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Adjuvant treatment of anaplastic oligodendrogliomas and oligoastrocytomas (Review)

Lecavalier-Barsoum M, Quon H, Abdulkarim B

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[Intervention Review]

Adjuvant treatment of anaplastic oligodendrogliomas and oligoastrocytomas

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ABSTRACT

Background

Standard care of adjuvant treatment for anaplastic oligodendrogliomas (AO) and anaplastic oligoastrocytomas (AOA) is not yet well defined. The benefit of adjuvant chemotherapy and radiotherapy (RT), given as single modalities or sequentially, is still unclear. Furthermore, insight into the predictive and prognostic impact of various biomarkers is surging.

Objectives

To compare postoperative sequential RT and chemotherapy to RT alone in adults with newly diagnosed AO or mixed AOA. To evaluate the predictive and prognostic impact of the following biomarkers: codeletion of chromosomes 1p and 19q, O^6-methylguanine-DNA methyltransferase (MGMT) promotor methylation and isocitrate dehydrogenase (IDH)-1 and -2 mutations.

Search methods

We searched the Cochrane Central Register for Controlled Trials (CENTRAL, Issue 1, 2014), MEDLINE (2006 to March week 2, 2014) and EMBASE (2006 to week 11, 2014). We scanned reference lists from relevant studies for any additional articles.

Selection criteria

We included randomized controlled trials (RCTs) of adults with AO, AOA or anaplastic astrocytoma (AA) comparing adjuvant treatment of chemotherapy, RT, or sequential chemotherapy and RT. We excluded no specific chemotherapy regimens.

Data collection and analysis

We critically appraised and extracted data from relevant studies. Based on the differences in participant selection with respect to the definition of AO (two versus three high-risk anaplastic features), the inclusion of AA and sequence of treatment (RT and chemotherapy), we could not consider the results from the three RCTs for meta-analysis.

Main results

Three RCTs, with 931 participants, tested different neoadjuvant treatments: RT alone; sequential RT and procarbazine, lomustine and vincristine (PCV) chemotherapy; PCV chemotherapy alone; and temozolomide chemotherapy alone. None of the studies blinded participants or personnel, and, therefore, are considered at high risk of performance and detection bias. The studies were otherwise at low risk of bias. One study, the European Organisation for Research and Treatment of Cancer (EORTC) trial, demonstrated a statistically significant overall survival (OS) benefit for RT plus PCV, with a median OS of 3.5 years compared with 2.6 years in the RT alone arm (P value = 0.018). This result was reported 10 years after the conclusion of the enrolment, and was not apparent in the original 2008 Cochrane review. Furthermore, with retrospective evaluation of biomarkers, codeletion of complete chromosome arms 1p and 19q and IDH-1 or -2

mutation were independent prognostic factors for OS in two of the RCTs (Radiation Therapy Oncology Group (RTOG) and EORTC), and were predictive for OS in one trial (RTOG). The third trial (NOA-04) evaluated these biomarkers prospectively and found them prognostic for progression-free survival.

Authors' conclusions

Early PCV, either before or after RT, appears to improve OS of participants with AO or AOA. Use of biomarkers including codeletion of chromosomes 1p and 19q with or without IDH-1 or -2 mutation identify a subset of people with increased sensitivity to combined PCV and RT. The important role of biomarkers was supported in all of the RCTs examined, and prospective evaluation should be undertaken in future studies. However, PCV was associated with significant grade 3 and 4 toxicities, and whether temozolomide can be substituted for this remains unclear.

PLAIN LANGUAGE SUMMARY

Does giving chemotherapy, radiotherapy or both improve survival in people with rare (anaplastic oligodendrogliomas and oligoastrocytomas) brain tumours?

Background

Traditionally, the standard of care for people with rare anaplastic oligodendrogliomas and anaplastic oligoastrocytomas (brain tumours) has been surgery followed by radiotherapy. However, the benefit of adjuvant (post-surgery) chemotherapy and radiotherapy is still unclear. In addition, the value of chromosome markers is also under investigation.

Study characteristics

We searched the scientific literature up to March 2014 for studies of adults over 18 years of age with a diagnosis of anaplastic oligodendrogliomas, anaplastic oligoastrocytomas or anaplastic astrocytomas. After surgery, the participants had to have received radiotherapy alone, chemotherapy alone or radiotherapy plus chemotherapy. In the first review on this topic in 2009, we found two trials to include. In this update, we identified another trial for inclusion, and updates from the two previously included trials were taken into consideration.

Key results

Three randomized controlled trials, which included 931 participants, assessed the role of chemotherapy alone or in addition to radiotherapy, or radiotherapy alone. One study was able to demonstrate a significant survival benefit for the addition of chemotherapy to radiotherapy after surgery, compared with radiotherapy alone. In addition, during examination of these brain tumour biopsy specimens, they found specific chromosome deletions and mutations in two studies, which helped to identify a group of participants with better survival outcomes. Furthermore, in one study, these specific chromosome deletions and mutations predicted which group of participants derived benefit from the addition of chemotherapy to radiotherapy after surgery.

Quality of the evidence

Evidence for giving radiotherapy and chemotherapy was of good quality, but sparse.

BACKGROUND

Oligodendroglial tumours are primary brain tumours representing 1.8% of primary central nervous system (CNS) tumours and 6.2% of all CNS gliomas (CBTRUS 2009). Since the early 1990s, knowledge gained has been prolific with regards to these tumours. Interest was first hastened by demonstration of chemosensitivity of oligodendroglial tumours (Cairncross 1994). The identification of predictive and prognostic markers, such as codeletion of chromosomes 1p and 19q, and isocitrate dehydrogenase (IDH)-1 and -2, have contributed significantly to the promotion of more biological research (Cairncross 1998; Smith 2000; van den Bent 2003), and have advanced our knowledge in the management of these tumours.

Previous review on anaplastic oligodendrogliomas and anaplastic oligoastrocytomas

We published a systematic review focusing on the role of adjuvant chemotherapy in addition to radiotherapy (RT) in the treatment of anaplastic oligodendrogliomas (AO) and anaplastic oligoastrocytomas (AOA) in 2008 (Quon 2008). This first review concluded that early procarbazine, lomustine and vincristine (PCV) chemotherapy in addition to standard treatment of surgery and RT improved progression-free survival (PFS), but did not improve overall survival (OS) in participants with AO and AOA. It also supported the idea that this increase in PFS was at the cost of increased toxicity. In addition, clear conclusions on the predictive value of codeletion of chromosomes 1p and 19q were not made because of lack of correlation in studies.

New molecular markers based on randomized controlled trials updates

Since this first systematic review, significant developments in predictive and prognostic markers for AO and AOA have been made. IDH-1 and -2 gene mutations have been recognized as important markers for glial tumours. Identified after sequencing of the genome of glioblastomas (GBM) in 2008 (Balss 2008; Hartmann 2009; Parsons 2008; Yan 2009), they were shown to be present in 55% to 80% of oligodendrogliomas and astrocytomas World Health Organization (WHO) grades II and III. IDH-1 and -2 mutations are also present in 50% to 100% of secondary GBM (Balss 2008; Ichimura 2009; Kloosterhof 2011; Sonoda 2009; Watanabe 2009; Yan 2009). GBM are classified as secondary when they arise from low-grade diffuse astrocytomas or anaplastic astrocytomas (AA), as compared with primary GBM that develop rapidly de novo, without clinical or histological evidence of a less malignant precursor lesion. In addition, IDH-1 and -2 mutations are thought to be initiating events in these glial tumour subtypes (Sonoda 2009; Watanabe 2009; Yan 2009). Interestingly, they are rare in primary GBM, as they are found in only 3% to 12% of them (Balss 2008; Hartmann 2009; Ichimura 2009; Kloosterhof 2011; Parsons 2008; Sonoda 2009; Watanabe 2009; Yan 2009). The status of the IDH-1 gene can be determined by immunohistochemistry with an antibody specific to the common mutant form of IDH-1 (Camelo-Piragua 2010).

The O^6-methylguanine DNA-methyltransferase (MGMT) gene encodes for a protein responsible for deoxyribonucleic acid (DNA) repair by removing alkyl groups from guanine, and MGMT promoter methylation was shown to be prognostic in GBM (Stupp 2005). Its link to the development of gliomas has been assessed, without a clear causal effect demonstrated (Boots-Sprenger 2013; Laffaire 2011). Its role as a biomarker for AO and AOA is not yet well defined.

Why it is important to do this review

In this systematic review, we sought to identify the role of sequential RT and chemotherapy compared with RT alone in adults with newly diagnosed AO or AOA; and to evaluate the predictive and prognostic impact of the following biomarkers: codeletion of chromosomes 1p and 19q, MGMT promotor methylation, and IDH-1and -2 mutations.

OBJECTIVES

To compare postoperative sequential RT and chemotherapy to RT alone in adults with newly diagnosed AO or mixed AOA. To evaluate the predictive and prognostic impact of the following markers: codeletion of chromosomes 1p and 19q, MGMT promoter methylation, and IDH-1and -2 mutations.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized controlled trials (RCTs) that limited enrolment to participants with AO, AOA or AA.

Types of participants

Adults over 18 years of age with a diagnosis of AO, AOA or AA.

Types of interventions

After surgery, participants were randomized to receive RT alone, chemotherapy alone or RT plus chemotherapy. No chemotherapy regimens were excluded.

Types of outcome measures

Primary outcomes

- OS: as defined from date of randomization to death from of any cause.

Secondary outcomes

- PFS: as defined from date of randomization to disease progression based on clinical or radiographic evidence.
- Treatment toxicity of grade 3 or greater.

Search methods for identification of studies

Electronic searches

The search was run for the original review in August 2006, and subsequently updated in Mar 2014.

We searched the following databases:

- Cochrane Central Register for Controlled Trials (CENTRAL) (Issue 1, 2014).(Appendix 1);
- MEDLINE (up to March week 2 2014) (Appendix 2);
- EMBASE (up to 2014 week 11) (Appendix 3).

We examined the reference lists from relevant articles and review articles to search for any additional articles.

Searching other resources

We searched no other resource, as we included only RCTs in this review.

Data collection and analysis

Selection of studies

We applied the search criteria and reviewed all titles and abstracts identified. Studies in which the relevance was unclear were further examined by retrieving the full article. All authors agreed on the study selection. We used the bibliographic software Endnote.

Data extraction and management

For included studies, we have extracted the following data:

- author, year of publication and journal citation (including language);
- country;
- setting;
- inclusion and exclusion criteria;
- study design, methodology;
- study population
  - total number enrolled,
  - participant characteristics,
  - age,
  - histological diagnosis,
  - number of anaplastic characteristic,
  - biomarkers status (codeletion of chromosomes 1p and 19q, IDH-1 and -2 mutations, MGMT methylation);
- intervention details
  - RT dose and fractionation,
  - chemotherapy agents, dose and number of cycles,
  - timing of intervention following surgery,
  - toxicity of intervention;
- comparison
  - timing of assessment of biomarkers (at time of accrual versus after accrual),
  - definition of progression,
  - treatment at progression;
- risk of bias in study (see Risk of bias in included studies);
- duration of follow-up;
- outcomes: for each outcome, we extracted the outcome definition and unit of measurement (when relevant). For adjusted estimates, we recorded variables adjusted for in analyses;
- results: we extracted the number of participants allocated to each intervention group, the total number analyzed for each outcome, and the missing participants.

In a future update, if a meta-analysis can be performed, the following methodology would be considered, with results extracted as follows:

- For time to event data (survival and disease progression), we would extract the log of the hazard ratio (log(HR)) and its standard error from trial reports. If these are not reported, we would attempt to estimate the log(HR) and its standard error using the methods of Parmar (Parmar 1998).
- For dichotomous outcomes (e.g. adverse events or deaths, if it is not possible to use a HR), we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio.
- For continuous outcomes (e.g. quality of life (QoL) measures), we will extract the final value and standard deviation 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 between treatment arms and its standard error.

Assessment of risk of bias in included studies

We assessed the risk of bias in included studies using The Cochrane Collaboration's tool (Higgins 2011). This included an assessment of:

1. selection bias: random sequence generation and allocation concealment;
2. performance bias: blinding of participants and personnel (participants and treatment providers);
3. detection bias: blinding of outcome assessment;
4. attrition bias: incomplete outcome data;
5. reporting bias: selective reporting of outcomes.

We classified the risk of these biases as 'low', 'high' or 'unclear' for each included study (Characteristics of included studies).

Measures of treatment effect

If the trials had had homogeneous patients' characteristics and interventions, we would have evaluated measures of treatment effect.

- For OS and PFS, we would have extracted the log(HR) and its standard error from trial reports.
- For toxicity, we would have extracted the number of participants in each treatment arm who experienced toxicity of grade 3 or greater and the number of participants assessed at endpoint, in order to estimate a risk ratio.

Dealing with missing data

We contacted the authors from the three trials to request further details. The principle investigator of the Radiation Therapy Oncology Group (RTOG) trial, Gregory Cairncross, informed us that an update on the trial, including information on IDH-1 and -2 mutations status, was to be published. This update was included in our review. No information beyond what is currently published was available for the two other trials.

Assessment of heterogeneity

The included studies present significant differences.

- Clinical diversity: the histological diagnosis of participants in the three studies differ, with different criteria for anaplasia in all studies and inclusion of AA in the NOA-04 study; the interventions are different in the three studies, with varying dosing and schedules of chemotherapy, with different sequences of treatment and with different chemotherapy agents being used.
- Methodological diversity: the European Organisation for Research and Treatment of Cancer (EORTC) trial analyzed their

results on an intention-to-treat (ITT) basis, whereas the RTOG and NOA-04 trials performed their statistical analyses on a participant eligible basis and modified ITT, respectively.

Assessment of reporting biases

We intended to construct a funnel plot of treatment effect versus precision in order to investigate the likelihood of publication bias if we had identified 10 or more studies. If these plots had suggested that treatment effects may not be sampled from a symmetric distribution, as assumed by the random-effects model, we had planned to perform further meta-analyses using the fixed-effect model.

Data synthesis

The results of the three selected studies were not amenable to a meta-analysis because of participant selection with respect to the pathological diagnosis (inclusion of AA in the NOA-04 study, and different criteria to define anaplasia), and also because of sequence of treatment (RT and chemotherapy). Therefore, we have described the results separately for each RCT.

Subgroup analysis and investigation of heterogeneity

If the trials had had homogeneous participants' characteristics and interventions, we would have performed subgroup analysis with regards to biomarker status.

RESULTS

Description of studies

Results of the search

For the updated review, the search found 70 publications on CENTRAL, 278 on MEDLINE and 193 on EMBASE.

Included studies

Three RCTs met the inclusion criteria. Two were included in the first Cochrane review in 2008 (Quon 2008). Several updates with analysis of biomarkers were published for both studies. The third study was published after the first review was developed.

The RTOG trial 9402 was a multicentre RCT (1994 to 2002) that included 289 participants older than 18 years of age with AO or AOA (Cairncross 2006). Since the first publication in 2006, three published updates have addressed the outcomes that we are evaluating, and the median follow-up is now 11.3 years. Anaplasia was identified based on five features (tumour cellularity, nuclear pleomorphism, mitotic activity, endothelial proliferation and necrosis). Anaplastic tumours had to contain two of five features, one of which was high mitotic activity or endothelial proliferation. An oligoastrocytoma had to have at least 25% oligodendroglioma component. Participants had a Karnofsky Performance Scale (KPS) score of at least 60 and were randomized within eight weeks of surgery and received up to four cycles of PCV followed by RT (147 participants) versus RT alone (142 participants). RT was identical in both treatment arms and was given to a total dose of 59.4 Gy in 33 fractions. Unplanned analysis of codeletion of chromosomes 1p and 19q by fluorescence in situ hybridization (FISH) analysis, and of IDH-1 and -2 mutations by immunohistochemistry and sequencing, started after the initiation of the trial as the importance of these markers was not known until after participant accrual had begun. The codeletion of chromosomes 1p and 19q status was obtained for 91% of the participants in the update of the study, as compared with only 70% in the original. The IDH-1 and -2 status was obtained in 72% of the participants. The primary endpoint was OS and secondary endpoints included PFS, frequency of severe (grade 3 or greater) treatment toxicities, cognition and QoL.

The EORTC trial 26951 was a multicentre RCT (1996 to 2002) that included 368 participants aged 16 to 70 years with newly diagnosed AO or AOA (van den Bent 2006). Since the first publication in 2006, eight published updates have addressed the outcomes that we are evaluating, and the median follow-up is now 11.7 years. In contrast to RTOG 9402, anaplastic tumours were defined as having at least three of five anaplastic features (high cellularity, mitosis, nuclear abnormalities, endothelial proliferation and necrosis). An oligoastrocytoma had to have at least 25% oligodendroglioma component. Participants with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 were eligible and randomized after surgery to either RT (59.4 Gy in 33 fractions) followed by up to 6 cycles of PCV (185 participants) versus RT alone (183 participants). As with the RTOG trial, assessment of codeletion of chromosomes 1p and 19q by FISH analysis was not started until the trial had begun and was available for 85.9% of participants. The assessment of MGMT methylation by semi-quantitative methylation-specific multiplex ligation-dependent probe amplification and of IDH-1 and -2 mutations by bidirectional cycle sequencing of polymerase chain reaction (PCR)-amplified fragments was done after the conclusion of enrolment for the study. Information on the MGMT methylation and on IDH-1 and -2 was found for 49.7% and 48.6% of participants, respectively. Primary endpoints were OS and PFS, and secondary endpoints included QoL and toxicity.

The Neuro-Oncology Working Group (NOA) of the German Cancer Society 04 was a multicentre RCT (1999 to 2005) that included 274 participants aged 18 years and over with newly diagnosed AO, AOA or AA who were followed for a maximum of 4.5 years (NOA-04 2009). Similarly to the EORTC study, at least three criteria of anaplastic features were required for the tumours to be defined anaplastic. Participants had a KPS score of 70 or greater, and were randomized in a 2:1:1 fashion to 60 Gy in 30 to 33 fractions of RT (139 participants) versus 4 cycles of 8 weeks of PCV (68 participants) versus 8 cycles of 4 weeks of temozolomide (67 participants). In contrast to the RTOG and EORTC studies, molecular analyses was assessed at randomization. Assessment of codeletion of chromosomes 1p and 19q was carried out by a multiplex ligation-dependent probe assay and was available for 56.9% of participants. MGMT methylation status was determined in 63.5% of participants by methylation-specific PCR. IDH-1 and -2 mutations were evaluated by gene amplification, and results were available for 61.3% of participants. The primary endpoint was time from operation to treatment failure. Secondary endpoints included response rate, PFS, OS, time to treatment failure stratified for histology, codeletion of chromosomes 1p and 19q, MGMT promoter methylation status, IDH-1 mutation and toxicity.

These studies are summarized in Table 1.

Limitations of studies

These three studies have significant differences worth mentioning.

First, there are noteworthy pathological characteristic distinctions in each study. The RTOG and EORTC studies included AOA and

AO only. However, the number of anaplastic characteristics a tumour required to be defined anaplastic differed in each study. Two criteria were required in the RTOG study, as long as high mitotic activity or endothelial proliferation was present. The EORTC study based the diagnosis of anaplastic tumours on the WHO 1993 grading, requiring three criteria, including tumours with necrosis. The NOA-04 study included not only AO and AOA, but also AA. In this study, grading of tumours was based on the WHO 2000 grading, requiring three criteria of anaplasia excluding necrosis.

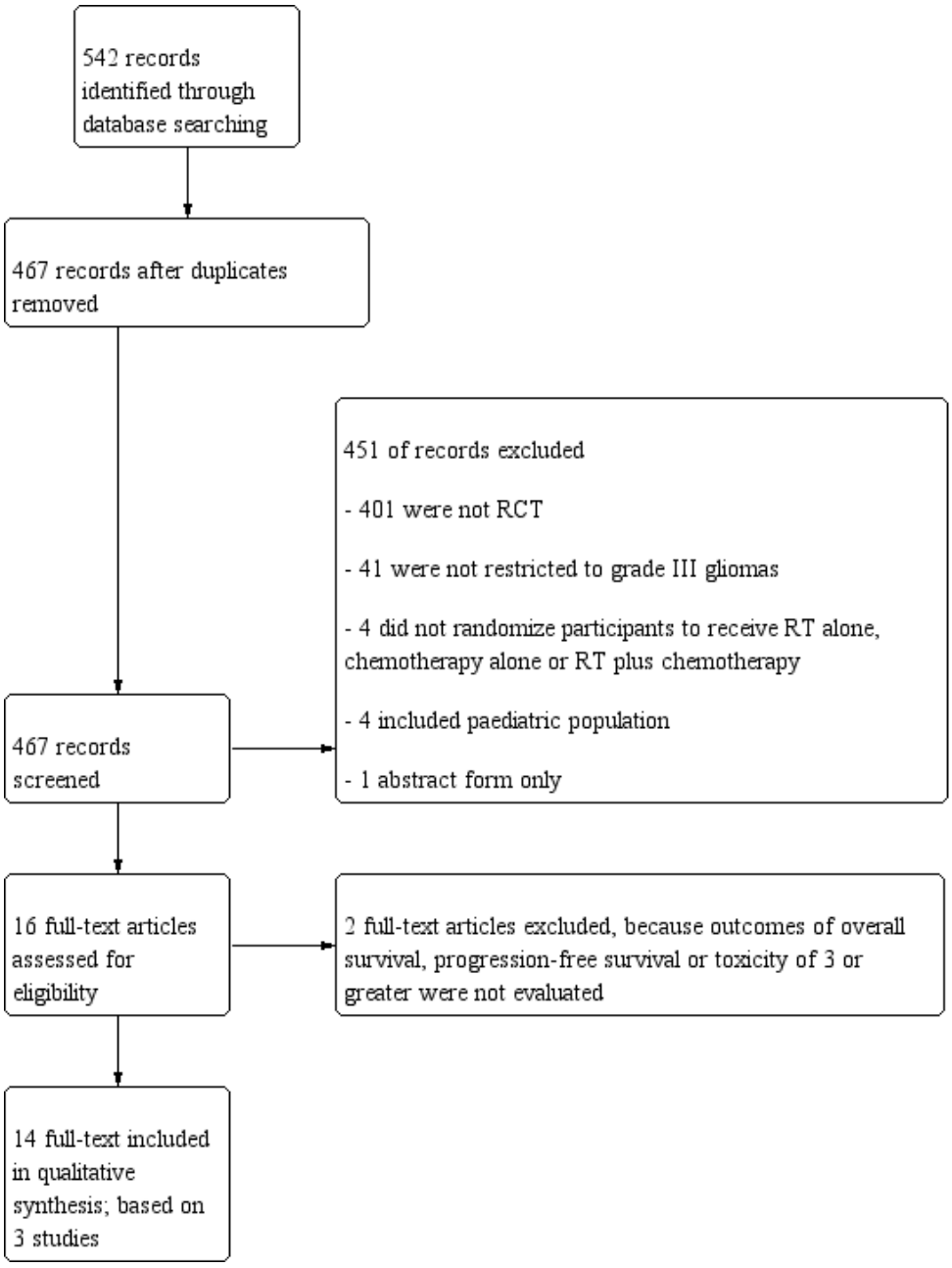
Second, assessment of chromosome 1p and 19q deletions and IDH-1 and -2 mutations were started after participant accrual had begun in the RTOG and EORTC studies. As a result, these studies assessed chromosome deletions and mutations in different proportions of their participant populations. As for MGMT methylation, it was not assessed in the RTOG study, and the EORTC group only began the analysis after the start of participant accrual. In contrast, all molecular analyses in the NOA-04 study were intended in the initial protocol.

Third, the treatments given were different. The RTOG and EORTC studies, although both comparing RT alone versus RT plus chemotherapy, had different sequences of treatment and doses of PCV in the experimental arms, with the RTOG 9402 study treating with up to four cycles of standard PCV prior to RT, and the EORTC 26951 trial delivering up to six cycles of standard PCV after RT. The chemotherapy arms of the NOA-04 included four cycles of higher dose PCV as well as eight cycles of temozolomide. The NOA-04 also standardized the treatments to be received at time of failure, with chemotherapy given to participants randomized to RT and vice-versa.

Excluded studies

We screened 467 records and excluded 453 records (Figure 1):

Figure 1. Study flow diagram.



- 401 were not RCTs;
- 41 were not restricted to grade III gliomas
- four did not randomize participants to receive RT alone, chemotherapy alone or RT plus chemotherapy;
- four included a paediatric population;
- two did not address the outcomes of OS, PFS or toxicity of grade 3 or greater;
- one was only in abstract form.

Risk of bias in included studies

The three trials randomized participants at a central data centre and used either a randomized permuted block within each stratification cell or a minimization technique to balance the treatment groups with respects to stratification factors.

Central pathology review was carried out in each study. However, the EORTC study included participants in which there was discrepancy between local and central pathology diagnosis, whereas the RTOG and NOA-04 trials had central pathology review prior to study entry.

The EORTC trial analyzed their results on an ITT basis, whereas the RTOG and NOA-04 trials performed their statistical analysis on a participant eligible basis and modified ITT, respectively.

In the three studies, the participants in each treatment arms were balanced with respect to known prognostic factors.

Allocation

In the RTOG and EORTC trials, there was low risk of allocation bias as stratification factors were taken into account at randomization. In the NOA-04 study, there was unclear risk of allocation bias as there was no clear indication of stratification.

Blinding

There was high risk of performance and detection bias in the three studies, as none was blinded. However, blinding would have been practically impossible given the nature and side effects of the treatments.

Incomplete outcome data

There was an unknown risk of attrition bias in the three studies, as none reported loss to follow-up.

Selective reporting

There was low risk of reporting bias in the three studies, as outcomes were reported adequately.

Other potential sources of bias

No other source of bias was found in the studies.

Effects of interventions

Overall survival

Only one study was able to demonstrate a statistically significant OS benefit for one of the treatment arms. In the EORTC trial, median OS in the RT plus PCV arm was 3.5 years compared with 2.6 years in the RT alone arm (HR 0.75; 95% confidence interval (CI) 0.60 to 0.95; P value = 0.018). This result was reported 10 years after the conclusion of the enrolment, and was not apparent in the first analysis. In the RTOG trial, median OS in the PVC plus RT arm was 4.6 years and in the RT alone group was 4.7 years (HR 0.79; 95% CI 0.60 to 1.04; P value = 0.1). In the NOA-04 study, median OS was 6.0 years in the RT arm compared with 6.9 years in the chemotherapy first arm. The OS advantage found in the EORTC trial might in part be explained by the inclusion of tumours with necrosis, which is more consistent with a diagnosis of GBM (Kouwenhoven 2009), for which the Stupp trial showed an OS advantage with combined chemo-radiotherapy (Stupp 2005).

Progression-free survival

In the review of 2008 (Quon 2008), it was already clear that sequential RT with PCV improved the PFS in a statistically significant way. Whereas the RTOG group did not update their result on this outcome, the update of the EORTC group reported PFS of 2.0 years after RT plus PCV compared with 1.1 years after RT alone (HR 0.66; 95% CI 0.52 to 0.83; P value = 0.0003). The NOA-04 trial found a PFS of 2.6 years in the RT arm compared with 2.7 years in the CT arm (HR 1.0; P value = 0.87), supporting the idea that the efficacy of sequential treatment is not influenced by the order of treatment.

Biomarkers

Codeletion of chromosomes 1p and 19q

The analysis of codeletion of chromosomes 1p and 19q was unplanned in the RTOG and EORTC trials. In the RTOG study, of the participants who were assessed for codeletion of chromosomes 1p and 19q, loss of 1p was detected in 54.2% and loss of 19q in 63.3%. Combined 1p and 19q deletions were present in 47.9%. Combined loss was associated with prolonged survival in both treatment arms, and improved survival with combination treatment in participants with codeleted tumours. The median OS for participants with codeletion of chromosomes 1p and 19q was 14.7 years in the chemotherapy plus RT arm versus 7.3 years in the RT alone arm (HR 0.59; 95% CI 0.37 to 0.95; P value = 0.03). Participants without codeletion of chromosomes 1p and 19q did not have significant differences in OS according to the treatment arm, with median survival of 2.6 years after chemotherapy plus RT versus 2.7 years after RT alone (HR 0.85; 95% CI 0.56 to 1.16; P value = 0.24), supporting codeletion as a predictive factor for OS. Codeletion of chromosomes 1p and 19q was also associated with prolonged PFS, with median PFS 8.4 years for participants treated with chemotherapy plus RT versus 2.9 years for participants treated with and RT alone(HR 0.47; 95% CI 0.3 to 0.72; P value < 0.001). No statistically significant difference in PFS was seen in participants without codeletion, with PFS of 1.2 years after chemotherapy and RT compared with 1.0 years after RT alone (HR 0.81; 95% CI 0.56 to 1.16; P value = 0.24) (Cairncross 2006).

In the EORTC trial, codeletion of chromosomes 1p and 19q was detected in 25.3% of participants for whom tissue was available for assessment. The median OS for participants with 1p and 19q codeletion was not reached in the RT plus chemotherapy arm versus 9.3 years in the RT alone arm (HR 0.56; 95% CI 0.31 to 1.03; P value = 0.059). The survival of participants without codeletion did not have significant differences according to the treatment arm, with median survival of 2.1 years after RT plus chemotherapy versus 1.8 years after RT alone (HR 0.83; 95% CI 0.62 to 1.1; P value = 0.185). Although there was a trend for codeletion to be a predictive factor for OS, it did not reach statistical significance. The PFS of participants with codeletion of chromosomes 1p and 19q who received PCV plus RT compared with RT alone was higher with PFS of 13.1 years with PCV plus RT versus 4.2 years with RT alone (HR 0.42; 95% CI 0.24 to 0.74; P value = 0.002). A smaller improvement in PFS was also observed in the non-codeleted group, with combined treatment resulting in 1.3 years of PFS compared with 0.8 years in participants treated with RT alone (HR 0.73; 95% CI 0.56 to 0.97; P value = 0.026) (van den Bent 2006).

In the NOA-04 study, the analysis of codeletion of chromosomes 1p and 19q was planned. Of the participants who were assessed for this biomarker, loss of 1p alone was detected in 26.5% of participants and loss of 19q alone in 20.4% of participants. Codeletion of chromosomes 1p and 19q was present in 40.9% of participants. No information on the effect of codeletion and treatment arm on OS or PFS was provided by the authors. On univariate analysis, participants with no codeletion had lower PFS in comparison with participants with codeletion (HR 3.2; 95% CI 2.0 to 5.0; P value < 0.001). On multivariate analysis, codeletion status remained a significant prognostic factor for PFS (HR 2.1; 95% CI 1.2 to 3.7; P value < 0.0092) (NOA-04 2009).

Isocitrate dehydrogenase-1 or isocitrate dehydrogenase-2 mutations

The analysis of IDH-1 mutation was unplanned in the RTOG and EORTC trials.

The RTOG group found IDH-1 or -2 to be mutated in 74% of evaluated participants. The survival for participants with IDH-1 or -2 mutations was 9.4 years in the chemotherapy plus RT arm versus 5.7

years in the RT alone arm (HR 0.59; 95% CI 0.40 to 0.86). In the latest analysis of the RTOG study, some participants without codeletion of chromosomes 1p and 19q still had benefit from combined PCV and RT. Participants without codeletion of chromosomes 1p and 19q but with IDH-1 or -2 mutations were found to have longer survival after chemotherapy plus RT compared with RT alone (5.5 years with chemotherapy plus RT versus 3.3 years with RT alone; HR 0.56; 95% CI 0.32 to 0.99). The survival of participants without IDH-1 or -2 mutations did not show significant differences with survival of 1.3 years after chemotherapy plus RT versus 1.8 years after RT alone (HR 1.14; 95% CI 0.63 to 2.04). Therefore, IDH-1 or -2 mutations were predictive for OS (Cairncross 2006).

The EORTC group found IDH-1 to be mutated in 44.9% of evaluated participants. The median OS for participants with IDH-1 mutation was not reached in the RT plus chemotherapy arm versus 5.4 years in the RT alone arm (HR 0.53; 95% CI 0.30 to 0.95). The OS of participants without IDH-1 mutation showed no significant differences according to the treatment arm, with median survival of 1.6 years after RT plus chemotherapy versus 1.2 years after RT alone (HR 0.78; 95% CI 0.52 to 1.8). Although OS did not reach statistical significance, there was a trend for IDH mutation to be predictive of OS. In multivariate analysis, IDH-1 mutation and codeletion of chromosomes 1p and 19q were found to be independent prognostic factors for OS. The PFS of participants with IDH-1 mutation who received PCV plus RT compared with RT alone was higher with PFS of 5.9 years with chemotherapy plus RT versus 3.0 years with RT alone (HR 0.49; 95% CI 0.29 to 0.84). A smaller improvement in PFS was also observed in the non-mutated group, with combined treatment resulting in 0.8 years of PFS compared with 0.6 years in participants treated with RT alone (HR 0.56; 95% CI 0.37 to 0.86) (van den Bent 2006).

In the NOA-04 trial, the analysis of IDH-1 mutation was planned. A large proportion (65.6%) of evaluated participants were found to have mutation in IDH-1. No information on the effect of IDH-1 mutation and treatment arm on OS or PFS were provided by the authors. On univariate analysis, participants with no mutation had lower PFS in comparison to participants with mutation (HR 2.4; 95% CI 1.7 to 3.5; P value < 0.001). In the multivariate model, absence of IDH-1 mutation was still associated with a lower PFS (HR 2.1; 95% CI 1.3 to 3.3; P value = 0.0021) (NOA-04 2009).

O^6-Methylguanine-DNA methyltransferase methylation

The analysis of MGMT methylation was not done in the RTOG trial, and was unplanned in the EORTC trial.

In the EORTC trial, the MGMT promoter was methylated in 43.7% of evaluated participants. The median OS for participants with MGMT methylation was 5.9 years in the RT plus chemotherapy arm versus 3.6 years in the RT alone arm (HR 0.65; 95% CI 0.43 to 0.98). The survival of participants without MGMT methylation did showed no significant differences according to the treatment arm, with median survival of 1.4 years after RT plus chemotherapy versus 1.3 years after RT alone (HR 0.81; 95% CI 0.44 to 1.49). The PFS of participants with MGMT methylation who received PCV plus RT compared with RT alone was higher with PFS of 4.6 years with PCV plus RT versus 1.3 years with RT alone (HR 0.52; 95% CI 0.35 to 0.76). No statistically significant improvement in PFS was observed in the non-methylated group, with combined treatment resulting in 0.8 years of PFS compared with 0.6 years in participants treated with RT alone (HR 0.63; 95% CI 0.34 to 1.16). In multivariate analysis, MGMT methylation did not affect OS (van den Bent 2006).

In the NOA-04 trial, the analysis of MGMT methylation was planned. Of the evaluated participants, 60.9% were found to have a methylated MGMT promoter. On univariate analysis, participants with the MGMT promoter gene unmethylated had lower PFS in comparison to participants with methylation (HR 2.0; 95% CI 1.4 to 2.9; P value < 0.001). In the multivariate analysis, unmethylated MGMT was associated with shorter PFS (HR 1.7; 95% CI 1.1 to 2.7; P value = 0.0216). Moreover, MGMT methylation was associated with a better PFS not only in the chemotherapy arms with an HR of 2.7 (95% CI 1.4 to 5.1; P value = 0.003), but also in the RT arm with an HR of 2.0 (95% CI 1.1 to 3.6; P value = 0.03) (NOA-04 2009).

Treatment toxicity

In the review of 2008, it was found that participants treated with combined modality experienced significant toxicity in both the RTOG and EORTC trials.

The RTOG group reported that 54% of the participants randomized to upfront chemotherapy plus RT received the four cycles of PCV as planned. They updated their results and there are now two early deaths attributable to PCV-induced neutropenia reported, as compared with only one in 2006. Severe late effects remained uncommon. In addition, both groups had similar Mini Mental Status Examination and QoL scores until the last years of life, when scores declined rapidly (Cairncross 2006).

The EORTC group did not update toxicity results, and 30% of the participants randomized to the upfront chemotherapy plus RT arm received the six cycles as intended (van den Bent 2006).

In the NOA-04 trial, 3% of participants undergoing RT experienced treatment interruption, as compared with 18% of participants undergoing PCV and 6% of participants undergoing temozolomide. Interruptions in the chemotherapy arms were related to haematological toxicity. All participants in the RT arm completed treatment. In the PCV arm, 9% of participants discontinued treatment, and dose reduction was required in 16% of participants. In the temozolomide arm, no discontinuation was required; however, dose reduction was required in 6% of participants (NOA-04 2009).

Treatment at progression

Many participants in the three trials who were randomized to RT alone received chemotherapy at progression. Seventy-nine per cent of participants in the RT group in the RTOG study (Cairncross 2006), 74.5% in the EORTC trial (van den Bent 2006), and 48% in the NOA-04 trial (NOA-04 2009) received chemotherapy at progression. Surgery at progression was less frequent. In the RTOG trial, 43% of the chemotherapy plus RT arm and 56% of the RT arm were operated at the time of progression (Cairncross 2006). In the EORTC trial, surgery at progression was given in 22.6% of participants in the chemotherapy plus RT arm and 18.6% of participants in the RT arm (van den Bent 2006). No information on surgery rates at time of progression was reported in the NOA-04 trial (NOA-04 2009).

DISCUSSION

Summary of main results

Although there is no consensus established yet for the treatment of anaplastic gliomas, results from three large RCTs are now leading to treatment decision based on codeletion of chromosomes 1p and 19q and IDH status.

Both the RTOG and the EORTC studies suggest that upfront treatment with both PCV and RT improves OS in participants with codeleted or IDH-1 or -2 (or both) mutated tumours (Cairncross 2006; van den Bent 2006). Furthermore, in the most recent RTOG analysis, upfront combined treatment improved OS of participants without 1p and 19q codeletion but with IDH-1 or -2 mutation. Participants without either codeletions or IDH mutations did not seem to benefit from the addition of PCV (Cairncross 2006). In the EORTC trial, no conclusions were reached in this subgroup of participants. Nonetheless, there was a trend for codeletion and IDH-1 mutation to predict OS according to treatment arm (van den Bent 2006). The NOA-04 study does not, for the moment, have enough follow-up to determine if participants with codeleted or IDH (or both) mutated tumours have a better survival depending on treatment arm (NOA-04 2009).

A striking difference between these studies was the difference in OS. The longest OS was reported by the NOA-04 study, with 6.0 years for the treatment arm of RT followed by chemotherapy and 6.9 years for chemotherapy arm followed by RT at the time of progression (NOA-04 2009). In the RTOG trial, the median OS for the combined treatment arm was 4.6 years as compared with 4.7 years for the sequential treatment arm (Cairncross 2006). In the EORTC trial, the median OS was of 3.5 years for the combined treatment arm as compared to 2.6 years for the RT first arm (van den Bent 2006). Despite the inclusion of AA in the NOA-04 study, a histology that is generally thought to be associated with poorer prognosis, it still reports the longest OS. The shorter survival in the EORTC trial may be secondary to the lower rate of codeletion and the inclusion of participants with necrosis, which would nowadays be classified as GBM.

Benefit of chemotherapy in anaplastic oligodendrogliomas and anaplastic oligoastrocytomas

Given that these three studies present significant differences in their design and participant population, certain principles still emanate. The RT alone treatment arms from the three studies should be seen as deferral of chemotherapy. In RTOG and EORTC, most participants in the RT alone arm received chemotherapy at the time of progression (Cairncross 2006; van den Bent 2006). However, the NOA-04 trial incorporated the idea of sequential treatment as standard treatment in the study design (NOA-04 2009). Therefore, the term RT alone can be seen as a misnomer, and the term sequential treatment should prevail.

In spite of the apparent benefit of adding PCV to RT in codeleted and IDH-1 or -2 mutated tumours, many oncologists are concerned about the significant toxicity, haematological and non-haematological, associated with this regimen. The long survival of participants with AO and AOA reinforces this concern. Commonly, PCV is replaced by temozolomide in this population. Although with limited follow-up and not powered to compare chemotherapy regimens, the NOA-04 revealed no difference in OS between PCV and temozolomide. Nevertheless, long-term data on the efficacy of temozolomide for AO and AOA are lacking. Furthermore, one large retrospective study from Lassman et al. suggested an improved survival in participants treated with PCV alone as compared with temozolomide alone, with a median time to progression of 7.6 years versus 3.3 years, respectively (P value = 0.019) (Lassman 2011).

Prognostic and predictive biomarkers

Both the EORTC and the RTOG trials support codeletion of chromosomes 1p and 19q to be an independent prognostic factor for PFS and OS (Cairncross 2006; van den Bent 2006). However, these studies were not designed to analyze this biomarker and stratification was done retrospectively. In the NOA-04, codeletion did not remain prognostic of PFS in multivariate analysis, but was underpowered to do so (NOA-04 2009). Nevertheless, evidence for the prognostic value of codeletion is growing (Lassman 2011; Li 2012). Furthermore, the RTOG trial found 1p and 19q codeletion to be a predictive factor for OS, and the EORTC trial reported a trend for codeletion to predict response to combined treatment.

The value of the IDH-1 or -2 biomarker is gaining in recognition. In the RTOG trial, participants with IDH-1 or -2 mutated tumours benefited from combined chemotherapy and RT, independently of codeletion status. It was found to be both prognostic and predictive for OS. In the EORTC trial, IDH mutation status was shown to be prognostic, and there was a trend towards a predictive value. In the NOA-04 study, multivariate analysis not only showed correlation between longer time to treatment failure and IDH-1 mutation, but it was also shown to confer a stronger risk reduction than codeletion, MGMT promoter methylation and AO or AOA histology as compared with AA. The prognostic value of IDH-1 or -2 was also supported by other studies (Li 2012; Yan 2009). Its potential as a predictive biomarker will nevertheless require to be studied further.

There are currently two large international phase 3 trials accruing anaplastic glioma participants and selecting participants according to codeletion status. The CATNON trial will focus on participants without codeletion and will randomize in four different treatment arms involving RT with or without temozolomide at different time points (NCT00626990). The CODEL study (NCT00887146) will include only participants with codeleted tumours will randomize participants to RT, temozolomide or RT with concurrent and adjuvant temozolomide.

AUTHORS' CONCLUSIONS

Implications for practice

Early procarbazine, lomustine and vincristine (PCV), either before or after radiotherapy (RT), appears to improve overall survival (OS) of participants with codeleted or isocitrate dehydrogenase (IDH)-1 or -2 (or both) mutated anaplastic oligodendrogliomas (AO) or anaplastic oligoastrocytomas (AOA). However, PCV is associated with significant grade 3 and 4 toxicities, and whether temozolomide can be substituted for this remains unclear. For the moment, there is no robust evidence that temozolomide has similar beneficial effect as PCV in AO and AOA, and the ongoing trials will hopefully clarify this issue.

Codeletion of chromosome 1p and 19q and mutation in IDH-1 or -2 are strong prognostic factors for progression-free survival (PFS) and OS and there is evidence to support the value of these biomarkers in predicting response to the addition of chemotherapy. Therefore,

biomarker profiles should be included in the next World Health Organization (WHO) AO tumour subclassification. The international trials, CODEL and CATNON, will define the best sequence of combined modality.

Implications for research

Developing future biomarkers for response, as well as molecular-targeted therapies, should be the focus of future studies in order to improve efficacy and to minimize long-term toxicities of conventional cytotoxic therapies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Cairncross 2006

Study characteristics	
Methods	Randomized controlled trial
Participants	289 AO or AOA 2 of 5 anaplastic features
Interventions	Surgery + PCV + RT vs. surgery + RT
Outcomes	Overall survival Progression-free survival Toxicity Quality of life
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ''Patients were (...) randomly assigned.'' Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: ''Patients were stratified by age less than 50 versus ≥ 50 years, KPS 60 to 70 versus > 80, and moderately anaplastic versus highly anaplastic.''; ''Random assignment was performed by randomised permutated block within each stratification cell.'' Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of loss to follow-up.
Selective reporting (reporting bias)	Low risk	Outcomes reported adequately.

NOA-04 2009

Study characteristics	
Methods	Randomized controlled trial
Participants	274

NOA-04 2009 *(Continued)*

	AO, AOA and AA 3 of 4 anaplastic features
Interventions	Surgery + RT and temozolomide vs. PCV at progression vs. surgery + temozolomide vs. PCV and RT at progression
Outcomes	Time from operation to treatment failure Overall survival Progression-free survival Toxicity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ''Patients were randomly assigned.'' Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Quote: ''Baseline characteristics between treatment groups were well balanced.'' Comment: no indication of stratification, but baseline characteristics indeed well balanced between treatment groups.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of loss to follow-up.
Selective reporting (reporting bias)	Low risk	Outcomes reported adequately.

van den Bent 2006

Study characteristics

Methods	Randomized controlled trial
Participants	368 AO or AOA 3 of 5 anaplastic features
Interventions	Surgery + RT + PCV vs. surgery + RT
Outcomes	Overall survival Progression-free survival Toxicity

van den Bent 2006 *(Continued)*

	Quality of life
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... patients were randomly assigned." Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were stratified by age (< 40 v ≥ 40 years), extent of resection (biopsy v resection), WHO ECOG PS (0 or 1 v 2), and possible prior surgery for low-grade oligodendroglioma (yes v no). Treatment was assigned using the minimization technique of Simon and Pocock to ensure balance with respect to the stratification factors." Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of loss to follow-up.
Selective reporting (reporting bias)	Low risk	Outcomes reported adequately.

AA: anaplastic astrocytoma; AO: anaplastic oligodendroglioma; AOA: anaplastic oligoastrocytoma; ECOG: Eastern Cooperative Oncology Group; KPS: Karnofsky Performance Scale; PCV: procarbazine, lomustine and vincristine; PS: performance status; RT: radiotherapy; WHO: World Health Organization.

ADDITIONAL TABLES

Table 1. Summary of the studies

	RTOG 9402	EORTC 26951	NOA-04
Histology	AO and AOA with at least 25% oligodendroglial elements	AO and AOA with at least 25% oligodendroglial elements	AO, AOA and AA
Pathological characteristics	2 of 5: high cellularity, nuclear polymorphism, mitotic activity, endothelial proliferation and necrosis At least 1 needs to be mitosis or endothelial proliferation	3 of 5: high cellularity, mitosis, nuclear abnormalities, endothelial proliferation and necrosis	3 of 4: high cellularity, mitotic activity, nuclear polymorphism and vascular proliferation No necrosis
Rate of codeletion of chromosomes 1p and 19q	47.9%	25.0%	40.9%

Table 1. Summary of the studies *(Continued)*

Number of participants randomly assigned	289	368	274
Randomization arms	- RT + PCV intensive regimen 4 cycles prior to RT (n = 147) - RT alone (n = 142)	- RT + PCV 6 cycles after RT (n = 185) - RT alone (n = 183)	- RT first, chemotherapy at recurrence (n = 139) - chemotherapy first, RT at recurrence (n = 135) PCV 4 cycles (n = 68) Temozolomide 8 cycles (n = 67)
Rate of chemotherapy a time of recurrence in RT arms	79.0%	74.5%	48%
Median survival	- 4.6 years for RT plus PCV - 4.7 years for RT alone	- 3.5 years for RT plus PCV - 2.6 years for RT alone	- 6.0 years for RT first - 6.9 years for chemotherapy first
Loss of heterozygosity	Prognostic and predictive for OS	Prognostic for OS	Prognostic for PFS
MGMT	NA	Not prognostic for OS	Prognostic for PFS
IDH-1 or -2	Prognostic and predictive for OS	Prognostic for OS	Prognostic for PFS
Author's clinical conclusion	For the subset of participants with 1p/19q codeleted or IDH-1 or -2 mutated AO/AOA, PCV plus RT may be an especially effective treatment	PCV plus RT increases both OS and PFS in AO/AOA. Codeleted tumours derive more benefit from adjuvant PCV compared with non-codeleted tumours	Initial RT or chemotherapy achieved comparable results in participants with anaplastic gliomas

AA: anaplastic astrocytoma; AO: anaplastic oligodendroglioma; AOA: anaplastic oligoastrocytoma; IDH: isocitrate dehydrogenase; MGMT: O^6-methylguanine-DNA methyltransferase; NA: not applicable; OS: overall survival; PCV: procarbazine, lomustine and vincristine; PFS: progression-free survival; RT: radiotherapy.

APPENDICES

Appendix 1. Cochrane Central Register for Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Oligodendroglioma] this term only
#2 MeSH descriptor: [Astrocytoma] this term only
#3 oligodendroglioma or oligoastrocytoma*
#4 #1 or #2 or #3
#5 MeSH descriptor: [Antineoplastic Agents] explode all trees
#6 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] this term only
#7 chemotherap*
#8 Any MeSH descriptor with qualifier(s): [Drug therapy - DT]
#9 #5 or #6 or #7 or #8
#10 Any MeSH descriptor with qualifier(s): [Radiotherapy - RT]
#11 MeSH descriptor: [Radiotherapy] explode all trees
#12 radiotherap* or radiation or irradiation
#13 #10 or #11 or #12

#14 #9 and #13
#15 MeSH descriptor: [Combined Modality Therapy] explode all trees
#16 #14 or #15
#17 MeSH descriptor: [Chromosomes, Human, Pair 1] explode all trees
#18 MeSH descriptor: [Chromosomes, Human, Pair 19] this term only
#19 MeSH descriptor: [DNAMutational Analysis] explode all trees
#20 MeSH descriptor: [Genotype] explode all trees
#21 MeSH descriptor: [Loss of Heterozygosity] explode all trees
#22 MeSH descriptor: [Genetic Markers] explode all trees
#23 #17 or #18 or #19 or #20 or #21 or #22
#24 #4 and (#16 or #23)

Appendix 2. MEDLINE

MEDLINE Ovid
1 Oligodendroglioma/
2 Astrocytoma/
3 (oligodendroglioma* or oligoastrocytoma*).mp.
4 1 or 2 or 3
5 drug therapy.fs.
6 exp Antineoplastic Agents/
7 Antineoplastic Combined Chemotherapy Protocols/
8 chemotherap*.mp.
9 5 or 6 or 7 or 8
10 radiotherapy.fs.
11 exp Radiotherapy/
12 (radiotherap* or radiation or irradiation).mp.
13 10 or 11 or 12
14 9 and 13
15 exp Combined Modality Therapy/
16 14 or 15
17 Chromosomes, Human, Pair 1/
18 Chromosomes, Human, Pair 19/
19 DNA Mutational Analysis/
20 exp Genotype/
21 exp "Loss of Heterozygosity"/
22 Genetic Markers/
23 17 or 18 or 19 or 20 or 21 or 22
24 4 and (16 or 23)
25 randomised controlled trial.pt.
26 controlled clinical trial.pt.
27 randomized.ab.
28 placebo.ab.
29 drug therapy.fs.
30 randomly.ab.
31 trial.ab.
32 groups.ab.
33 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 24 and 33
35 exp animals/ not humans.sh.
36 34 not 35

key:
mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier
fs=floating subheading
pt=publication type
sh=subject heading
ab=abstract

Appendix 3. EMBASE search strategy

EMBASE Ovid

1 oligodendroglioma/
2 astrocytoma/
3 (oligodendroglioma* or oligoastrocytoma*).mp.
4 1 or 2 or 3
5 dt.fs.
6 exp chemotherapy/
7 exp antineoplastic agent/
8 chemotherap*.mp.
9 5 or 6 or 7 or 8
10 rt.fs.
11 exp radiotherapy/
12 (radiotherap* or radiation or irradiation).mp.
13 10 or 11 or 12
14 9 and 13
15 multimodality cancer therapy/
16 14 or 15
17 chromosome 1p/
18 chromosome 19q/
19 exp chromosome deletion/
20 exp gene mutation/
21 exp genetic marker/
22 heterozygosity loss/
23 chromosome mutation/
24 17 or 18 or 19 or 20 or 21 or 22 or 23
25 4 and (16 or 24)
26 crossover procedure/
27 double-blind procedure/
28 randomised controlled trial/
29 single-blind procedure/
30 random*.mp.
31 factorial*.mp.
32 (crossover* or cross over* or cross-over*).mp.
33 placebo*.mp.
34 (double* adj blind*).mp.
35 (singl* adj blind*).mp.
36 assign*.mp.
37 allocat*.mp.
38 volunteer*.mp.
39 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40 25 and 39

key:
[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

WHAT'S NEW

Date	Event	Description
10 June 2020	Review declared as stable	Research area no longer active due to changes in the WHO classification of oligoastrocytomas. See https://braintumor.org/wp-content/assets/WHO-Central-Nervous-System-Tumor-Classification.pdf.

HISTORY

Review first published: Issue 2, 2008

Date	Event	Description
2 April 2014	New search has been performed	Literature searches re-run. New author added to team.
2 April 2014	New citation required and conclusions have changed	One new study added
18 February 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

M Lecavalier-Barsoum, H Quon and B Abdulkarim all searched and identified relevant articles, extracted the data, analyzed and interpreted the results.

The final version produced in response to the peer review process was revised by all authors.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- None, Other

External sources

- None, Other

INDEX TERMS

Medical Subject Headings (MeSH)

Astrocytoma [*drug therapy] [*radiotherapy] [surgery]; Brain Neoplasms [*drug therapy] [*radiotherapy] [surgery]; Chemotherapy, Adjuvant; Oligodendroglioma [*drug therapy] [*radiotherapy] [surgery]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans