Use of amifostine to ameliorate the toxic effects of chemotherapy in the treatment of cancer

Systemic Treatment Disease Site Group

CRD summary
This review examined the use of amifostine to ameliorate the toxic effects of chemotherapy in the treatment of cancer. The data presented support the authors’ conclusions that amifostine can be used routinely to reduce the incidence and severity of neurotoxicity, ototoxicity and clinically relevant nephrotoxicity among people with non-leukaemic cancer scheduled to receive high doses of cisplatin.

Authors' objectives
The authors assessed the efficacy and safety of amifostine for people with solid tumours. They addressed the following questions.

Does amifostine ameliorate the clinically important adverse effects of chemotherapy in people with solid tumours, with acceptable toxicity and no significant tumour protection?

Does the addition of amifostine to chemotherapy improve survival and/or quality of life over strategies such as dose reduction or drug substitution for people with solid tumours?

Searching
MEDLINE (from 1966 to October 2002), Cancerlit (from 1983 to October 2002) and the Cochrane Library (Issue 3, 2002) were searched. The authors also checked the reference lists of relevant studies, and searched the PDQ database and the Proceedings of the Annual Meeting of the American Society of Clinical Oncology (1995 to 2000) for reports of newly completed and ongoing trials.

Study selection

Study designs of evaluations included in the review
Reviews and randomised trials were eligible for inclusion. Phase II randomised trials were included if the participants were randomly allocated to the treatment groups. Studies available only in abstract form were considered. Trials of amifostine in bone marrow transplantation or radiotherapy, letters and editorials, and papers published in languages other than English were excluded.

Specific interventions included in the review
Studies were eligible for inclusion in the review if they compared amifostine plus chemotherapy to chemotherapy alone or chemotherapy plus placebo. The studies included a variety of treatment regimens, disease types and outcome assessments. The most common amifostine regimen was a 15-minute intravenous infusion of 740, 910 or 1,000 mg/m2. The chemotherapy regimens included: mitomycin; carboplatin; cyclophosphamide plus cisplatin; cisplatin; paclitaxel; cisplatin plus 5-fluorouracil (5-FU); cisplatin, carboplatin, doxorubicin and ifosfamide; ifosfamide, carboplatin and etoposide; oxaliplatin plus 5-FU; carboplatin plus etoposide; and more complex regimens. Full details (including doses) are available on the Cancer Care Ontario website. See Web Address at end of abstract. The duration of treatment varied between the studies.

Participants included in the review
The studies in the review included people with non-leukaemic cancer who were receiving conventional doses of alkylating agents and/or moderate or higher doses of cisplatin. The participants (n=868) had epithelial ovarian cancer (242), small-cell lung cancer (135), head and neck cancer (132), colorectal adenocarcinoma or cancer (128), non-small-cell lung cancer (66), metastatic breast cancer (40), non-metastatic paediatric osteosarcoma (39), and various advanced malignancies and solid tumours (86). The authors did not provide a breakdown in terms of gender and age.

Outcomes assessed in the review
Studies were eligible for the review if they measured haematological toxicity, nephrotoxicity and neurotoxicity.
(including ototoxicity). The toxicity measurements varied in the different studies. The authors used definitions from the original studies. Survival and tumour response rate were also reported in the review. The authors planned to assess quality of life, but this was not measured fully in any of the studies included in the review.

**How were decisions on the relevance of primary studies made?**
The authors stated that evidence was selected and reviewed by two medical oncologists and methodologists (unspecified number). Apart from this, 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. Data were extracted on the study design, disease site, number of participants, intervention, survival and toxicities.

**Methods of synthesis**

**How were the studies combined?**
The authors undertook a narrative synthesis of the data. They stated that it was inappropriate to pool the data using a meta-analysis due to variations between the trials, including differences in the reporting of outcomes.

**How were differences between studies investigated?**
The authors did not report a method for assessing differences between the studies.

**Results of the review**
Fourteen studies were included. One was a practice guideline based on the same trials included in this review. The other 13 studies were unblinded, non-placebo controlled randomised trials (n=868).

The authors suggested that it was difficult to draw conclusions given the differences between the studies, treatment regimens, sample sizes and disease types included in the review. The authors found some evidence that amifostine had a protective effect against toxicity from chemotherapy, especially when high-dose cisplatin was used. The optimum dose of amifostine remains uncertain.

There was some evidence that amifostine may protect bone marrow against myelosuppression due to alkylating agents. Seven out of 12 randomised trials found a protective effect against haematological toxicity. Five studies found no significant differences between the groups. The outcome measures for haematologic effects varied in each trial. Full details are available on the Cancer Care Ontario website. See Web Address at end of abstract.

Nephrotoxicity is an adverse effect specific to cisplatin and carboplatin. Three out of 5 randomised trials found that amifostine had a protective effect against nephrotoxicity. Three out of 5 randomised trials found that amifostine had a protective effect against neurotoxicity.

None of the 13 randomised trials included in the review found a difference in objective tumour response rates between the amifostine and control groups. From the limited data available, the authors concluded that amifostine does not provide tumour protection. None of the 7 trials that included survival data found a significant difference between the amifostine and control groups. However, the authors noted that the confidence intervals for outcomes such as response rate and survival were wide. Large samples would be needed to completely rule out a protective effect.

The main adverse effect associated with amifostine was hypotension during administration, usually occurring towards the end of the 15-minute infusion period. Nausea and vomiting were also reported in some trials.
Cost information
The authors reported two economic studies of amifostine, one based on Canadian data and one based on US data. Amifostine costs about $780 per cycle (Canadian dollars); granulocyte-colony stimulating factor, an alternative, costs $2,000 per cycle.

Authors' conclusions
Amifostine can be used to reduce toxicity among people receiving high-dose cisplatin, but there is no evidence that amifostine improves survival by dose maintenance. The authors suggested that amifostine can be used routinely to reduce the incidence and severity of neurotoxicity, ototoxicity and clinically relevant nephrotoxicity among people with non-leukaemic cancer scheduled to receive high doses of cisplatin (greater than or equal to 100 mg/m² per cycle, or cumulative doses greater than or equal to 600 mg/m²). There was limited evidence of the efficacy and safety of amifostine for people receiving lower per cycle or cumulative doses of cisplatin.

CRD commentary
The search strategy for this review was reasonably comprehensive. The literature search was originally conducted in June 1998 (Vincent et al., see Other Publications of Related Interest), and was updated in October 2002 for this report. However, there were some potential sources of bias. Non-English language studies were excluded. The authors made an attempt to include unpublished studies, searching conference proceedings and including papers available only in abstract form. They did not report whether they approached experts or industry for additional studies.

It was difficult to assess the overall quality of the review since the methods were not fully reported. General inclusion and exclusion criteria were reported, but these were broad; this means that a wide variety of disease types and treatment regimens were eligible. The authors did not report the methods for assessing the validity of the included studies, nor did they describe how the data were extracted for the review or what quality checks were in place.

This review sought to address two defined research questions. The authors reported clearly on whether amifostine ameliorates the adverse effects of chemotherapy in people with solid tumours and data on toxicity, tumour protection and survival. They did not, however, fully address one component of their research question: to compare amifostine outcomes with alternative strategies such as dose reduction or drug substitution. This means that part of the research question remains unanswered.

The authors provided a detailed narrative synthesis, describing features of each study. They did not perform a meta-analysis, which appears to have been appropriate given that the disease types, chemotherapy regimens and outcome measurements varied widely in the included studies.

The authors’ conclusions appear to be supported by the data presented. However, as they noted, the conclusion that amifostine may have a protective effect against toxicity is based on a limited number of trials (one large study in ovarian cancer and four smaller studies on various malignancies). The chemotherapy regimen used in the largest study is outdated. At least three trials are ongoing on this topic; it is therefore likely that there will be additional information to add to this review in future.

Implications of the review for practice and research
Practice: The authors stated that amifostine can be used routinely to reduce the incidence and severity of neurotoxicity, ototoxicity and clinically relevant nephrotoxicity among people with non-leukaemic cancer scheduled to receive high doses of cisplatin (greater than or equal to 100 mg/m² per cycle, or cumulative doses greater than or equal to 600 mg/m²).

Research: The authors stated that randomised studies are needed to assess the effects of amifostine on survival, health care costs and quality of life, as well as to examine the optimal dose and pharmacokinetics.

Funding
Bibliographic details
Accessed May 2013
This paper is produced by Cancer Care Ontario Practice Guidelines Initiative. The series is published on the Internet and updated regularly. To ensure that you are viewing the most up to date version, go to the Cancer Care Ontario website at: https://www.cancercare.on.ca/ This abstract is based on the web version accessed in February 2004

Original Paper URL

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Indexing Status
Subject indexing assigned by CRD

MeSH
Amifostine /adverse effects /therapeutic use; Neoplasms; Radiation-Protective Agents /adverse effects /therapeutic use

AccessionNumber
12003008184

Date bibliographic record published
31/05/2004

Date abstract record published
31/05/2004

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.