Clinical impact of adjuvant chemotherapy in glioblastoma multiforme: a meta-analysis

Spiegel B M, Esrailian E, Laine L, Chamberlain M C

CRD summary
This review concluded that nitrosourea compounds, local therapy and temozolomide are effective treatments for glioblastoma multiforme, but local therapy and temozolomide may have a greater response. The evidence appears to support the authors' conclusions, but limitations in the review methods and the quality of the included studies may undermine the reliability of these findings.

Authors' objectives
To evaluate adjuvant chemotherapy for patients with glioblastoma multiforme (GBM).

Searching
MEDLINE and EMBASE were searched from 1966 to 2006 for studies published in English; the search terms were reported.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review. In the included chemotherapy versus no chemotherapy studies, the duration of follow-up ranged from 12 to 115 months.

Specific interventions included in the review
Studies that compared initial chemotherapy treatment with no chemotherapy, or compared multi-agent with single-agent chemotherapy following surgery, were eligible for inclusion. The included studies compared nitrosourea compounds, local therapy (carmustine-polymer wafers or cisplatin-polymer implant), temozolomide and other treatments with no chemotherapy, or compared nitrosourea-based multi-agent therapy with single-agent nitrosourea-based therapy. Further details were provided in the review.

Participants included in the review
Studies that included adults with newly diagnosed GBM were eligible for inclusion if the data were reported separately for patients with GBM. Studies that only included children or adolescents (younger than 18 years of age) were excluded, as were studies of only recurrent GBM. In the included chemotherapy versus no chemotherapy studies, the mean age of the patients ranged from 49 to 59 years.

Outcomes assessed in the review
Studies that assessed survival were eligible for inclusion. In the review, survival was assessed at 6, 12, 18 and 24 months.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies.

Assessment of study quality
Two reviewers independently assessed validity using the criteria of the Jadad scale: adequacy of randomisation, allocation concealment, double-blinding, and handling of withdrawals and drop-outs. Any disagreements were resolved by discussion and consensus with a third reviewer. Studies scoring 3 or more points out of 5 were classified as high quality.

Data extraction
Two reviewers independently extracted the data from full papers and resolved any disagreements through consensus with a third reviewer. Data were extracted using a standardised form for all potential direct treatment comparisons. Relative risks (RRs) and the number-needed-to-treat (NNT), both with 95% confidence intervals (CIs), were calculated. In addition, standard deviations were used to calculate standardised effect sizes (ES) using the methods of Cohen and
defined as the absolute difference in survival. The area under the curve (AUC) for survival curves was also calculated.

Methods of synthesis
How were the studies combined?
The studies were grouped by intervention and time of follow-up (6, 12, 18 and 24 months). Pooled RRs of survival were calculated for clinically homogeneous studies using a fixed-effect model; a random-effects model was used where significant heterogeneity was found. If studies had more than one relevant comparison, all comparisons were included in the meta-analysis. The pooled absolute benefit increase, NNT, ES and AUC were also calculated. Publication bias was assessed using a funnel plot and tested using Egger's test.

How were differences between studies investigated?
Clinical homogeneity was assessed with respect to patient characteristics, timing of chemotherapy and surgery, completeness of surgical resection, and performance status at baseline. Statistical heterogeneity was also assessed, taking a p-value of less than 0.1 to indicate significant heterogeneity; however, the methods used were not reported in the review. Indirect comparisons of individual chemotherapeutic agents were planned, but event rates differed across the common ‘no chemotherapy’ control groups.

Results of the review
Sixteen RCTs (n=2,792) compared chemotherapy with no chemotherapy. Five RCTs (n=666) compared single- with multi-agent chemotherapy.

Chemotherapy versus no chemotherapy.

The mean Jadad score was 1.5 out of 5. Three studies were classified as high quality. Two studies were double-blinded, two described allocation concealment. Thirty-one per cent of studies described withdrawals and drop-outs.

Patients who received chemotherapy were significantly more likely to be alive at 6 months (RR 1.18, 95% CI: 1.08, 1.30), 12 months (RR 1.53, 95% CI: 1.26, 1.86), 18 months (RR 2.15, 95% CI: 1.46, 3.16) and 24 months (RR 2.12, 95% CI: 1.60, 2.80) than those who did not receive chemotherapy. Patients who received nitrosourea compounds were also significantly more likely to be alive at 6, 12 and 18 months than those who did not receive chemotherapy, but there was no significant difference between treatments in survival at 24 months (NNT 100; ES 0.17). Patients who received local therapy or temozolomide were significantly more likely to be alive at 6, 12, 18 and 24 months than those who did not (RR at 24 months with local therapy 4.22, 95% CI: 1.08, 16.48; NNT 20; ES 0.71; RR at 24 months with temozolomide 2.84, 95% CI: 1.93, 4.17; NNT 5.9; ES 0.74).

The funnel plot was asymmetrical, suggesting the absence of small negative studies. Egger's test was also significant (p=0.002).

The authors stated that visual inspection of the AUC survival plots suggested that local treatment efficacy peaked at 12 months and temozolomide treatment efficacy peaked at 18 months.

Multi-agent versus single-agent chemotherapy.

None of the studies were double-blinded and none were classified as high quality. There was no significant difference between multi-agent and single-agent chemotherapy in survival at 6, 12 or 24 months.

Authors' conclusions
Nitrosourea compounds, local therapy and temozolomide are effective treatments for GBM, but local therapy and temozolomide may have a greater response. Further research is required.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. However, inclusion was limited to studies reported in English and statistical tests suggested some evidence of publication bias, although the reliability of these tests is unclear given the small number of included studies. Review
methods sought to minimise reviewer error and bias at all stages of the review process, and study validity was assessed using specified established criteria.

The data were pooled using meta-analysis, but the main outcome measures were RRs rather than the more usual hazard ratios for survival data. However, the authors justified this on the grounds of easier interpretation of their selected statistics. The authors stated that they calculated statistical heterogeneity but not all data were reported. Most of the studies were methodologically flawed which, as the authors acknowledged, might have affected the reliability of the review findings. Where multiple comparison groups shared a control group, no adjustment was made for statistical dependency; however indirect comparisons of chemotherapeutic agents were appropriately discarded after discovering that event rates differed across the common ‘no chemotherapy’ control groups. Overall, the evidence appears to support the authors’ conclusions, but limitations in the review methods and the quality of the included studies may undermine the reliability of these findings.

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

Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies should evaluate the combination of local treatments and systemic temozolomide for patients with GBM, and the combination of carmustine wafers with EORT/NCIC temozolomide treatment for newly diagnosed patients with GBM who are younger than 70 years of age. These patients should have good performance status and image-verified complete or near complete tumour resection.

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