Effect of amifostine on response rates in locally advanced non-small-cell lung cancer patients treated on randomized controlled trials: a meta-analysis


CRD summary
This review concluded that amifostine has no effect on tumour response in patients with locally advanced non-small-cell lung cancer treated with radiotherapy alone or in combination with chemotherapy. However, interpretation of the results is limited by the small data set and uncertain quality of the included studies.

Authors’ objectives
To determine the efficacy of amifostine on tumour response rates in patients with locally advanced non-small-cell lung cancer (NSCLC).

Searching
MEDLINE, the Cochrane Controlled Trials Register and ClinicalTrials.gov were searched without language restrictions for relevant papers; the search terms were reported. Conference proceedings of the American Society of Clinical Oncology and the European Society of Medical Oncology were also searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared amifostine with no cytoprotectant therapy or placebo were eligible for inclusion. Studies were eligible irrespective of treatment modality (amifostine given during radiotherapy (RT) alone or combination chemotherapy and RT) or sequencing of combined modality therapy. Amifostine doses ranged from 300 to 740 mg/m2 (daily), 500 mg (twice a week) and 500 mg (four times a week), and was administered intravenously in the majority of trials. Five trials involved concurrent chemoradiotherapy.

Participants included in the review
Studies of patients with locally advanced NSCLC (stage III-IV, or inoperable stage II) who had been treated with RT with or without chemotherapy were eligible. The majority of included patients had stage III NSCLC.

Outcomes assessed in the review
The primary outcomes of interest were the complete response rate, partial response rate and overall response rate.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Each trial was evaluated for the method of determining the response rates. Two reviewers independently assessed the quality of the included studies, with a third reviewer involved in cross-checking.

Data extraction
Two reviewers independently extracted the data from the included studies, with a third reviewer involved in cross-checking. Where additional information was necessary, the reviewers contacted the authors of the primary studies. The response rates extracted were reported on an intention-to-treat basis.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis using a random-effects model. Summary estimates were reported as risk
ratios (RRs) with 95% confidence intervals (CIs).

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochran Q test and the I-squared statistic. Two sensitivity analyses were performed: one assessed the effect on each RR estimate of excluding studies on an individual basis, while the other included the results from one study that had been excluded from the main analysis for ambiguous reporting of response rates.

Results of the review
Seven RCTs (n=601) were included in the review; response rates were available in 6 studies (n=552).

Two trials explicitly stated the method used to define the response rates.

No statistically significant between-group differences were found for overall response rate (RR 1.07, 95% CI: 0.97, 1.18; 6 RCTs, n=552). A greater effect, in favour of amifostine, was found with the exclusion of the largest trial (RR 1.62, 95% CI: 0.97, 2.73) but this was not statistically significant. No statistically significant between-group differences were found for complete response rate (RR 1.21, 95% CI: 0.83, 1.78; 6 RCTs, n=552) or partial response rate (RR 0.99, 95% CI: 0.78, 1.26; 6 RCTs, n=552). The sensitivity analyses did not significantly alter these findings. There was no evidence of statistical heterogeneity.

Authors’ conclusions
Amifostine has no effect on tumour response rates and no clinically significant tumour protective effect in patients with locally advanced NSCLC treated with RT alone or in combination with chemotherapy.

CRD commentary
The review question was supported by clear inclusion criteria. Several sources were searched without language restrictions for relevant studies. The methods used to extract the data were likely to have minimised reviewer error or bias; it is unclear whether similar methods were undertaken to select papers for inclusion. Validity was assessed although this appears to have been limited to determining the method of response rate. The analyses appeared appropriate and statistical heterogeneity was assessed. The authors made some attempt to investigate possible sources of bias between the studies. The authors highlighted a number of caveats, such as response rates as a measure of tumour control and the misspecification of tumour response. Interpretation of the results is limited by the small data set and uncertain quality of the included studies.

Five authors have received honoraria from Medimmune, Inc. and one author has received honoraria from Schering Plough SA.

Implications of the review for practice and research
Practice: The authors stated that the results do not support a clinically important tumour protective effect of amifostine in patients with locally advanced NSCLC.

Research: The authors stated that additional studies would be necessary to exclude any adverse effects of amifostine on long-term tumour control.

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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 the reliability of the review and the conclusions drawn.