treated with TMZ or Procarbazine only.

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-OOC-15005759 2015

Trial name or title	ChiCTR-OOC-15005759. A study to evaluate the safety and effectiveness of PCV chemotherapy in patients with recurrent high-grade glioma with IDH1/2 mutation
Methods	Quasi-randomised controlled study being conducted by Dept. of Neurosurgery, Beijing Tiantan Hospital.
Participants	Participants in the age group of 18 to 70 with diagnosis of recurrent HGG with IDH1/2 mutation quasi-randomised to intervention arm with PCV and control arm.
Interventions	PCV in standard dose.
Outcomes	Progression-free survival, 6-month progression-free survival rate, 12-month progression-free survival rate, 6-month survival rate, 12-month survival rate, 6-month life quality, 12-month life quality.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ChiCTR-OOC-15005759 2015 *(Continued)*

Starting date	Feb 2015 until Dec 2017.
Contact information	Department of Neurosurgery, Beijing Tiantan Hospital, 6 Tiantanxili, Dongcheng District, Beijing cnpsycho@163.com +86 13910713896
Notes	In recruitment phase

ADDITIONAL TABLES

Table 1. MacDonald criteria

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks; no new lesions; no corticosteroids; and stable or improved clinically.
Partial response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no new lesions; stable or reduced corticosteroid dose; and stable or improved clinically.
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; and stable clinically.
Progression	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions; any new lesion; or clinical deterioration.

Table 2. RANO criteria

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions; and participant must be off corticosteroids or on physiological replacement doses only, and stable or improved clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.
Partial response	Requires all of the following: ≥ 50% decrease, compared with baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of non-measurable disease; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and participant must be taking a corticosteroid dose not greater than the dose at the time of baseline scan and is stable or improved clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.
Stable disease	Stable disease occurs if participant does not qualify for complete response, partial response, or progression (see next section) and requires the following: stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan and clinically stable status. In the event that corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression; the last scan considered to

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 2. RANO criteria *(Continued)*

	show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Progression is defined by any of the following: ≥ 25% increase in sum of products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events; appearance of any new lesions; clear progression of non-measurable lesions; or definite clinical deterioration not attributable to other causes apart from the tumour, or to decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Glioma] explode all trees
#2 (glioma* or astrocytoma* or oligodendroglioma* or oligoastrocytoma* or glioblastoma*)
#3 #1 or #2
#4 PCV
#5 MeSH descriptor: [Procarbazine] explode all trees
#6 MeSH descriptor: [Lomustine] explode all trees
#7 MeSH descriptor: [Vincristine] explode all trees
#8 (procarbazine or matulane or natulan)
#9 (lomustine or cecenu or ceenu or ccnu or belustine or nsc 79037 or nsc79037)
#10 (vincristin* or vincrisul or cellcristin or oncovin* or onkocristin or farmistin or leurocristine or vincasar or vintec or citomid)
#11 #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 #3 and #11

Appendix 2. MEDLINE search strategy

1. exp Glioma/
2. (glioma* or astrocytoma* or oligodendroglioma* or oligoastrocytoma* or glioblastoma*).mp.
3. 1 or 2
4. PCV.mp.
5. Procarbazine/
6. exp Lomustine/
7. Vincristine/
8. (procarbazine or matulane or natulan).mp.
9. (lomustine or cecenu or ceenu or ccnu or belustine or nsc 79037 or nsc79037).mp.
10. (vincristine* or vincrisul or cellcristin or oncovin* or onkocristin or farmistin or leurocristine or vincasar or vintec or citomid).mp.
11. 4 or 5 or 6 or 7 or 8 or 9 or 10
12. 3 and 11
13. randomised controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. clinical trials as topic.sh.
18. randomly.ab.
19. trial.ti.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 12 and 20

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Appendix 3. Embase search strategy

1 exp glioma/
2 (glioma* or astrocytoma* or oligodendroglioma* or oligoastrocytoma* or glioblastoma*).mp.
3 1 or 2
4 PCV.mp.
5 procarbazine/
6 lomustine/
7 vincristine/
8 (procarbazine or matulane or natulan).mp.
9 (lomustine or cecenu or ceenu or ccnu or belustine or nsc 79037 or nsc79037).mp.
10 (vincristin* or vincrisul or cellcristin or oncovin* or onkocristin or farmistin or leurocristine or vincasar or vintec or citomid).mp.
11 4 or 5 or 6 or 7 or 8 or 9 or 10
12 3 and 11
13 crossover procedure/
14 double-blind procedure/
15 randomized controlled trial/
16 single-blind procedure/
17 random*.mp.
18 factorial*.mp.
19 (crossover* or cross over* or cross-over*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
20 placebo*.mp.
21 (double* adj blind*).mp.
22 (singl* adj blind*).mp.
23 assign*.mp.
24 allocat*.mp.
25 volunteer*.mp.
26 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27 12 and 26

Appendix 4. Data collection form template

Review author(s)
Study ID /
Date completed
Authors Contact Details
ELIGIBILITY
Confirm eligibility
Reason for exclusion
METHODS
Study Design
Power Calculation
Proper Randomization
Groups similar at baseline

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(Continued)

Investigators/Outcome assessors / Patient blinded
Eligibility criterion stated
Outcome measure objective
Duration
RISK OF BIAS assessment - as per Cochrane risk assessment tool
Participants
Total number
Setting
Diagnostic Criteria
Age
Sex
Prior treatment
Country /Language
Ethnicity
Date of study
Histology
KPS
Interventions
Total no of intervention groups
Specific intervention
Follow - up
Details
Outcomes
Outcomes and time points collected and reported
Overall survival (To calculate the Hazard ratio)
PFS
Quality of life using QLQ-C30 and / or BCM scale, FACT-G or FACT-Br scale
Scale used for QoL data

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(Continued)

Grades of toxicity using CTCAE v4.0	
Hematological	
Gastrointestinal	
Genitourinary	
Skin	
Neurological	
Pulmonary	
RESULTS	
Number of participants allocated to each intervention group	
Analysis on ITT basis	
All patients accounted for	
Inter-center consistency	
Withdrawal specified	
OS	Sample Size
	Missing participant
	Summary data for each intervention group
	Estimate of effect with confidence interval (P value)
	Subgroup analysis
PFS	Sample Size
	Missing participant
	Summary data for each intervention group
	Estimate of effect with confidence interval (P value)
	Subgroup analysis
Miscellaneous	
Correspondence required	
Reference to other studies	
Conflict of interest	

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(Continued)

Key conclusion of the study

WHAT'S NEW

Date	Event	Description
26 July 2017	Amended	Author order amended

CONTRIBUTIONS OF AUTHORS

SP: design of the protocol, analysis and writing of the text. GT: analysis. JG: risk of bias assessment and statistics. JV: original idea of the protocol and helped draft the initial protocol and was third review author in case of conflict. MR: original idea.

The search strategies were provided by the Cochrane Gynaecological, Neuro-oncology and Orphan Cancers Group.

DECLARATIONS OF INTEREST

John L Villano: none known.
Myrna Rosenfeld: none known.
Saurabh Parasramka: none known.
Goutham Talari: none known.
Jing Guo: none known.

SOURCES OF SUPPORT

Internal sources

- University of Kentucky, Lexington, Kentucky, USA.

  Online medical library access, workstation, and space access

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we specified the definition of PFS as time from randomizations to progression; however in Brada 2010 the PFS definition also included death. We specified we would handsearch the *Journal of Neuro-oncology*, which we did up to 2007 (as we had access to hard copies until then in our library) and after that we undertook an electronic search. We also added an electronic search of *Neuro-oncology* from 1999 to June 2016. We included electronic searches of conference abstracts of ASCO published in the *Journal of Clinical Oncology* (JCO) from 2004 to June 2016. John VIllano (JV) was replaced by Goutham Talari (GT) as the second review author. JV provided the guidance and oversaw the process and acted as arbitrator in case of conflict. Jing Guo (JG) was the statistician for the review.

We did not mention 'Summary of findings' tables in the protocol. We reconsidered this and decided that 'Summary of findings' tables were necessary and would help the reader to obtain the important information quickly. Therefore, we added the tables to the review. WHO PS 1982 score was included for performance measure.

Assessment of heterogeneity, assessment of reporting bias, subgroup analysis and sensitivity analysis were planned but not performed because it was not applicable as the studies were not combined.

We planned to assess heterogeneity by visual inspection of the forest plot, looking at the overlap of confidence intervals (CIs), and formal statistical tests such as the Chi^2 test on N−1 degrees of freedom, with an alpha of 0.1 for statistical significance; and the I^2 statistic, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. It was not applicable as meta-analysis was not performed.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

We assessed reporting bias as described in the 'Assessment of risk of bias in included studies' section. A funnel plot of treatment effect versus precision with the data from all studies was planned in order to investigate the likelihood of publication bias if there were at least 10 studies (Higgins 2011). This was not applicable as we had only two studies which could not be pooled.

Subgroup analyses were planned with respect to IDH mutational status, MGMT promoter methylation status, 1p/19q co-deletion status, receipt of first-line chemotherapy with or without radiation therapy, surgical resection status, gender, age, and performance status. They could not be performed.

Sensitivity analysis was not applicable as pooling of the studies could not be done.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [adverse effects] [*therapeutic use]; Brain Neoplasms [*drug therapy] [mortality]; Cytarabine [administration & dosage]; Dacarbazine [administration & dosage] [adverse effects] [analogs & derivatives]; Disease Progression; Disease-Free Survival; Drug Administration Schedule; Glioma [*drug therapy] [mortality]; Hydroxyurea [administration & dosage]; Lomustine [*administration & dosage] [adverse effects]; Methylprednisolone [administration & dosage]; Neoplasm Recurrence, Local [*drug therapy] [mortality]; Procarbazine [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Temozolomide; Vincristine [administration & dosage] [adverse effects]

MeSH check words

Adult; Humans; Middle Aged

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.