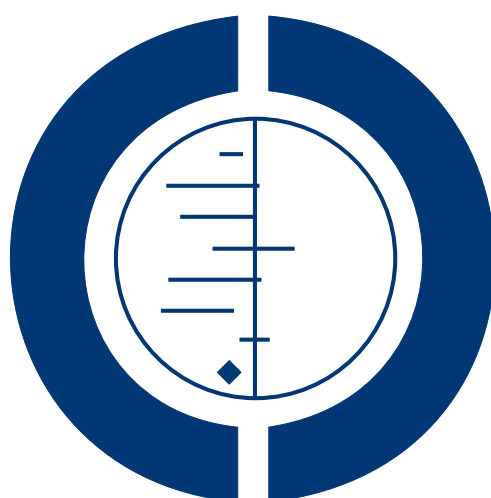


Adjuvant treatment of anaplastic oligodendrogliomas and oligoastrocytomas (Review)

Quon H, Abdulkarim B



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[Intervention Review]

Adjuvant treatment of anaplastic oligodendrogliomas and oligoastrocytomas

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ABSTRACT

Background

Anaplastic oligodendrogliomas (AO) and anaplastic oligoastrocytomas (AOA) are known to be chemosensitive tumors. However, the impact of adding chemotherapy to surgery and radiotherapy has not been studied. Also, the value of chromosome 1p and 19q deletions as prognostic and predictive markers is only beginning to be defined.

Objectives

After surgery, to compare radiotherapy (RT) plus chemotherapy versus RT alone (standard of care) in adults with newly diagnosed AO or mixed AOA. To investigate the prognostic and predictive value of loss of heterozygosity of chromosomes 1p and 19q. Outcomes analyzed include overall survival (OS), progression-free survival (PFS), and treatment toxicity greater than or equal to grade 3.

Search strategy

Cochrane Central Register for Controlled Trials (CENTRAL, Issue 4,2006), MEDLINE (1966 to 2006) and EMBASE (1988 to 2006) were searched. Reference lists from relevant studies were scanned for any additional relevant articles.

Selection criteria

RCTs of adults with AO or mixed AOA comparing surgery plus RT versus surgery plus RT plus chemotherapy were included. No specific chemotherapy regimens were excluded.

Data collection and analysis

Relevant studies were critically appraised and data was extracted. Based on the differences in patient selection with respect to the definition of AO (2 versus 3 high risk anaplastic features) and sequence of treatment (RT and chemotherapy), the results from the two RCTs were not able to be considered for meta-analysis.

Main results

Two RCTs have tested surgery plus RT plus early procarbazine, lomustine, and vincristine (PCV) chemotherapy versus surgery plus RT alone. Neither study observed a survival benefit with the addition of early PCV chemotherapy. However, both studies found a statistically significant increase in PFS associated with the administration of PCV chemotherapy before surgery or after surgery and RT.

with the benefit ranging from 10 to 11 months. Co-deletion of chromosomes 1p and 19q identifies a favorable subgroup of tumors with better overall survival outcomes. The predictive value of 1p and 19q co-deletions is less clear with one study observing a longer PFS with chemotherapy, while the other study did not.

Authors' conclusions

Early PCV chemotherapy in addition to standard treatment of surgery and RT does not improve OS in patients with AO or AOA. However, it does improve PFS. It also is associated with significant toxicities. Tumors with 1p and 19q co-deletions are associated with better OS and may indicate a more chemo-responsive tumor.

PLAIN LANGUAGE SUMMARY

Anaplastic oligodendrogliomas (AO) and anaplastic oligoastrocytomas (AOA) are relatively rare brain tumors. They have been traditionally treated with surgery followed by radiotherapy

Two randomized controlled trials (RCTs) have found that, although the addition of procarbazine, lomustine, and vincristine (PCV) chemotherapy to standard treatment does not prolong survival, it does delay progression of these tumors. However, this chemotherapy is associated with many serious side effects. Also, during pathologic examination of these brain tumor specimens, there are specific chromosome deletions which can identify a group of patients with better survival outcomes.

BACKGROUND

Oligodendroglial tumors are rare brain tumors, comprising 3.7% of primary brain tumors and 9.2% of all Central Nervous System (CNS) gliomas (CBTRUS 2005). Over the last two decades, there has been renewed interest in these tumors with the discovery that they are chemosensitive, with greater than 70% responding to PCV chemotherapy (Cairncross 1994). In addition, several studies have shown that loss of heterozygosity (LOH) for chromosomes 1p and 19q have value in predicting response to chemotherapy and prognostic value being associated with a longer overall survival (Cairncross 1998; Smith 2000; van den Bent 2003).

Due to their relative rarity, oligodendroglial tumors have often been grouped together with other gliomas in clinical trials. This has prevented any significant conclusions to be drawn regarding oligodendroglial tumors specifically, as they often comprise less than 20% of the patient population in these studies. Since the discovery of their relative chemosensitivity and the significance of 1p and 19q deletions, there has been increasing interest in studying patients with oligodendrogliomas.

Traditionally, the treatment of Anaplastic oligodendrogliomas (AO) and anaplastic oligoastrocytomas (AOA) has been surgical resection followed by radiotherapy. Chemotherapy has often been reserved for disease progression. However, there has been increasing interest in using chemotherapy in combination with surgery

and radiation. The optimal timing and sequence of these treatments, as well as the ideal chemotherapy regimen, have not been clearly identified.

In this systematic review, we sought to identify the role of adjuvant chemotherapy in addition to radiotherapy in the treatment of AO and mixed AOA.

OBJECTIVES

- To compare postoperative RT plus chemotherapy versus RT alone in adults with newly diagnosed AO or mixed AOA.
- To investigate the prognostic and predictive value of loss of heterozygosity of chromosomes 1p and 19q.

Outcomes included OS, PFS, and treatment toxicity greater than or equal to grade 3. Survival outcomes were measured from the date of randomization.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs which limited enrollment to patients with AO or mixed AOA.

Types of participants

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

Types of interventions

After surgery, patients were randomized to receive RT plus chemotherapy versus RT alone. No chemotherapy regimens were excluded.

Types of outcome measures

- OS - as defined from date of randomization to death of any cause.
- PFS - as defined from date of randomization to progression based on clinical or radiographic evidence.
- Treatment toxicity greater than or equal to grade 3

Search methods for identification of studies

Cochrane Central Register for Controlled Trials (CENTRAL) (Issue 4, 2006) was searched. The highly sensitive search strategy (HSSS) from the Cochrane Handbook (Higgins 2005) was used for terms #1-20 to search MEDLINE. Reference lists from relevant articles and review articles were examined to search for any additional articles.

Studies relating to objective 1: To compare surgery plus RT plus chemotherapy versus surgery plus RT alone in adults with newly diagnosed AO or mixed AOA.

MEDLINE (1966 to Aug 2006)

- 1 Randomized Controlled Trial.pt.
- 2 Controlled Clinical Trial.pt.
- 3 Randomized Controlled Trials.sh.
- 4 Random Allocation.sh.
- 5 Double Blind Method.sh.
- 6 Single Blind Method.sh.
- 7 1 or 2 or 3 or 4 or 5 or 6
- 8 (Animals not Human).sh.
- 9 7 not 8
- 10 Clinical Trial.pt.
- 11 exp Clinical Trials/
- 12 (clin\$ adj25 trial\$).ti,ab.
- 13 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.

- 14 Placebos.sh.
 - 15 placebo\$.ti,ab.
 - 16 random\$.ti,ab.
 - 17 Research Design.sh.
 - 18 or/10-17
 - 19 18 not 8
 - 20 19 not 9
 - 21 9 OR 20
 - 22 exp Oligodendroglioma/
 - 23 exp Antineoplastic Combined Chemotherapy Protocols
 - 24 exp Combined Modality Therapy
 - 25 exp Chemotherapy, Adjuvant
 - 26 23 OR 24 OR 25
 - 27 exp Radiotherapy
 - 28 21 AND 22 AND 26 AND 27
- For the EMBASE search strategy see [Appendix 1](#).
2. Studies relating to objective 2: To investigate the prognostic and predictive value of loss of heterozygosity of chromosomes 1p and 19q.
- MEDLINE (1966 to Aug 2006)
- 1 Randomized Controlled Trial.pt.
 - 2 Controlled Clinical Trial.pt.
 - 3 Randomized Controlled Trials.sh.
 - 4 Random Allocation.sh.
 - 5 Double Blind Method.sh.
 - 6 Single Blind Method.sh.
 - 7 1 or 2 or 3 or 4 or 5 or 6
 - 8 (Animals not Human).sh.
 - 9 7 not 8
 - 10 Clinical Trial.pt.
 - 11 exp Clinical Trials/
 - 12 (clin\$ adj25 trial\$).ti,ab.
 - 13 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
 - 14 Placebos.sh.
 - 15 placebo\$.ti,ab.
 - 16 random\$.ti,ab.
 - 17 Research Design.sh.
 - 18 or/10-17
 - 19 18 not 8
 - 20 19 not 9
 - 21 9 OR 20
 - 22 exp Oligodendroglioma
 - 23 exp Chromosomes, Human, Pair 1
 - 24 exp Chromosomes, Human, Pair 19
 - 25 exp DNA Mutational Analysis
 - 26 exp Genotype
 - 27 exp Loss of Heterozygosity
 - 28 exp Genetic Markers
 - 29 23 OR 24 OR 25 OR 26 OR 27 OR 28
 - 30 21 AND 22 AND 29
- For the EMBASE search strategy see [Appendix 2](#).

Data collection and analysis

Selection of studies

The search criteria were applied and all titles and abstracts identified were reviewed. Studies in which the relevance was unclear were further examined by retrieving the full article.

Assessment of risk of bias in included studies

The checklist outlined in the JAMA Users' Guides for an Article About Therapy (Guyatt 2002) was used to critically appraise the articles which met the criteria for review. This checklist examines issues relating to randomization, data analysis and follow-up.

RESULTS

Description of studies

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

Two RCTs (Cairncross 2006; van den Bent 2006) met the inclusion criteria.

The Radiation Therapy Oncology Group (RTOG) trial 9402 (Cairncross 2006) was a multi-centre RCT (1994 to 2002) which included 289 patients age greater than 18 years with an AO or AOA who were followed for a median of 5.1 years. Anaplasia was identified based on five features (tumor cellularity, nuclear pleomorphism, mitotic activity, vascular proliferation, and necrosis). Anaplastic tumors 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. Patients had a Karnofsky performance score (KPS) of at least 60 and were randomized within eight weeks of surgery to up to four cycles of PCV followed by RT (n = 147) versus RT alone (n = 142). RT was identical in both arms and was given to a total dose of 59.4 Gy in 33 fractions. The evaluation of chromosome 1p and 19q deletions by fluorescence in situ hybridization (FISH) analysis started after the initiation of the trial as the importance of these deletions was not known until after patient accrual had begun. The 1p and 19q deletion status was obtained for 70% of the patients. The primary end point was OS and secondary endpoints included PFS, frequency of severe (grade 3 or greater) treatment toxicities, and quality of life (QoL).

The European Organisation for Research and Treatment of Cancer (EORTC) trial 26951 (van den Bent 2006) was a multi-centre RCT (1996 to 2002) which included 368 patients aged 16 to 70 years with newly diagnosed AO or AOA who were followed for a median of 5 years. In contrast to RTOG 9402, anaplastic

tumors 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. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and were randomized after surgery to either RT (59.4 Gy in 33 fractions) followed by up to 6 cycles of PCV (n = 185) versus RT alone (n = 183). As with the RTOG trial, assessment of chromosomal loss of 1p and 19q by FISH analysis was not started until the trial had begun and was available for 85% of patients. The primary end point was OS and secondary endpoints included PFS and toxicity.

There are some important differences to note between the two studies. Firstly, the definition of an anaplastic tumor differed based on the number of anaplastic features. Two were required in the RTOG study as long as high mitotic activity or endothelial proliferation were present and three were required in the EORTC trial. Also, assessment of chromosome 1p and 19q deletions were started after patient accrual had begun. As a result, these studies assessed chromosome deletions in differing proportions of their patient populations. Finally, the sequence of treatment and dose of PCV in the experimental arms of these two studies were different with the RTOG 9402 treating with up to 4 cycles of higher dose PCV prior to RT, and the EORTC 26951 trial delivering up to 6 cycles of standard PCV after RT.

Risk of bias in included studies

Both of the included studies randomized patients at a central data center and used either a randomized permuted block within each stratification cell or a minimization technique to balance the treatment groups with respect to stratification factors. Stratification was performed according to factors known to affect prognosis. In the RTOG trial this included age, KPS and tumor grade of moderately anaplastic (2 to 3 anaplastic features) versus highly anaplastic (4 to 5 anaplastic features). In the EORTC patients were stratified according to age, extent of resection, ECOG performance status, and possible prior surgery for low-grade oligodendroglioma. Central pathology review was carried out in each study. The EORTC trial analyzed their results on an intent-to-treat (ITT) basis whereas the RTOG trial performed their statistical analysis on a patient-eligible basis. The patients in the two treatment arms of each study were balanced with respect to known prognostic factors.

Effects of interventions

Based on the differences in patient selection with respect to the definition of AO (2 versus 3 high risk anaplastic features) and sequence of treatment (RT and chemotherapy), the results from the two RCTs were not able to be considered for meta-analysis. The results are thus described separately for each RCT.

Overall survival

Neither study was able to demonstrate a statistically significant OS benefit with early PCV plus RT versus RT alone. In the RTOG trial, median OS for patients treated with RT alone was 4.7 years and for those with PCV plus RT it was 4.9 years (HR = 0.90; 95% CI 0.66 to 1.24; P = 0.26). In the EORTC trial, median OS in the RT alone arm was 2.6 years compared to 3.4 years in the RT plus PCV arm (HR = 0.85; 95% CI 0.65 to 1.1; P = 0.23). However, given that both trials did show a non-statistically significant benefit in favor of early PCV plus RT treatment, a small potential benefit cannot be completely excluded.

Progression-free survival

PFS for patients treated with early PCV plus RT was significantly better than for those treated with RT alone in both the RTOG and EORTC trials. In the RTOG study, median PFS was 2.6 years with PCV plus RT compared with 1.7 years with RT alone (HR = 0.69; 95% CI 0.52 to 0.91; P = 0.004). Similarly, in the EORTC trial, median PFS was 1.9 years with RT plus PCV versus 1.1 years with RT alone (HR = 0.68; 95% CI 0.53 to 0.87; P = 0.0018).

Treatment toxicity

Patients on the combined modality arms of each study experienced significant toxicity. In the RTOG trial dose-intensive PCV regimen prior to RT, 65% of patients had a grade 3 (33%) or grade 4 (32%) toxicity. Most of these were related to hematologic (56%), neurologic (13%), and GI (9%) systems. One treatment related death occurred in a neutropenic patient with severe pulmonary infection. Only 48% of patients randomized to receive PCV plus RT were able to complete the planned 4 cycles.

In the EORTC trial, PCV was only moderately well tolerated with grade 3 or 4 hematologic toxicity in 46% of patients and severe GI toxicity in 12%. Of the patients who started PCV chemotherapy, only 30% were able to complete the intended 6 cycles.

Quality of life

Both studies collected data on QOL. However, these results are to be reported separately and have not been published to date.

Treatment at progression

Most patients in both studies who were randomized to RT alone received chemotherapy at progression. Eighty percent of patients in the RT group in the RTOG study and 82% in the EORTC trial received chemotherapy at progression. In the RTOG study, of all patients in the RT group who experienced progression, the salvage chemotherapy regimen consisted of PCV (21%), temozolomide (10%), PCV and temozolomide (11%), or other regimens. In the EORTC trial, salvage chemotherapy given to patients in the RT

group included PCV in 65% and temozolomide in 46% of cases. The salvage regimens in that study which included both PCV and temozolomide together was not reported.

1p and 19q deletions

Unplanned analyses of 1p and 19q deletions were performed in both studies. In the RTOG study, of the patients who were assessed for 1p and 19q deletions, loss of 1p was detected in 54% and loss of 19q in 61%. Combined 1p and 19q deletions were present in 46%. Combined loss was associated with prolonged survival with the median OS not reached at time of analysis versus 2.8 years in patients without co-deletion (HR = 0.31; 95% CI 0.20 to 0.47; P < 0.001). In patients with 1p and 19q co-deletion, those treated with PCV plus RT versus RT alone did not have any significant difference in OS. For patients with either 1p or 19q deletion, or neither deletion, treatment similarly did not have any effect on OS. In contrast, patients with 1p and 19q co-deletion who received PCV plus RT had a longer PFS compared with RT alone with the median PFS not reached versus 2.6 years with RT alone (HR = 0.42; 95% CI 0.24 to 0.75; P = 0.001). For patients with other genotypes, treatment did not have any effect on PFS (HR = 0.78; 95% CI 0.51 to 1.18; P = 0.12).

In the EORTC trial, combined 1p and 19q loss was detected in 25.1% of evaluable patients. This co-deletion was associated with significantly better median and 5-year OS and PFS. For patients with 1p and 19q co-deletion, treatment did not have any effect on OS or PFS, in contrast to the RTOG study. Median OS and PFS have not been reached for patients with combined 1p and 19q losses, regardless of treatment arm. For all other patients, median OS and PFS were 2.1 and 1.3 years in the RT plus PCV arm and 1.8 and 0.7 years in the RT alone arm.

DISCUSSION

Despite their differences in patient selection and administration of chemotherapy either before or after RT, both the RTOG 9402 and EORTC 26951 trials have found that treatment of AO and AOA with early PCV chemotherapy does not prolong OS but does prolong PFS. This finding may in part be due to the efficacy of salvage chemotherapy, as almost 80% of patients in the RT alone arm received some form of chemotherapy at progression. As such, these studies can be interpreted to suggest that early PCV chemotherapy produces equivalent survival compared with delayed chemotherapy at progression.

Apart from the lack of significant OS benefit within these studies, another striking finding is the difference in survival outcomes between the studies. In the RTOG trial, the median OS for the PCV plus RT and RT alone arms were 4.9 years and 4.7 years, respectively. This is in contrast to the EORTC trial which found

median OS of 3.4 years and 2.6 years for the RT plus PCV and RT only groups, respectively. This is nearly a 1.5 to 2 year difference in OS between the trials. Similarly, differences were seen between the median PFS of the two studies when comparing the PCV plus RT versus RT arms for the RTOG (2.6 and 1.7 years) and EORTC (1.9 and 1.1 years) trials. The better OS and PFS in the RTOG trial may relate to the selection criteria to include patients with only two anaplastic features and the higher percentage of patients with 1p and 19q co-deletions.

Without an OS benefit, the optimal timing of chemotherapy will likely depend on whether a longer PFS translates into a prolonged duration of improved QoL. Although both studies collected QoL data, neither study has yet reported this information. These QoL studies will be crucial in determining the optimal timing of PCV chemotherapy. Presumably, progressive disease will eventually lead to symptoms, which should impact on QoL. Thus, delaying progression of disease might improve QoL. However, chemotherapy such as PCV is not well tolerated, with large proportions of study patients unable to complete the intended chemotherapy regimens. Studies are ongoing into the treatment of AO and AOA with temozolomide, which is much better tolerated (Hoang-Xuan 2004).

The RTOG 9402 and EORTC 26951 studies are the only large prospective, RCTs to date which have collected information on 1p and 19q chromosome deletions. Both studies have shown that 1p and 19q co-deletions have prognostic significance, being associated with superior OS and PFS. What is less clear is the predictive value of these chromosome co-deletions to determine response to chemotherapy. In the RTOG study, treatment had no effect on OS when analyzed by 1p and 19q status. However, there was a longer PFS associated with PCV plus RT compared to RT alone in patients with 1p and 19q deletions only. This differs from the EORTC trial, in which none of the genotypes were associated with significantly different OS or PFS when comparing the RT plus PCV to RT only groups. It should be stressed that these analyses relating genotype to outcome were unplanned, and should be interpreted cautiously.

Given the recent randomized data showing an OS benefit with temozolomide in treating patients with grade IV astrocytoma (

Stupp 2005), the results from trials using this drug to treat AO and AOA is eagerly awaited. In the authors daily practice, AO and AOA are currently being treated with temozolomide concurrently with RT. Future investigations with temozolomide and RT, in conjunction with additional studies examining the predictive value of 1p and 19q deletions, have the potential to improve upon the suboptimal current care for these patients.

AUTHORS' CONCLUSIONS

Implications for practice

Early PCV, either before or after RT, does not improve the OS of patients with AO or AOA when salvage chemotherapy is given at progression. However, early PCV does result in a statistically significant prolongation of PFS by approximately 10 months. Caution must be used in prescribing PCV, as it is associated with significant grade 3 and 4 toxicities. Deletion of chromosome 1p and 19q is an important prognostic factor as it predicts a significantly superior OS and PFS. The evidence for these chromosome deletions to predict response to chemotherapy is not as clear and remains to be defined. As a result, chromosome 1p and 19q deletions should not be used in determining whether to administer chemotherapy for patients with AO and AOA at this time.

Finally, depending on the criteria used to identify AO and AOA, this may produce different patient populations with significantly different tumor characteristics such as 1p and 19q deletions, as well as different OS and PFS outcomes.

Implications for research

AO and AOA with 1p and 19q deletions are clearly a separate group of tumors with a much better prognosis. Future studies must include testing for these chromosome deletions and stratify patients according to genotype. Also, due to the subjective nature of identifying AO and AOA, significant differences between studies can occur due to these different criteria. A more objective method of assessment would clearly help to eliminate this problem. Further studies of treatment of these tumors should also include QoL assessments to aid treatment decision making.

REFERENCES

References to studies included in this review

Cairncross 2006 *{published data only}*

Cairncross G, Berkey B, Shaw E, Jenkins R, Scheithauer B, Brachman D, et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. *Journal of Clinical Oncology* 2006;**24**(18):2707–14.

van den Bent 2006 *{published data only}*

van den Bent MJ, Carpentier AF, Brandes AA, Sanson M, Taphoorn MJ, Bernsen HJ, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. *Journal of Clinical Oncology* 2006;**24**(18):2715–22.

Additional references

Cairncross 1994

Cairncross G, Macdonald D, Ludwin S, Lee D, Cascino T, Buckner J, et al. Chemotherapy for anaplastic oligodendroglioma. National Cancer Institute of Canada Clinical Trials Group. *Journal of Clinical Oncology* 1994;**12**(10):2013–21.

Cairncross 1998

Cairncross JG, Ueki K, Zlatescu MC, Lisle DK, Finkelstein DM, Hammond RR, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *Journal of the National Cancer Institute* 1998;**90**(19):1473–79.

CBTRUS 2005

Central Brain Tumor Registry of the United States. Primary brain tumors in the United States statistical report, 1998-2002 (Years Data Collected). <http://www.cbtrus.org/reports/reports.html> 2005.

Guyatt 2002

Guyatt G, Drummond R, editors. *Users' guides to the medical literature: essentials of evidence-based clinical practice*. Chicago, IL: AMA Press, 2002.

Higgins 2005

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.6 [updated eptember 2006]. *The Cochrane Library, Issue 4, 2006*. Chichester, UK: John Wiley & Sons, Ltd..

Hoang-Xuan 2004

Hoang-Xuan K, Capelle L, Kujas M, Taillibert S, Duffau H, Lejeune J, et al. Temozolomide as initial treatment for adults with low-grade oligodendrogliomas or oligoastrocytomas and correlation with chromosome 1p deletions. *Journal of Clinical Oncology* 2004;**22**(15):3133–38.

Smith 2000

Smith JS, Perry A, Borell TJ, Lee HK, O'Fallon J, Hosek SM, et al. Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. *Journal of Clinical Oncology* 2000;**18**(3): 636–45.

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**:987–96.

van den Bent 2003

van den Bent MJ, Looijenga LH, Langenberg K, Dinjens W, Graveland W, Uytendewilligen L, et al. Chromosomal anomalies in oligodendroglial tumors are correlated with clinical features. *Cancer* 2003;**97**:1276–84.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Cairncross 2006

Methods	RCT
Participants	289 AO or AOA 2 of 5 anaplastic features
Interventions	Surgery + PCV + RT vs. surgery + RT
Outcomes	OS PFS Toxicity QoL
Notes	

van den Bent 2006

Methods	RCT
Participants	368 AO or AOA 3 of 5 anaplastic features
Interventions	Surgery + RT + PCV vs. surgery + RT
Outcomes	OS PFS Toxicity
Notes	

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. EMBASE search strategy for studies relating to objective 1

(1988 to 2006 Week 33)

- 1 Clinical Trial
- 2 Controlled Study
- 3 Crossover Procedure
- 4 Double Blind Procedure
- 5 Single Blind Procedure
- 6 exp Randomization
- 7 exp Placebo
- 8 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
- 9 Oligodendroglioma
- 10 Adjuvant Chemotherapy
- 11 Multimodality Cancer Therapy
- 12 Cancer Chemotherapy
- 13 Chemotherapy
- 14 Cancer Combination Chemotherapy
- 15 Combination Chemotherapy
- 16 10 OR 11 OR 12 OR 13 OR 14 OR 15
- 17 Cancer Radiotherapy
- 18 Radiotherapy
- 19 Irradiation
- 20 17 OR 18 OR 19
- 21 8 AND 9 AND 16 AND 20

Appendix 2. EMBASE search strategy for studies relating to objective 2

(1988 to 2006 Week 33)

- 1 Clinical Trial
- 2 Controlled Study
- 3 Crossover Procedure
- 4 Double Blind Procedure
- 5 Single Blind Procedure
- 6 exp Randomization
- 7 exp Placebo
- 8 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
- 9 Oligodendroglioma
- 10 exp Chromosome 1p
- 11 exp Chromosome 19q
- 12 Chromosome Deletion
- 13 Gene Mutation
- 14 Genetic Marker
- 15 Heterozygosity Loss

16 Chromosome Mutation
17 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
18 8 and 9 and 17

WHAT'S NEW

Last assessed as up-to-date: 17 February 2008.

7 August 2008	Amended	Converted to new review format.
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HISTORY

Review first published: Issue 2, 2008

18 February 2008	New citation required and conclusions have changed	Substantive amendment
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CONTRIBUTIONS OF AUTHORS

H Quon and B Abdulkarim both searched and identified relevant articles, extracted the data, analysed and interpreted the results. The final version produced in response to the peer review process was revised by both authors.

DECLARATIONS OF INTEREST

None.

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