The role of amifostine as a radioprotectant in the management of patients with squamous cell head and neck cancer

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CRD summary
This review assessed amifostine as a radioprotectant for patients with squamous cell head and neck cancer. The authors' concluded that amifostine is an effective treatment option for the reduction of acute and chronic xerostomia. Although some details of the review methodology were omitted making it difficult to assess its overall quality, the authors did highlight limitations in the evidence base.

Authors' objectives
To evaluate, for patients with squamous cell head and neck cancer, whether amifostine safely and effectively ameliorates important side-effects of radiotherapy with acceptable toxicity and no tumour protection.

Searching
MEDLINE (from 1966 to October 2003), Cancerlit (1983 to October 2002), EMBASE (from 1980 to October 2003), the Cochrane Library (Issue 3, 2003), PDQ, CMA Infobase: Clinical Practice Guidelines and the National Guideline Clearinghouse were searched. The authors also searched abstracts published in the proceedings of meetings of relevant societies (details given). Personal files and the reference lists from relevant articles and reviews were checked for additional trials. Only English language articles were included.

Study selection
Study designs of evaluations included in the review
Primary studies were included in the review if they used random allocation of the participants. Phase I and II trials and editorials and letters were not excluded a priori, but a decision to exclude them was made before the review was updated. The authors also included practice guidelines, systematic reviews and meta-analyses.

Specific interventions included in the review
Studies were included if they compared patients receiving treatment with or without amifostine. In the included studies, amifostine was administered with variations in the route, dose and timing as detailed in the report.

Participants included in the review
Studies were included if they included adults with any stage squamous cell head and neck cancer who were having conventionally fractionated radical radiotherapy or concurrent radiochemotherapy, encompassing at least 75% of the parotid glands. Conventionally fractionated radiotherapy was defined as single daily fractions ranging from 1.8 to 2.5 Gy to a total of 50 to 74 Gy.

Outcomes assessed in the review
Studies were included if they reported outcomes relating to radiation-induced side-effects, quality of life or survival. The main outcomes of interest were xerostomia (defined as grade 2 or above), mucositis (defined as grade 3 or above) and the anti-tumour effects of amifostine.

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
The authors did not state that they assessed validity.
**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

**Methods of synthesis**
**How were the studies combined?**
A narrative synthesis of the studies was undertaken. Where common outcome measures were used, the studies were combined by meta-analyses of odds ratios (ORs). The meta-analyses were conducted using both fixed-effect and random-effects models, with the latter being the primary method if statistically significant heterogeneity was detected. Publication bias was investigated using funnel plots, Begg's test and Egger's test. The analysis was performed using RevMan software.

**How were differences between studies investigated?**
Differences between the included studies were discussed narratively and subjected to a chi-squared test.

**Results of the review**
Eight randomised controlled trials (7 published and 1 presented as an abstract), 1 quality-of-life paper and 1 practice guideline were eligible for inclusion in the systematic review of the evidence.

**Mucositis.**
The pooled data suggested no significant difference between mucositis scores, whether or not amifostine was used (OR 0.11, 95% confidence interval, CI: 0.01, 1.26, P=0.08; chi-squared 13.31, d.f.=3, P=0.004). These data were based on the 4 studies which reported standard outcome measures. A pre-specified subgroup analysis found that amifostine was beneficial in patients undergoing radiochemotherapy (2 studies; OR 0.03, 95% CI: 0.00, 0.83, P=0.04; chi-squared 2.07, d.f.=1, P=0.15). This analysis was conducted for the first edition of the review. In the update, 2 additional studies were added, but one did not report any results for this outcome and the other had only four cases; as such the meta-analysis was not re-run. Two trials in patients having radiochemotherapy found a beneficial effect of amifostine (OR 0.03, 95% CI: 0.00, 0.83, P=0.04).

**Xerostomia.**
The pooled data suggested that amifostine was beneficial in acute xerostomia (OR 0.10, 95% CI: 0.02, 0.48, P=0.004), but significant heterogeneity was present (chi-squared 6.87, d.f.=2, P=0.032). These data were based on the 3 studies which reported standard outcome measures. Studies reporting non-standard outcome measures also reported benefits of the drug. The pooled data also suggested that amifostine was beneficial in late xerostomia (OR 0.19, 95% CI: 0.05, 0.64, P=0.008), but again, significant heterogeneity was present (chi-squared 5.32, d.f.=2, P=0.07). These data were also based on the 3 studies which reported standard outcome measures.

**Tumour protection.**
The results indicated that amifostine does not affect the anti-tumour effectiveness of radiotherapy with or without concurrent chemotherapy with carboplatin.

In terms of side-effects, nausea, vomiting, hypotension, asthenia and allergic reactions were the most commonly reported side-effects of amifostine, but they were rarely severe (grade 3 and above).

One study reported quality of life data. No differences were seen at baseline between patients with or without amifostine, but those treated with amifostine had a significantly better quality of life scores at 1, 7 and 11 months than those patients not treated with the drug.

In terms of the route of administration, similar results were found in one small study of patients treated with subcutaneous (19% incidence) and intravenous (23% incidence) amifostine (P-value or CIs were not reported).
The results of the analysis of publication bias were not presented. However, the authors reported that while the funnel plots appeared to be asymmetrical, Egger's and Begg's tests did not prove publication bias.

Authors' conclusions
Data on the protective effect of amifostine on mucositis are inconclusive at this time. There were no statistically significant differences in the overall incidence of mucositis in the studies found.

Amifostine is recommended as an effective treatment option for the reduction of acute and chronic xerostomia associated with radical conventionally fractionated radiotherapy, given to patients in the head and neck region encompassing at least 75% of the parotid glands, with or without standard dose carboplatin. The recommended dose is a standard dose of 500 mg or doses in the range of 200 to 300 mg/m2, given 15 to 30 minutes before radiotherapy.

CRD commentary
This systematic review answered a clearly defined question. The literature search was extensive, but the exclusion of non-English language studies may mean some information relevant to the question was omitted. No formal quality assessment method was reported, but issues of quality were considered. Some details of the review methodology were omitted, making it difficult to assess the overall quality of the review. While the studies were combined even in the presence of statistical heterogeneity, the authors were clear in reporting this limitation in their results. The review authors were careful to draw conclusions taking account of limitations in the evidence base.

Implications of the review for practice and research
Practice: On the basis of the available data, amifostine is recommended as an effective treatment option for the reduction of acute and chronic xerostomia associated with radical conventionally fractionated radiotherapy, given to patients in the head and neck region encompassing at least 75% of the parotid glands, with or without standard dose carboplatin. The recommended dose and administration of amifostine is an intravenous infusion 15 to 30 minutes prior to radiation, with standard doses of 500 mg or doses ranging from 200 to 300 mg/m2.

Research: The Head and Neck Cancer Disease Site Group would be supportive of randomised trials designed to compare amifostine delivered subcutaneously versus intravenously.

Funding
Cancer Care Ontario; Ontario Ministry of Health and Long-term Care.

Bibliographic details

Original Paper URL

Other publications of related interest
Indexing Status
Subject indexing assigned by CRD

MeSH
Amifostine /therapeutic use; Antineoplastic Combined Chemotherapy Protocols; Carcinoma, Squamous Cell /radiotherapy; Head and Neck Neoplasms /radiotherapy; Mouth Mucosa /radiation effects; Radiation Injuries /prevention & control; Radiation-Protective Agents /adverse effects; Stomatitis /prevention & control; Vomiting /chemically induced; Xerostomia /prevention & control

AccessionNumber
12004008006

Date bibliographic record published
31/08/2004

Date abstract record published
31/08/2004

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.