Concomitant or adjuvant temozolomide with whole-brain irradiation for brain metastases: a meta-analysis
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**CRD summary**
This review concluded that temozolomide and whole-brain irradiation may moderately improve response rates, but the combination increased incidence of gastrointestinal symptoms and myelosuppression. The authors’ conclusions reflected the results of the review, but the small poor-quality studies and the inability to pool median survival suggested that, as acknowledged by the authors, the findings should be interpreted with caution.

**Authors' objectives**
To assess the efficacy and safety of concomitant or adjuvant temozolomide with whole-brain irradiation in patients with brain metastases.

**Searching**
MEDLINE, EMBASE, The Cochrane Library and Chinese Biomedical Literature Database were searched without language or publication restrictions from inception to June 2008; search terms were reported. Other potentially relevant articles were identified through manual searching of references and abstracts in Proceedings of the Annual meetings of the American Society of Clinical Oncology.

**Study selection**
Randomised controlled trials (RCTs) that compared concomitant or adjuvant temozolomide with whole-brain irradiation alone in patients with single or multiple site brain metastases were eligible for inclusion. Eligible patients had histologically proven brain metastases at a primary site (lung, breast or melanoma) or from an unknown primary tumour; this had to be assessed by contrast-enhanced computed tomographic scan or gadolinium-enhanced magnetic resonance imaging.

All patients received whole-brain irradiation. The treatment group received concomitant or adjuvant temozolomide chemotherapy; during the radiation treatment this was at a dosage of 75 or 200mg/m²/day or 150 to 200mg/m²/day over five days every 28 days following whole-brain irradiation from the first treatment day and continued until disease progression or toxicity reached unacceptable levels. Planned whole-brain irradiation was administered over two to four weeks with a total dose of 30 to 40Gy in 10 to 20 fractions. Outcomes included response rate, stable disease, progressive disease and toxicity as well as median survival and progression-free survival. In the included studies, where stated, participant ages ranged from at least 18 to 70 years. The lung was the primary tumour site for most patients.

Two reviewers independently screened titles and abstracts for inclusion.

**Assessment of study quality**
Two reviewers independently assessed study quality according to Quality Access Criteria for RCTs: randomisation method; allocation concealment; blinding; and loss to follow-up. Where all criteria were satisfied study quality was highest and the possibility of bias smallest; if none of the criteria were met, bias was considered severe. Disagreements were resolved through consensus.

**Data extraction**
Two reviewers independently extracted data to estimate risk ratios (RR) and 95% confidence intervals (CI). Disagreements were resolved through consensus.

**Methods of synthesis**
Risk ratios and 95% CIs were pooled in a fixed-effect meta-analysis; a random-effects model was used if significant heterogeneity was present. $X^2$ and $I^2$ statistics were used to investigate heterogeneity.
Sensitivity analysis was carried out to examine the impact of excluding poor quality trials or where significant clinical heterogeneity was present.

Results of the review
Four trials (n=280, range 45 to 103) were included. Duration of follow-up ranged from four to 22 months. The randomisation method was adequate in one study and unclear in three. Allocation concealment and blinding were unclear in all studies. Loss to follow-up was reported in two studies.

Compared to whole-brain irradiation alone, temozolomide with whole-brain irradiation yielded superior partial response (RR 1.89, 95% CI 1.19 to 3.02; three studies), progressive disease (RR 0.25, 95% CI 0.10 to 0.78; three studies) and objective response (RR 1.72, 95% CI 1.32 to 2.24; four studies). There was no significant heterogeneity for these comparisons. There was no significant difference between whole-brain irradiation alone and temozolomide with whole-brain irradiation for the outcomes of complete response, headache or fatigue.

Incidence of gastrointestinal symptoms (RR 3.75, 95% CI 1.04 to 13.44; three studies) and ≥grade 3 myelosuppression (RR 13, 95% CI 1.75 to 96.79; two studies) was significantly higher for patients who received temozolomide with whole-brain irradiation compared to those who received whole-brain irradiation alone. There was significant heterogeneity for the comparison of gastrointestinal symptoms ($I^2=72\%$).

Median survival was greater in all four studies for patients who received temozolomide with whole-brain irradiation, but these findings were not pooled, and there was no significant difference for progression-free survival (one study).

Authors' conclusions
The combination of temozolomide and whole-brain irradiation may moderately improve the response rate, but accordingly increase incidence of gastrointestinal symptoms and myelosuppression.

CRD commentary
The review question and the inclusion criteria were clear. The authors searched four relevant databases and additional sources; the lack of language or publication status restrictions reduced the chance of relevant studies being omitted and bias being introduced. Publication bias was not formally assessed, but the authors considered that it was present due to the small number of included trials. The authors reported that they used methods designed to reduce reviewer bias and error at all stages of the review process. Appropriate criteria were used to assess study validity. The decision to use meta-analyses was appropriate. Reasonable measures were used to assess and explore heterogeneity between studies.

The authors’ conclusions reflected the results of this well-conducted review. The included studies were small and of poor quality and it was not possible to pool median survival; as acknowledged by the authors, the findings should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that large-scale high-quality placebo-controlled double-blind trials were required to assess the clinical efficacy and safety of temozolomide with whole-brain irradiation in patients with brain metastases.

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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
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