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Treatment options for recurrent glioblastoma: a network meta-analysis (Protocol)

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Treatment options for recurrent glioblastoma: a network meta-analysis.
Cochrane Database of Systematic Reviews 2020, Issue 4. Art. No.: CD013579.
DOI: 10.1002/14651858.CD013579.

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TABLE OF CONTENTS

[Intervention Protocol]

Treatment options for recurrent glioblastoma: a network meta-analysis

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Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: New, published in Issue 4, 2020.

Citation: Lawrie TA, McBain C, Rogozińska E, Kernohan A, Robinson T, Lawrie I, Jefferies S. Treatment options for recurrent glioblastoma: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No.: CD013579. DOI: 10.1002/14651858.CD013579.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the effectiveness of further treatment/s for first and subsequent recurrence of glioblastoma multiforme (GBM) among people who have received the standard of care for primary treatment of the disease (chemoradiotherapy) or following development of GBM from a lower grade (radiotherapy with subsequent temozolomide at relapse); and to prepare a brief economic commentary on the available evidence.

BACKGROUND

Description of the condition

Gliomas are brain tumours that develop from supporting tissue of the brain known as glial cells. The most common and most malignant type of glioma is glioblastoma multiforme (GBM). The standard of care for treating GBM in the first instance is surgery, to remove as much of the tumour as possible, followed by radiotherapy (60 Gy in 30 fractions) and chemotherapy (concurrent and adjuvant temozolomide) (NCCN 2018). This initial treatment takes approximately nine months to complete. Chemoradiotherapy has been associated with a median progression-free survival of 6.5 months and a median overall survival of 14.6 months among reasonably fit people less than 70 years old (Stupp 2005). Approximately 25% of people receiving chemoradiotherapy are likely to be alive two years after diagnosis compared with approximately 10% who receive radiotherapy alone (Stupp 2005).

Younger people respond better to first-line treatment than older people, and those with O^6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation respond better to temozolomide than those with MGMT-unmethylated status (Malmstrom 2012; Wick 2012). Amongst fitter elderly patients treated with chemoradiotherapy, MGMT-methylated status confers a survival advantage, with a median survival of 13.5 months reported for this subgroup in a recent trial (Perry 2017). When GBM is diagnosed among patients who have had lower-grade gliomas initially treated with radiotherapy only, they are generally treated with temozolomide after surgical confirmation of recurrence as GBM. Not all people receive radiotherapy or chemotherapy (or both) after surgery, however, and best supportive care (palliative care) may be the preferred option, particularly for elderly people and those with poor performance status (NCCN 2018).

After the initial treatment phase, guidelines issued by the National Institute for Health and Care Excellence (NICE) suggest that routine follow-up by magnetic resonance imaging (MRI) be performed at 3 to 6 month intervals for the first two years, 6 to 12 monthly until five years, and then annually thereafter (NICE 2018). GBM progression or recurrence may be detected by these regular surveillance scans or identified upon the development of new symptoms (Thompson 2019). Making a diagnosis of GBM progression or recurrence can, however, be complicated in the first few months after initial treatment by the fact that its appearance on MRI may be indistinguishable from pseudoprogression (NCCN 2018).

As treatment of GBM is not curative, most people who respond to radiotherapy and temozolomide chemotherapy, in combination or sequentially, will experience a recurrence of the disease at some point thereafter, which is usually in the form of local tumour progression (Thon 2013). Following recurrence after chemoradiotherapy, a proportion of people will go on to receive further treatment; however, elderly and frail people are unlikely to do so.

Description of the intervention

The Multinational Association for Supportive Care in Cancer defines supportive care as "the prevention and management of the adverse effects of cancer and its treatment. This includes management of physical and psychological symptoms and side effects across the continuum of the cancer experience, from diagnosis through anti-cancer treatment to post-treatment care. Enhancing rehabilitation, secondary cancer prevention, survivorship and end of life care are integral to supportive care" (MASCC 2019). People with GBM experience deteriorating neurological function as well as cancer effects; therefore supportive (palliative) care to improve quality of life and mitigate these effects has an important role to play in the management of this disease from an early stage (EANO 2017). Best supportive (palliative) care only is considered a valid alternative to active treatment of recurrent GBM (Easaw 2011; NICE 2018).

Active treatment options for recurrent GBM include a second surgical resection, re-irradiation, and chemotherapy with alkylating agents, such as temozolomide, PCV (procarbazine, lomustine, vincristine) or other single agent nitrosoureas (NICE 2018; Niyazi 2011). Chemotherapy is the most common approach to treating recurrent disease (Thon 2013). In a chemotherapy-naive population with a first recurrence, single agent temozolomide and PCV has been shown to have a similar effect on survival, with a median overall survival from re-challenge of approximately seven months (Brada 2010; Parasramka 2017).

Re-irradiation in the context of recurrent GBM is usually given as a single high fraction dose (stereotactic radiotherapy) for small tumour volumes or as hypofractionated radiotherapy, where the required dose is divided into a number of fractions for larger tumour volumes, with or without chemotherapy (concurrently and/or adjuvantly) (Chapman 2019; Niyazi 2011). A second surgical resection at recurrence may be possible in up to a quarter of people with recurrent disease depending on the infiltrative nature of the recurrence (Mandl 2008; Niyazi 2011). This also gives the opportunity for molecular analysis that is helpful in guiding further treatment.

There are several novel treatments for GBM recurrence that have been evaluated or are undergoing evaluation in clinical trials but few have been introduced into practice. These include anti-angiogenic therapy, local drug delivery, targeted molecular therapy, vaccines, and electric field therapy. The most intensively investigated of these alternatives is the anti-angiogenic agent, bevacizumab. While this agent is currently licensed for use in the USA for treatment of recurrent GBM (Thon 2013), a review of anti-angiogenic agents for GBM concluded that there was insufficient evidence to support the use of bevacizumab in recurrent disease (Ameratunga 2018).

How the intervention might work

Supportive care in the context of GBM commonly includes the treatment of seizures, brain oedema, nausea, venous thromboembolism, and cognitive dysfunction (Batchelor 2006). The mechanism of action of the alkylating chemotherapy agents (e.g. temozolomide, nitrosoureas, procarbazine, carboplatin) is to interfere with DNA synthesis by causing cross-linkage between the strands and DNA breakage, thereby preventing tumour cell division (Drugs.com). Bevacizumab, the most common targeted therapy, is a monoclonal antibody that binds to and inhibits vascular endothelial growth factor, interfering with tumour blood supply and inhibiting vessel proliferation (Niyazi 2011). Stereotactic radiotherapy aims to deliver very high targeted radiotherapy doses to the tumour, whilst sparing the surrounding normal tissue (Niyazi 2011). Repeated surgical resection aims to reduce the tumour bulk and may only be effective if followed by chemotherapy or stereotactic radiotherapy (Mandl 2008).

Why it is important to do this review

There is a general acceptance that radiotherapy and temozolomide are the two best lines of therapy in GBM; there is, however, no consensus on how to use these and other modalities after primary GBM treatment. The 2015 James Lind Alliance research prioritisation setting process highlighted the need for more research guidance on GBM treatment after recurrence (JLA 2015). In particular, a better understanding of the balance between desirable and undesirable effects associated with treating recurrent GBM is necessary.

There are also significant resource implications associated with the management of GBM. A review by Messali 2014 found that the reported costs of managing GBM ranged from USD 4755 to USD 195,773 across five cost-of-illness studies (US dollar (USD) 2013). A greater understanding of the optimum management strategies for GBM will aid in the allocation of future health care resources in the most efficient way to maximise patient health. The aim of this review is therefore to identify and evaluate the best evidence on second and subsequent treatment options for when GBM recurs. This should inform conversations between people affected and health professionals, and the effective use of healthcare resources.

OBJECTIVES

To evaluate the effectiveness of further treatment/s for first and subsequent recurrence of glioblastoma multiforme (GBM) among people who have received the standard of care for primary treatment of the disease (chemoradiotherapy) or following development of GBM from a lower grade (radiotherapy with subsequent temozolomide at relapse); and to prepare a brief economic commentary on the available evidence.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), quasi-randomised trials, non-randomised studies, and controlled before-and-after studies that include relevant concurrent comparison groups. We do not expect to find cluster-randomised trials. In view of the non-stable nature of the conditions under review we will not include studies using cross-over designs, nor will we include case-control studies, or studies without a control group. Studies should include a minimum of 20 participants.

Types of participants

People aged 16 years of age and older diagnosed with a recurrence following primary treatment (surgery and chemoradiotherapy) for glioblastoma multiforme (GBM). Participants with first and subsequent recurrences will be included. Where studies include participants with grades 3 and 4 gliomas, we will try to contact study authors for data relevant to GBM (grade 4 tumours) only. If we are unable to obtain separate data, we will reach agreement on whether or not to include the study data through discussion among two or more review authors. We will not exclude studies of participants with recurrent GBMs that have transformed from low grade gliomas but will manage these data as a separate subgroup if found.

Types of interventions

Any active treatment (chemotherapy, radiotherapy, surgery or another experimental treatment) or treatment combination compared with another active treatment, best supportive (palliative) care or no active treatment.

Types of outcome measures

There are two primary and three secondary outcomes.

Primary outcomes

- Overall survival: survival from date of randomisation until death from all causes, or as reported by investigators
- Health-related quality of life (QoL): as measured using a standardised questionnaire, e.g. the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 or QLQ-BN20 (specific for brain cancer), or the Functional Assessment of Cancer Therapy scale (FACT-G (general) or FACT-Br (specific for brain cancer))

Secondary outcomes

- Progression-free survival (survival from date of randomisation to disease relapse, or as defined by investigators)
- Severe adverse events (grade 3 or higher according to a standardised measurement tool, such as the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0)
- Seizure control (as measured by study investigators)

Search methods for identification of studies

Electronic searches

For evidence on the effectiveness of interventions, we will prepare the search strategies and conduct the searches of the following databases from 2005 (the threshold for the start of the current standard of care, namely maximal surgical resection followed by chemoradiotherapy) onwards.

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library
- MEDLINE Ovid (from 2005 onwards)
- Embase Ovid (from 2005 onwards)

For economic evidence, we will search the EED database from 2005 up to the end of December 2014 (when the last records were added to that database); and MEDLINE and Embase from 1 January 2015, as NHS EED already included comprehensive searches of these databases prior to 2015. We will also consider relevant grey literature — such as health technology assessments, reports and working papers — for inclusion.

Please refer to Appendix 1 for draft MEDLINE search strategy. We will not apply language restrictions to any of the searches.

Searching other resources

Study authors will search the following for ongoing trials.

- ClinicalTrials.gov
- International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch)

If through these searches we identify ongoing trials that have not been published, we will approach the principal investigators to ask for an update on the trial status and relevant data. We will use the 'related articles' feature of PubMed and handsearch the reference lists of included studies to identify newly published articles and additional studies of relevance. We will search conference abstracts in the following journals from 2014 onwards.

- Journal of Clinical Oncology
- Neuro-oncology

Data collection and analysis

Selection of studies

The Information Specialist at the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group (CGNOC) will download all titles and abstracts retrieved by electronic searching to EndNote® and remove duplicates and those studies that clearly do not meet the inclusion criteria. A minimum of two review authors will independently screen the search results, rejecting all clearly irrelevant records and categorising the remaining articles. The categories will be included studies, excluded studies, ongoing studies and studies awaiting classification. We will record reasons for exclusion. We will identify any articles that relate to the same study and group them. We will obtain the full text of potentially eligible articles and attempt to contact study investigators to obtain more information if eligibility is unclear. Review authors will try to resolve any disagreements by discussion but they will consult the other review authors if they cannot reach agreement.

Data extraction and management

Two review authors will independently extract data, including the following items, from eligible studies using a piloted data extraction form.

- Author contact details
- Country
- Setting
- Dates of participant accrual
- Trial registration number/identification
- Funding source
- Declarations of interest
- Participant inclusion and exclusion criteria
- Study design and methodology
- Study population and baseline characteristics
  - Number of participants enrolled/analysed
  - Age
  - Gender
  - Performance status
  - MGMT-methylation status
  - Type of primary surgery (biopsy or resection)
  - Details of initial treatment
  - Details of treatment of first recurrence
  - Time from initial diagnosis
- Intervention details
  - Description of intervention
  - Description of comparator
- Primary outcome/s of the study
- Risk of study bias (see below)
- Review outcomes
  - For time-to-event data (survival and disease progression), we will extract the log of the hazard ratio (log(HR)) and its standard error from trial reports.
  - For dichotomous outcomes, we will record the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed.
  - For continuous outcomes, we will record the value and standard deviation of the outcome of interest and the number of participants assessed at the relevant time point in each group. We will also record change-from-baseline score data where reported and note the type of scale used.

We will extract both unadjusted and adjusted statistics where reported. Where possible, we will extract data to allow an intention-to-treat analysis, in which participants are analysed in the groups to which they were assigned (if data for such analysis are not reported in published reports we will try to obtain further information from trialists). We will resolve any differences between review authors by discussion or by appeal to the other review authors.

Assessment of risk of bias in included studies

For randomised trials, we will assess risk of bias using Cochrane's tool and the criteria specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). This includes assessment of:

- random sequence generation;
- allocation concealment;
- blinding of participants and healthcare providers;
- blinding of outcome assessors;
- incomplete outcome data (more than 20% missing data considered high risk);
- selective reporting of outcomes;
- other possible sources of bias, e.g. lack of a power calculation, baseline differences in group characteristics.

For non-randomised studies, we will also assess the risk of bias due to confounding under the 'other bias' criterion of the Cochrane 'Risk of bias' tool according to the following study details.

- Relevant details of criteria for assignment of people with the condition to treatments.
- Representative group of people with the condition who received the experimental intervention.
- Representative group of people with the condition who received the comparison intervention.
- Baseline differences between groups controlled for, in particular with reference to age, gender, first or subsequent recurrence, extent of primary resection and molecular biomarker status.

Two review authors (TL, EW) will assess risk of bias independently and resolve differences by discussion or by appeal to a third review author. We will summarise judgements in 'Risk of bias' tables along with the characteristics of the included studies. We will include both a risk of bias graph and a risk of bias summary. We will consider the 'Risk of bias' assessment in our interpretation of the evidence.

Measures of treatment effect

We will use the following measures to evaluate treatment effect.

- For time-to-event data (e.g. death or disease progression) we will use the hazard ratio (HR) with 95% confidence intervals (CIs).
- For dichotomous outcomes, we will calculate the effect size as a risk ratio (RR) with its 95% CIs.
- For continuous outcomes measured using the same scale, we will report the mean difference (MD) between treatment groups with 95% CIs. For continuous outcomes (e.g. QoL scores) in which different measurement scales have been used, or if studies report change-from-baseline instead of final values, we will combine these data using the (unstandardised) mean difference method in Review Manager 5 (RevMan 5) (Review Manager 2014)

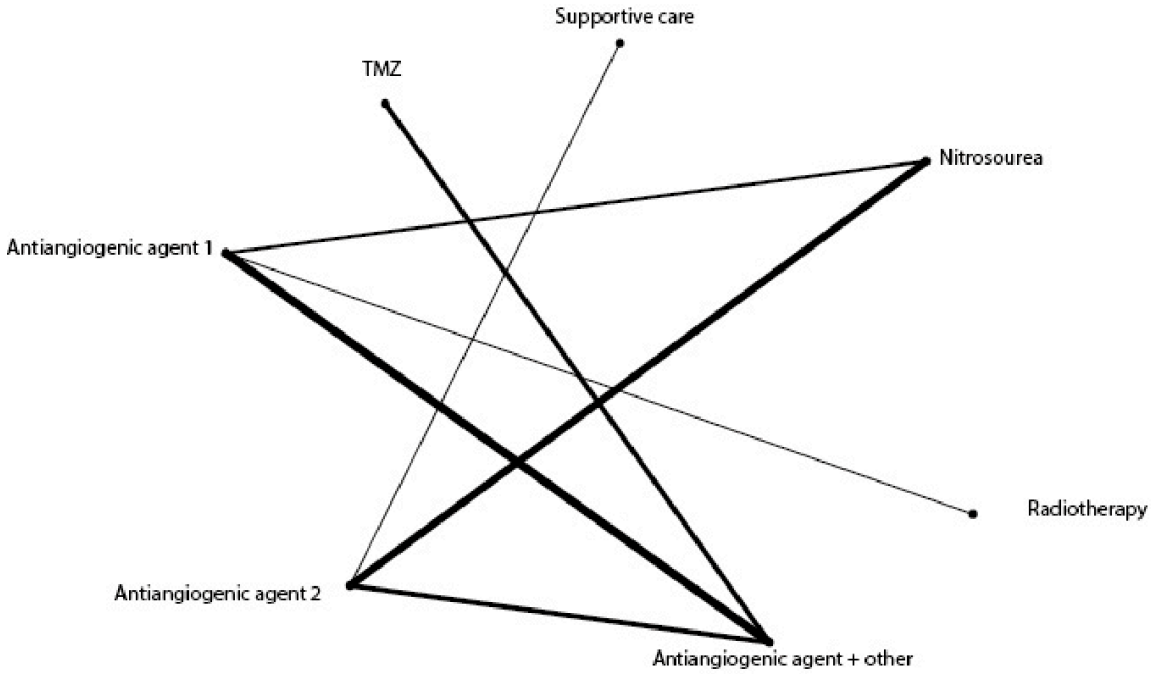
Network structure

Where possible, the network will compare and rank the following types of interventions with each other.

- Supportive care
- Radiotherapy
- Chemoradiotherapy
- Temozolomide
- Platinum compounds
- Nitrosoureas-based chemotherapy (i.e. PCV, CCNU, BCNU, etc.)
- Antiangiogenic agents (e.g. bevacizumab and other)
- Immunotherapy, e.g. tumour-derived vaccine, dendritic cell therapy
- Second surgical resection
- Tumour-treating fields

The network will also include combinations of these or other interventions and intervention combinations if relevant studies are found. Figure 1 shows an illustrative network diagram.

Figure 1. Illustrative network diagram



Unit of analysis issues

Two review authors (TL and ER) will review any unit-of-analysis issues according to Higgins 2019 for each included study and we will resolve any differences through discussion. We will consider issues such as where there are multiple observations for the same outcome, e.g. repeated measurements with different scales, or outcomes measured at different time points to those stipulated in

the review protocol. An example of where this might occur is with the outcome 'quality of life'.

Multi-arm trials

If we identify multi-arm trials, we will treat the multiple comparisons as independent in pairwise meta-analyses. In the network meta-analysis, we will account for the correlation between the effect sizes derived from the same study.

Dealing with missing data

We will not impute missing data. In the event of missing data, we will write to study authors to request data. Where missing data are substantial, this will be taken into consideration in our grading of the evidence.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity

We will assess clinical heterogeneity between studies by comparing the studies' characteristics of included participants, and interventions in each meta-analysis of each comparison; by visual inspection of forest plots; by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003); and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there is evidence of substantial heterogeneity, we will investigate and report the possible reasons for this.

Assessment of consistency across treatment comparisons

We will examine the assumption of consistency by assessing the distribution of potential effect modifiers across the pair-wise comparisons. The assumption will hold if the following is true.

- The common treatment used to compare different interventions indirectly is similar when it appears in different trials.
- All pairwise comparisons do not differ with respect to the distribution of effect modifiers.

The potential treatment modifiers are as follows.

- Extent of resection
- MGMT-methylation status
- First or subsequent resection
- Time from primary diagnosis

Assessment of statistical heterogeneity and inconsistency

Assumptions when estimating the heterogeneity

We will estimate heterogeneity indicators for each pairwise comparison. In network meta-analysis, we will assume a common estimate for the heterogeneity variance across the different comparisons.

Measures and tests for heterogeneity

We will perform the presence of statistical heterogeneity within the pairwise comparisons using the I^2 statistic, which is the percentage of variability that cannot be attributed to random error. We will base the assessment of statistical heterogeneity in the network on the magnitude of the heterogeneity variance parameter (Tau^2) estimated from the network meta-analysis models.

Assessment of statistical inconsistency

We will evaluate the statistical agreement between the various sources of evidence in a network of interventions (consistency) by global and local to complement the evaluation of consistency (Efthimiou 2016).

Assessment of reporting biases

We will assess each paper for the extent and transparency of reporting and for suggestion of reporting bias. We do not expect to find sufficient studies to assess publication bias using funnel plots.

Data synthesis

For effectiveness studies

Methods for direct treatment comparisons

We will carry out meta-analyses in RevMan 5, pooling data from studies measuring the same outcomes. Assuming that we find at least two included studies that are sufficiently similar for the findings to be clinically meaningful, we will use the random-effects models with inverse variance weighting for all meta-analyses. If any studies contributing to a meta-analysis have multiple intervention groups, we will divide the 'shared' comparison group into the number of treatment groups and comparisons between each treatment group and treat the split comparison group as independent comparisons. If meta-analysis is not possible due to the timing of assessment or the type of outcome measure used, we will attempt to synthesise data narratively.

Methods for indirect and mixed comparisons

We will attempt to conduct network meta-analyses, providing that populations of included studies are sufficiently similar to satisfy the assumption of joint randomisation and that the interventions connect, creating a network. We plan to use the random-effects model in Stata fitting a multivariate network meta-analysis (White 2015). We will report the value of mean rank and proportion of the surface under the cumulative ranking (SUCRA) probabilities for all included treatments (Chaimani 2015).

For outcomes where meta-analysis is not possible, we will apply a narrative synthesis and assess these using the GRADE approach (Murad 2017). We will interpret the quality of the evidence based on the Cochrane Effective Practice and Organisation of Care (EPOC) Group's guidance (EPOC 2015).

'Summary of findings' table and results reporting

Based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019), we will prepare a 'Summary of findings' table to present the results of the primary outcomes, namely:

- overall survival;
- QoL.

We will use the GRADE system to rank the quality of the evidence (Schünemann 2019). Two review authors will independently grade the evidence and will resolve any differences by discussion or, if necessary, by involving a third review author. We will interpret the results of the graded evidence based on Cochrane Effective Practice and Organisation of Care guidance (EPOC 2015).

Brief economic commentary

We will include a brief economic commentary that will summarise the availability and principal findings of the economic evaluations relevant to this review. This will include evaluations alongside trials and model-based evaluations. The work will be performed in line with current guidelines, including a supplementary search to identify economic studies (Shemilt 2019).

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses and investigate heterogeneity if possible according to first or subsequent recurrence, MGMT promotor methylation status, and time from primary diagnosis. We will consider not pooling subgroup data if the tests for subgroup differences suggest that effects are significantly different (P value ≤ 0.05) for different subgroups. Transformed GBM will be analysed separately from recurrence arising from primary GBM.

Sensitivity analysis

In the network meta-analyses, we intend to explore how the following factors affect the ranking of interventions.

- Study quality, by excluding studies at high risk of bias to investigate how study quality affects the evidence on effects and the certainty of findings.
- Combination of change in scores with final values, by investigating how the pooled MD is affected when studies reporting the outcome using the less common format are removed.
- If the effects from a multiarm trial creates a single loop in the network (no other loops available), we will explore how exclusion of one of the arms affects the NMA findings.

ACKNOWLEDGEMENTS

We thank Robin Grant, Co-ordinating Editor, and Gail Quinn and Clare Jess, Managing Editors from Cochrane Gynaecological, Neuro-oncology and Orphan Cancers, for their advice and support in the preparation of this protocol. We also thank the Information Specialist, Jo Platt, for designing the search strategy.

This project is supported by the National Institute for Health Research (NIHR), via Cochrane Programme Grant funding - 16/144 to Cochrane Gynaecological, Neuro-oncology and Orphan Cancers. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service, or the Department of Health.

The authors and Cochrane Gynaecological, Neuro-oncology and Orphan Cancers Team are grateful to the following peer reviewers for their time and comments: Helen Bulbeck, Sara Erridge, Michael Hart and Fiona McKevitt.

REFERENCES

Additional references

Ameratunga 2018

Ameratunga M, Pavlakis N, Wheeler H, Grant R, Simes J, Khasraw M. Anti-angiogenic therapy for high-grade glioma. *Cochrane Database of Systematic Reviews* 2018, Issue 11. [DOI: 10.1002/14651858.CD008218.pub4]

Batchelor 2006

Batchelor TT, Byrne TN. Supportive care of brain tumor patients. *Hematology/oncology Clinics of North America* 2006;**20**(6):1337-61.

Brada 2010

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;**28**(30):4601-8.

Chaimani 2015

Chaimani A, Salanti G. Visualizing assumptions and results in network meta-analysis: the network graphs package. *Stata Journal* 2015;**15**(4):905-50.

Chapman 2019

Chapman CH, Hara JH, Molinaro AM, Clarke JL, Oberheim Bush NA, Taylor JW, et al. Reirradiation of recurrent high-grade glioma and development of prognostic scores for progression and survival. *Neuro-Oncology Practice* 2019;**6**(5):364-74.

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Chapter 15: Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. Systematic Reviews in Health Care: Meta-Analysis in Context. 2nd Edition. London: BMJ Publication Group, 2001.

Drugs.com

Drugs.com. Alkylating agents. www.drugs.com/drug-class/alkylating-agents.html (accessed 9 December 2019).

EANO 2017

Pace A, Dirven L, Koekkoek JAF, Golla H, Fleming J, Ruda R. European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma. *Lancet Oncology* 2017;**18**(6):e330-e340.

Easaw 2011

Easaw JC, Mason WMP, Perry J, Laperrière N, Eisenstat DD, Del Maestro R, et al. Canadian recommendations for the treatment of recurrentor progressive glioblastoma multiforme. *Current Oncology (Toronto, Ont.)* 2011;**18**(3):126-36.

Efthimiou 2016

Efthimiou O, Debray TP, van Valkenhoef G, Trelle S, Panayidou K, Moons KG, et al. GetReal in network meta-analysis: a review of the methodology. *Research Synthesis Methods* 2016;**7**(3):236-63.

EPOC 2015

Cochrane Effective Practice, Organisation of Care (EPOC). EPOC resources for review authors. 2015. epoc.cochrane.org/epoc-specific-resources-review-authors (accessed 6 July 2016).

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2019

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 [updated July 2019]. The Cochrane Collaboration, 2019. Available from www.cochrane-handbook.org 2019.

JLA 2015

MacDonald L, on behalf of the Neuro-Oncology Group. Top 10 priorities for clinical research in primary brain and spinal cord tumours. www.jla.nihr.ac.uk/priority-setting-partnerships/neuro-oncology/downloads/Neuro-Oncology-Group-Final-Report-June-2015.pdf (accessed 1 March 2018).

Malmstrom 2012

Malmstrom A, Grønberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncology* 2012;**13**(9):916-26.

Mandl 2008

Mandl ES, Dirven CM, Buis DR, Postma TJ, Vandertop WP. Repeated surgery for glioblastoma multiforme: only in combination with other salvage therapy. *Surgical Neurology* 2008;**69**(5):506-9.

MASCC 2019

Multinational Association of Supportive Care in Cancer. What is supportive care. www.mascc.org/about-mascc (accessed 8 October 2019).

Messali 2014

Messali A, Villacorta R, Hay JW. A review of the economic burden of glioblastoma and the cost effectiveness of pharmacologic treatments. *PharmacoEconomics* 2014;**32**:1201-12.

Murad 2017

Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty of the evidence in the absence of a single estimate of effect. *Evidence-based Medicine* 2017;**22**(3):85-7.

NCCN 2018

National Comprehensive Cancer Network. NCCN Guidelines version 1. 2018. Central Nervous System Cancers. https://www.optune.com/Content/pdfs/CNS_FlashCard_4Page.pdf (accessed 5 April 2020).

NICE 2018

National Institute for Health and Care Excellence. Brain tumours (primary) and brain metastases in adults. Available at www.nice.org.uk/guidance/ng99.

Niyazi 2011

Niyazi M, Siefert A, Schwarz SB, Ganswindt U, Kreth FW, Tonn JC, et al. Therapeutic options for recurrent malignant glioma. *Radiotherapy and Oncology* 2011;**98**(1):1-14.

Parasramka 2017

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. [DOI: 10.1002/14651858.CD011773.pub2]

Perry 2017

Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, et al. Short-course radiation plus temozolomide in elderly patients with glioblastoma CNO - CN-01366980. *New England Journal of Medicine* 2017;**376**(11):1027-37.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schünemann 2019

Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, et al. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors) editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019:Available from https://training.cochrane.org/handbook/current/chapter-15 (Accessed 5 April 2020).

Shemilt 2019

Shemilt I, Aluko P, Graybill E, Craig D, Henderson C, Drummond M, et al. on behalf of the Campbell and Cochrane Economics Methods Group. Chapter 20: Economic evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Stupp 2005

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

Thompson 2019

Thompson G, Lawrie TA, Kernohan A, Jenkinson MD. Interval brain imaging for adults with cerebral glioma. *Cochrane Database of Systematic Reviews* 2019, Issue 12. [DOI: 10.1002/14651858.CD013137.pub2]

Thon 2013

Thon N, Kreth S, Kreth FW. Personalized treatment strategies in glioblastoma: MGMT promoter methylation status. *OncoTargets and Therapy* 2013;**6**:1363–72.

White 2015

White IR. Network meta-analysis. *Stata Journal* 2015;**15**(4):951-85.

Wick 2012

Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon M, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *Lancet Oncology* 2012;**13**(7):707-15.

APPENDICES

Appendix 1. Medline Search Strategy

Intervention Medline search:

1. astrocytoma/
2. glioblastoma/
3. (glioblastom* or GBM* or astrocytom* or gliosarcom*).mp.
4. 1 or 2 or 3
5. neoplasm recurrence, local/
6. (recurren* or return* or relapse*).mp.
7. 5 or 6
8. 4 and 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. clinical trials as topic.sh.
14. randomly.ab.
15. trial.ti.
16. (before adj3 after adj3 (study or studies)).mp.
17. (CBA adj (study or studies)).mp.
18. interrupted time series.mp.
19. exp Cohort Studies/

20. (cohort* or prospective* or retrospective*).mp.
21. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. (animals not (humans and animals)).sh.
23. 21 not 22
24. 8 and 23
25. (2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019*).ed.
26. 24 and 25

Key:
mp = title, original title, abstract, name of substance word, subject heading word, unique identifier
pt = publication type
ab = abstract
fs = floating subheading
sh = subject heading

Economic Medline search:

1. astrocytoma/
2. glioblastoma/
3. (glioblastom* or GBM* or astrocytom* or gliosarcom*).mp.
4. 1 or 2 or 3
5. neoplasm recurrence, local/
6. (recurren* or return* or relapse*).mp.
7. 5 or 6
8. 4 and 7
9. economics/
10. exp "costs and cost analysis"/
11. economics, dental/
12. exp "economics, hospital"/
13. economics, medical/
14. economics, nursing/
15. economics, pharmaceutical/
16. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
17. (expenditure$ not energy).ti,ab.
18. (value adj1 money).ti,ab.
19. budget$.ti,ab.
20. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. ((energy or oxygen) adj cost).ti,ab.
22. (metabolic adj cost).ti,ab.
23. ((energy or oxygen) adj expenditure).ti,ab.
24. 21 or 22 or 23
25. 20 not 24
26. letter.pt.
27. editorial.pt.
28. historical article.pt.
29. 26 or 27 or 28
30. 25 not 29
31. Animals/
32. Humans/
33. 32 not (32 and 33)
34. 30 not 33
35. 8 and 34
36. (2015* or 2016* or 2017* or 2018* or 2019*).ed.
37. 35 and 36

Key:
mp = title, original title, abstract, name of substance word, subject heading word, unique identifier
pt = publication type
ab = abstract
fs = floating subheading
sh = subject heading

CONTRIBUTIONS OF AUTHORS

Theresa Lawrie wrote the first draft of the protocol. All authors advised on and approved the final version of the protocol.

DECLARATIONS OF INTEREST

Theresa Lawrie: none declared
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Sarah Jefferies: none declared

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR 16/144 Cochrane Programme Grant Scheme, UK, UK.