Multi-drug versus single agent chemotherapy for high grade astrocytoma; results of a meta-analysis

Huncharek M, Muscat J, Geschwind J F

Authors' objectives
To evaluate the proportion of patients surviving one year treated with multi-drug regimen, versus single agent treatment (usually BCNU) for high grade astrocytoma.

Searching
A MEDLARS search was conducted exploding the MESH search terms "glioma" and "brain neoplasms". Subheadings applied to these terms included "therapy", "drug therapy", "radiation therapy" and "surgery". The MESH term "combined modality therapy" was also exploded. Cancerlit and EMBASE were fully explored. The CD-ROM version of current contents was also searched independently. All years from 1970 to 1996 were searched and the following languages were included: English, French, German, Spanish and Italian. All proceedings of the American Society of Clinical Oncology (ASCO) and the American Association for Cancer Research back to 1985 were reviewed. Only published studies were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs). Studies with "control" arms consisting of single drug therapy and "experimental" arm(s) employing multi-drug treatment schedules.

Specific interventions included in the review
Patients received post-operative radiation and chemotherapy in both "control" and "treatment" arms.

Single drug treatment (control groups) received: carmustine (BCNU) lomustine, dibromodulcitol and procarbazine. Multi-drug treatment (experimental) groups received: carmustine, procarbazine, lomustine, vincristine, methylprednisolone, semustine and decarbazine. Five of the RCTs incorporated carmustine into both the control and experimental arm. Treatment protocols of the included RCTs all specified concurrent chemo-radiation therapy with the exception of one study, which employed either sequential BCNU or PVC following radiation therapy. In general, radiation therapy consisted of 60 Gy total dose in both single drug and combination chemotherapy arms, one fraction per day. One study used a somewhat lower mean dose (approximately 51 Gy) than the others used in the analysis.

Reports involving immunotherapy, photodynamic therapy, or in vitro studies were excluded.

Participants included in the review
Patients over the age of 18 years with primary intracranial anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM). All patients included in this analysis also underwent surgery and radiation therapy as part of their clinical management.

Studies involving animals were not included.

Outcomes assessed in the review
The primary outcome of interest was one-year survival.

How were decisions on the relevance of primary studies made?
The initial citations (in the form of abstracts) were screened by a physician investigator to exclude those that did not meet the inclusion criteria. The number of reviewers who made decisions on relevance of primary studies once the full papers had been obtained was The authors do not state how the papers were selected for review, or how many of the
authors performed the selection.

**Assessment of study quality**
The authors did not state that they assessed validity.

**Data extraction**
A data extraction form was custom designed for recording the relevant information from each selected paper. Data were extracted by at least 2 research physicians (one of whom was an oncologist) and differences were resolved in a consensus conference.

**Methods of synthesis**
How were the studies combined?
Data analysis was performed using a fixed-effect model according to procedures previously published by Peto et al (see Other Publications of Related Interest). Data were arranged in a 2 X 2 matrix, and a summary odds ratio and its 95% confidence interval were calculated.

How were differences between studies investigated?
A Q test for homogeneity was performed.

**Results of the review**
Nine studies, comprising 2179 participants were included. The 9 RCTs contributed 11 single drug therapy arms (control arms) and 11 combination chemotherapy arms (experimental arms) consisting of 1091 and 1088 patients respectively. However, a table of study details reported the number of included participants to be 2171.

Overall mean survival for single drug arm patients was 49.8 months versus 60.3 months for patients on multi-drug regimens (median of 55.0 and 50.0 months respectively).

Heterogeneity was not found to be present (Q =16.72, 10 df, p>0.05). The Peto odds ratio for one-year survival was 1.22 (95% CI: 0.99, 1.36), which was not significant.

**Authors’ conclusions**
This analysis suggests that the available data do not support the use of combination chemotherapy regimens in this patient population. Additional randomised clinical trials are needed to clearly determine whether any multi-drug treatment scheme is superior to currently available single agent therapies.

**CRD commentary**
The review focuses on a well-defined question. Inclusion criteria were appropriate. The primary studies were combined appropriately. The literature search covered a number of databases, but could have been extended to involve handsearching and an attempt to contact experts in the field for further information. Unpublished studies were not included and therefore publication bias can not be ruled out. The validity of the included studies was not assessed, which means that inappropriately high weighting may have been given to methodologically poor studies.

Some details of the individual studies were given, although it would have also been useful to report the age and sex of participants, and the number who dropped out of treatment. The authors note that a major limitation of the existing clinical trial data is the failure to stratify patients by histology. They note that this is unfortunate since tumour grade and histology are well recognised prognostic factors.

It may have been more appropriate to conclude that there was no significant difference between multi-drug versus single agent chemotherapy for high grade astrocytoma, rather than concluding that the available data do not support the
use of combination chemotherapy regimen in this patient population.

**Implications of the review for practice and research**

**Practice:** The authors concluded that the available data do not support the use of combination chemotherapy regimens in this patient population.

**Research:** The authors stated that further work is needed to determine whether differences exists between glioblastoma multiforme (GBM) and anaplastic astrotoma (AA) in their response to various drug interventions. In addition, the impact of other potential prognostic factors such as degree of resection and functional status should be considered. Further attention also needs to be given to the sequencing of therapy i.e. concommitant versus sequential treatment. The majority of studies analysed in the present report used concommitant chemo-radiation protocols. The influence of therapy sequencing remains an open question.

**Bibliographic details**


**PubMedID**

9891542

**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Antineoplastic Agents /therapeutic use; Antineoplastic Combined Chemotherapy Protocols /therapeutic use; Astrocytoma /drug therapy /mortality; Brain Neoplasms /drug therapy /mortality; Humans; MEDLARS; Randomized Controlled Trials as Topic; Survival Analysis

**AccessionNumber**

11999003453

**Date bibliographic record published**

30/06/2000

**Date abstract record published**

30/06/2000

**Record Status**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.