Cancer Care Ontario Practice Guidelines Initiative

Sponsored by: Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

Use of Amifostine to Ameliorate the Toxic Effects of Chemotherapy in the Treatment of Cancer

Practice Guideline Report # 12-6

ORIGINAL GUIDELINE: December 1998
MOST RECENT LITERATURE SEARCH: October 2002
NEW EVIDENCE ADDED TO GUIDELINE REPORT: January 2003

New evidence found by update searches since completion of the original guideline is consistent with the original recommendations.

SUMMARY

Guideline Questions

- Does amifostine safely and effectively ameliorate the clinically important side effects of chemotherapy in patients with solid tumours, with acceptable toxicity from amifostine and no significant degree of tumour protection?
- Does amifostine, when added to chemotherapy in patients with solid tumours, result in a meaningful increase in survival and/or an improvement in quality of life, over and above what can be achieved by alternative strategies such as dose reduction of the chemotherapy or drug substitution?

Target Population

These recommendations apply to patients with non-leukemic cancer using conventional doses of alkylating agents and/or moderate or higher doses of cisplatin.

Recommendations

Key Recommendations

- In patients scheduled to receive high per cycle doses of cisplatin ($\geq$100 mg/m^2) or high cumulative doses ($\geq$ 600 mg/m^2), amifostine is a reasonable therapeutic option to reduce the incidence and severity of neurotoxicity, ototoxicity or clinically relevant nephrotoxicity. There are currently no data to determine whether amifostine produces similar benefits at lower per cycle doses or cumulative doses of cisplatin. However, the incidence of neurotoxicity is predicted to rise at cumulative doses of cisplatin $\geq$ 300 mg/m^2 and the use of amifostine could be considered in this setting.

- Amifostine is one of several reasonable therapeutic options to reduce myelosuppression. In assessing the effects of amifostine on quality of life, particularly when amifostine is used as part of palliative treatment, acute toxic effects of amifostine, such as nausea and vomiting and hypotension, need to be weighed against its ability (based on one randomized study) to reduce the morbidity of myelosuppression (episodes of neutropenic fever).
- If the objective of treatment with amifostine is to improve survival by means of dose maintenance of chemotherapy, there is no evidence to justify the routine use of amifostine.

Qualifying Statements

- Although the limited number of randomized controlled trials to date indicate no adverse impact of amifostine on tumour response or survival, the lack of a tumour protective effect in all situations should not yet be automatically assumed. Consequently the use of amifostine in the curative or adjuvant setting should preferably take place in the context of a clinical trial.
- There are limited data regarding the potential for interaction between amifostine and some other cytotoxic agents. Use of amifostine with non-platinum non-alkylating cytotoxic agents should preferably take place in the context of a clinical trial.

Methods

Entries to MEDLINE (through to October 2002), CANCERLIT (through to October, 2002) and Cochrane Library (through to Issue 3, 2002) databases and abstracts published in the 1995-2002 proceedings of the annual meetings of the American Society of Clinical Oncology were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by two medical oncologists, one of whom is a member of the Cancer Care Ontario Practice Guidelines Initiative's (CCOPGI) Systemic Treatment Disease Site Group (STDSG) and methodologists. This practice guideline has been reviewed and approved by the Systemic Treatment DSG, which comprises medical oncologists, pharmacists and one community representative.

External Review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The CCOPGI has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Key Evidence

Thirteen randomized controlled trials (RCTs) that evaluated the effects of amifostine on chemotherapy-induced toxicities were identified: twelve trials compared chemotherapy plus amifostine with chemotherapy alone, and one trial compared chemotherapy plus amifostine with chemotherapy plus granulocyte-colony stimulating factor (G-CSF). Eleven trials used platinum-based regimens in patients with a variety of malignancies, one trial used paclitaxel in patients with metastatic breast cancer, and one trial used mitomycin-C in patients with colorectal adenocarcinoma.

Eight trials showed a trend in favour of amifostine for the protection of bone marrow against the hematologic toxic effects of chemotherapy. One large RCT involving ovarian cancer patients receiving cyclophosphamide and cisplatin showed statistically significant differences in favour of the amifostine group in the number of patients experiencing grade 4 neutropenia in course one (10% vs. 21%; p=0.019), in the number of patients failing to recover from grade 4 neutropenia after courses two to four (44% vs. 65%; p=0.004), and in the number of patients discontinuing treatment due to hematologic toxicity (1% vs. 7%; p=0.016). A smaller RCT involving breast cancer patients treated with paclitaxel with or without amifostine showed no protective benefits for amifostine on any measure of hematologic toxicity. Another RCT involving patients with

small-cell lung cancer receiving ifosfamide, carboplatin and etoposide with or without amifostine showed no benefits for amifostine on any measure of hematologic toxicity. A statistically significant difference in favour of amifostine was noted for both the length of hospital stays and the time on antibiotics in one trial reporting these outcomes.

Renal toxicity was measured in six trials, and in all six, amifostine use was associated with significantly favourable outcomes on measures of renal toxicity. Amifostine protection against neurotoxicity (including ototoxicity) was reported in two of the four studies that measured neurotoxicity. No difference was detected for survival or tumour response rates in the nine studies reporting these outcomes.

The most concerning side effect of amifostine is hypotension during administration, resulting in discontinuation of amifostine in 25% to 62% of those being treated. Nausea and vomiting occurred more often in the amifostine groups in all four trials reporting this outcome. Other, more mild side effects included flushing, sneezing, dizziness, hiccoughs and chills.

Future Research

Data from randomized studies are limited; therefore, it is strongly recommended that patients be enrolled in randomized controlled trials designed to address the effects of amifostine on survival, health care costs, optimal dose, quality of life and pharmacokinetics.

Prepared by the Systemic Treatment Disease Site Group

For further information about this practice guideline, please contact: Dr. Brent Zanke, Chair, Systemic Treatment Disease Site Group, Cancer Care Ontario, 620 University Avenue Toronto, Ontario, Canada M5G 2L7 Tel: 416-9800 x2229 sec x1328 Fax: 416-217-1281
E-Mail: brent.zanke@cancercare.on.ca

PREAMBLE: About Our Practice Guideline Reports

The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the CCOPGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, community representatives and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the CCOPGI and the Program, please visit our Internet site at:
http://www.cancercare.on.ca/ccopgi/
For more information, contact our office at:
Phone: 905-525-9140, ext. 22055
Fax: 905-522-7681

Copyright

This guideline is copyrighted by Cancer Care Ontario; the guideline and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

FULL REPORT

I. QUESTIONS

- Does amifostine safely and effectively ameliorate the clinically important side effects of chemotherapy in patients with solid tumours, with acceptable toxicity from amifostine and no significant degree of tumour protection?
- Does amifostine, when added to chemotherapy in patients with solid tumours, result in a meaningful increase in survival and/or an improvement in quality of life, over and above what can be achieved by alternative strategies such as dose reduction of the chemotherapy or drug substitution?

II. CHOICE OF TOPIC AND RATIONALE

Amifostine (previously WR-2721), a spin-off of the nuclear warfare program, is a cytoprotector capable of protecting normal but theoretically non-malignant tissue against the toxic effects of alkylating agents and/or radiation. Amifostine is dephosphorylated to the active principal (free thiol) by a cell-bound alkaline phosphatase either not present in tumours or not active in the low pH found in tumours. The free thiol is transported selectively into normal cells where it is able to bind and inactivate the active species of alkylating agents, including platinum-based cytotoxins. It also acts to scavenge free radicals, whether derived from radiation or specific drugs like doxorubicin. Amifostine may be able to protect normal tissues from the toxicity of taxanes by these or other mechanisms (1,2). However, there is concern that amifostine alters the pharmacokinetics of paclitaxel, and research is currently underway to examine this effect. It has been claimed that amifostine provides an enhanced antitumour effect when combined with chemotherapy (3).

There is evidence to show that amifostine can reduce the incidence and severity of a wide range of toxic effects associated with a surprisingly broad spectrum of anti-cancer drugs. These side effects include myelosuppression or hematological toxicity, neurotoxicity, ototoxicity and nephrotoxicity. The evidence also suggests that amifostine exerts a protective effect in normal tissues without affecting the tumour's response to chemotherapy. What is less clear is whether these improvements are clinically relevant, and more important, whether they are greater than the improvements seen with alternative treatment strategies such as dose reduction, drug substitution or cessation of chemotherapy. Since amifostine is already approved in Canada as a cytoprotective agent against the cumulative renal toxicities associated with cisplatin and the hematologic toxicities of cyclophosphamide and platinum-based agents in patients with advanced solid tumours of non-germ cell origin, the Systemic Treatment Disease Site Group (STDSG) of Cancer Care Ontario (formerly the Systemic Treatment Program Committee) felt it was timely to critically review the evidence and develop a practice guideline on this topic.

III. METHODS

Guideline Development

This practice guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle (1u). Evidence was selected and reviewed by two medical oncologists, one of whom is a member of the CCOPGI's Systemic Treatment Disease Site Group (STDSG) and methodologists. Members of the STDSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of amifostine to ameliorate the toxic effects of chemotherapy in the treatment of cancer, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The report is intended to enable evidence-based practice. The Practice

Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The CCOPGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

The MEDLINE (1966 to June 1998) and CANCERLIT (1983 to June 1998) databases were searched using the medical subject heading (MeSH) terms: amifostine, neoplasms, double-blind method, single-blind method, placebos, and random (truncated); and the text words: amifostine, WR-2721, cancer, tumour (or tumor), and random (truncated). The search also included the publication types: practice guideline, meta-analysis and randomized controlled trial. The Physician Data Query (PDQ) database and the Proceedings of the Annual Meeting of the American Society of Clinical Oncology (ASCO) (1995 to 1998) were searched for reports of newly completed or ongoing trials. The search was originally performed in December 1997 for the evidence-based recommendation, and was updated in June 1998 for the final version of this practice guideline. Articles identified by the searches or cited in the relevant papers were retrieved and reviewed, and the reference lists of relevant articles were scanned for additional studies.

Update

The original literature search has been updated using MEDLINE (through October 2002), CANCERLIT (through October 2002), the Cochrane Library (through Issue 3 2002) and the 1995-2002 proceedings of the annual meeting of ASCO.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- Randomized controlled trials (RCTs) comparing amifostine with placebo or observation in patients receiving chemotherapy for solid tumours.
- Trials measuring hematological toxicity, nephrotoxicity, neurotoxicity or ototoxicity.
- Phase II trials were included if patients were randomly allocated to treatment groups.
- Abstracts of trials were considered.

Exclusion Criteria

- Trials of amifostine used in bone marrow transplantation or radiotherapy were excluded.
- Letters and editorials were not considered.
- Papers published in a language other than English were not considered.

Synthesizing the Evidence

The trials of amifostine employed a variety of treatment regimens in different disease settings, and examined the effect of amifostine on a range of toxic effects of several chemotherapeutic agents. Due to the inconsistency in reporting outcomes, as well as other important differences among the trials, it was judged inappropriate to pool the data by performing a meta-analysis.

IV. RESULTS

Literature Search Results

One practice guideline was found in the literature search which dealt with the administration of amifostine, and was based on several phase I and II studies (4). It did not, however, address the questions posed in this guideline: whether the use of amifostine improves clinically important outcomes over and above the improvement seen with the alternative strategies such as dose reduction of the chemotherapy or drug substitution. As well, several descriptive reviews were also identified, but no systematic reviews or meta-analyses.

Five RCTs were identified which met the eligibility criteria noted above (5-10). One trial was reported in two articles (7,8). Three were phase III (5,7,8,10) and two were phase II trials (6,9). A summary of the trials included in this guideline report appears below in Table 1. Dose and scheduling information can be found in Appendix 1. An interpretive summary follows the discussion of trial results.

All five trials used various outcome measures for hematologic toxic effects (listed in Table 2). Only one trial (7,8) reported on neurotoxicity and nephrotoxicity outcomes. For the question of the effect of amifostine on tumour response and survival, data were available from four trial reports. Quality of life was not assessed in any of the trial reports, but one trial (7,8) reported the number of days spent in hospital and the number of days on antibiotics. These factors could influence the patient's quality of life, and may be appropriate proxy measures for quality of life. It should also be noted that none of these trials evaluated the use of amifostine in the setting of cytotoxic potentiation in tumours or protection against the toxicity of paclitaxel.

Of the trials comparing chemotherapy plus amifostine with chemotherapy alone, none of them used a placebo control to effectively conceal the group to which patients were assigned. The report of the trial comparing amifostine with G-CSF made no mention of concealing the treatment group into which patients were placed. This lack of blinding may have led to biased assessments of treatment effects, and a weakening of the strength of evidence contained in these trial reports.

Update

One practice guideline was located in the literature update searches (2u,3u). This guideline, developed by ASCO, was based on the same evidence as this report. Appendix 2 contains a comparison of the ASCO guideline with this guideline.

Eight RCT's that met the eligibility criteria were located in literature update searches (4u-11u. None of these trials were placebo-controlled. These trials have been added to Tables 1 and 2. Five trials reported hematologic toxic effects using various outcome measures (4u-8u,10u,11u). Four trials reported on nephrotoxicity outcomes (4u,6u,7u,9u) and four trials reported on neurotoxicity outcomes including ototoxicity (4u,5u,7u,10u). Survival and/or tumour response data were available from five trial reports (4u-6u,8u,11u). Quality of life was not assessed in any of the new trials.

Table 1. Randomized trials of amifostine in patients receiving chemotherapy.

Author/ Year	Ref	Study Design	Disease Site	No. rand. pts	Intervention
Poplin 1994	5	unblinded, no placebo control	colorectal adenocarcinoma	97	Rx1: Mitomycin-C + amifostine (n = 48) Rx2: Mitomycin-C (n = 49)
Betticher 1995	6	unblinded, no placebo control	non-small-cell lung cancer	21	Rx1: Carboplatin + amifostine (n = 11) Rx2: Carboplatin (n = 10)
Kemp 1996 Rose 1996	7,8	unblinded, no placebo control	epithelial ovarian cancer	242	Rx1: Cyclophosphamide + cisplatin + amifostine (n = 122) Rx2: Cyclophosphamide + cisplatin (n=120)
Budd 1997	9	unblinded, no placebo control	various advanced malignancies	55	Rx1: Carboplatin + amifostine (n = 24) Rx2: Carboplatin (n = 31)
Anderson 1998	10	unblinded, no placebo control	non-small-cell lung cancer	45	Rx1: Carboplatin + amifostine (n = 24) Rx2: Carboplatin + G-CSF (n = 21)
Planting 1999	4u	unblinded, no placebo control	head and neck cancer	74	Rx1: Cisplatin + amifostine (n = 37) Rx2: Cisplatin (n = 37)
Gelmon 1999	5u	unblinded, no placebo control	metastatic breast cancer	40	Rx1: Paclitaxel + amifostine (n = 20) Rx2: Paclitaxel (n = 20)
Jost 1999	6u	unblinded, no placebo control	head and neck cancer	58	Rx1: Cisplatin + 5-FU + amifostine (n = 27) Rx2: Cisplatin + 5-FU (n = 31)
Petrilli et al, 1999	7u	unblinded, no placebo control	non-metastatic pediatric osteosarcoma	39	Rx1: Cisplatin + carboplatin + doxorubicin + ifosfamide + amifostine (n = 20) Rx2: Cisplatin + carboplatin + doxorubicin + ifosfamide (n = 19)
Johnson et al, 2001	8u	unblinded, no placebo control	small-cell lung cancer	84	Rx1: Ifosfamide + carboplatin + etoposide + amifostine (n = 42) Rx2: Ifosfamide + carboplatin + etoposide (n = 42)
Hartmann et al, 2000	9u	unblinded, no placebo control	solid tumours	31	Rx1: etoposide + ifosfamide + cisplatin (VIP) + G-CSF + amifostine or paclitaxel + ifosfamide + cisplatin (TIP) + G-CSF + amifostine (n=16) Rx2: VIP or TIP + G-CSF (n=15)
Rudolph et al, 2001 abstract	10u	unblinded, no placebo control	colorectal cancer	31	Rx1: oxaliplatin + FA/5-FU + amifostine Rx2: oxaliplatin + FA/5-FU
Bildat et al, 2001 abstract	11u	unblinded, no placebo control	small-cell lung cancer	51	Rx1: carboplatin + etoposide + amifostine (n = 25) Rx2: carboplatin + etoposide (n = 26)

NOTE: Rx1 = experimental arm; Rx2 = control arm; 5-FU = 5-Fluorouracil.

Outcomes

Hematological Protection

There is evidence from five RCTs that amifostine protects bone marrow against the toxic effects of alkylating agents (5-10). Reported outcome measures for hematologic toxic effects vary across trials, and these are listed in Table 2 below.

A study by Poplin and colleagues (5) described hematologic protective effects in patients with advanced 5-fluorouracil-refractory colon cancer. Ninety-seven patients were randomly allocated to receive mitomycin-C (MMC) alone (n=49) or combined with amifostine (MMC+A) (n=48). The mechanism of action of MMC is complex, but does include alkylation. Only one-third of patients received more than two cycles, and consequently, cumulative myelosuppression was not an end-point. However, the first course platelet nadirs were higher on average in patients in the MMC+A group compared with those in the MMC group (159 x 10^9/L v. 120 x 10^9/L; p=0.03). Patients receiving MMC+A experienced a less pronounced drop from baseline platelet count to nadir compared with MMC alone (52% v. 60%; p=0.049). In the first cycle, grade 3 or 4 thrombocytopenia was less frequent with MMC+A compared with MMC alone (10% v. 23%;

p=0.10). The overall mean hemoglobin levels in each of the treatment groups were similar over the course of the study (9.9 g/dL for MMC+A v.10.1 g/dL for MMC; p=0.52).

Betticher and colleagues (6) reported on a study in which all patients received the first cycle of chemotherapy without amifostine, and then were randomly allocated to receive either carboplatin with amifostine (CA) (n=11) or carboplatin alone (C) (n=10) in subsequent cycles. There were no differences between the groups in hemoglobin, neutrophil counts or platelet nadirs, either after the first cycle or after the fourth cycle. However, amifostine conferred a statistically significant benefit in terms of time to platelet recovery to a level >100 x 10^9/L in cycles two to four (21 days for C v. 13.5 days for CA; p=0.04). This did not result in any significant difference in the average platelet transfusion requirements (5.6 v. 5.7). Red blood cell transfusions were identical in both groups (2.6 units/course). The number of patients in both groups who either discontinued therapy or had chemotherapy doses reduced were small, and no difference between groups was detected.

Kemp, Rose and colleagues (7,8) reported results from a large study of patients with advanced carcinoma of the ovary. Two hundred and forty-two patients were randomly allocated to receive either cisplatin and cyclophosphamide alone (CP) (n=120) or with amifostine (CP+A) (n=122) for up to six cycles. The primary outcome for hematologic toxicity was the cumulative incidence of grade 4 neutropenia associated with fever and/or infection requiring antibiotics. Over the six cycles, a 62% relative reduction in neutropenic events was seen for patients receiving amifostine over patients in the control group (59 v. 197; p=0.005). Reductions in the doses of both cytotoxic drugs for grade 4 hematologic toxicity in the earlier cycles were comparable between the two treatment arms. In the last cycle, the frequency of grade 4 neutropenia was lower in the CP+A group than in the control group (22% v. 43%; p=0.001). However, neither report of this study presented the actual number of dose reductions or the cumulative doses given.

There were also fewer cases of grade 4 neutropenia in those receiving amifostine, as measured by a failure of the neutrophil count to recover to at least 1500/µL (*sic*) by the next cycle (44% for CP+A v. 65% for CP; p=0.004). These benefits became more apparent in later cycles of chemotherapy. Fewer patients on amifostine were withdrawn from chemotherapy due to hematologic toxicity (1 v. 8; p=0.016). Non-significant trends were observed in favour of amifostine in the number of red blood cell units transfused (p=0.230) and in the number of platelet units transfused (p=0.169).

Budd and colleagues (9) reported on a randomized trial in which 52 patients with a variety of cancers were assigned to receive carboplatin (500 mg/m^2) with amifostine, or the same dose of carboplatin alone. Patients receiving chemotherapy with amifostine had a median platelet nadir (127 x 10^9/L) that was statistically significantly higher compared with the control arm (88 x 10^9/L), over all cycles of therapy (p=0.023). These differences in favour of amifostine were seen in each cycle of therapy, though not all were statistically significant.

Anderson and colleagues (10) reported, in abstract form, on a small randomized study comparing the hematologic toxic effects of high dose carboplatin (AUC 9) plus amifostine with high dose carboplatin (AUC 9) plus G-CSF. The amifostine arm was associated with fewer episodes of grade 4 thrombocytopenia (p<0.001), fewer platelet transfusions (p=0.017), a higher median platelet nadir (p=0.0001), and shorter times to platelet recovery to 50,000/mm^3 (p=0.002) and 100,000/mm^3 (p=0.011). Amifostine appeared to exercise at least as good a protective effect on the neutrophil series as G-CSF.

In summary, these trials indicate a consistent effect for amifostine in the protection against myelosuppression due to alkylating agents. In the large trial of patients with ovarian cancer by Kemp and colleagues (7,8) employing relatively standard doses of two alkylating agents over a protracted chemotherapy course, the difference between the control and the amifostine arms in hematological toxic effects was clinically, and statistically, significant. The results reported by

Anderson and colleagues (10), while statistically significant, were not particularly clinically relevant as standard chemotherapy doses were not used in the trial.

Update

Planting and colleagues (4u) randomized 74 patients with head and neck cancer to receive cisplatin (70 mg/m^2 for six cycles) alone or preceded by 740 mg/m^2 of amifostine. There was no difference in the occurrence of leucopenia or neutropenia between the two arms. In the cisplatin-alone arm, grade 3 or 4 thrombocytopenia was observed in six of 206 cycles, versus one of 184 cycles in the combination arm (p=0.035). Treatment was delayed for a total of 15 weeks in the combination arm because of hematologic toxicity versus 25 weeks in the cisplatin only arm, but this difference was not significant (p=0.17).

In the trial by Gelmon et al (5u), 40 women with metastatic breast cancer were randomized to receive either 250 mg/m^2 of paclitaxel alone or preceded by 910 mg/m^2 of amifostine. There were no significant differences between the two treatment groups for any measure of hematologic toxicity including grade 4 neutropenia, thrombocytopenia and mild anemia.

In abstract form, Jost et al (6u) reported the results of a randomized trial of amifostine in patients with head and neck cancer. Fifty-eight patients were treated with a combination of cisplatin, 5-fluorouracil (5-FU) with or without amifostine (910 mg/m^2). The incidence of grades 3 or 4 neutropenia and thrombocytopenia were measured. There were no significant differences between the two treatment arms in either of these measures of hematologic toxicity.

Petrilli et al (7u) reported, in abstract form, a trial of amifostine in pediatric osteosarcoma. Thirty-nine patients receiving chemotherapy that included cisplatin, carboplatin, doxorubicin and ifosfamide were included in the trial. Twenty patients received amifostine and 19 did not. The incidence of neutropenia and leucopenia were significantly lower in the group of patients receiving amifostine ($p<0.02$), but no values were reported.

Johnson et al (8u) reported on a randomized trial of amifostine in patients with small-cell lung cancer receiving chemotherapy consisting of ifosfamide, carboplatin and etoposide. Forty-two patients were randomized to receive amifostine, and the other 42 patients received chemotherapy alone. There was no significant difference between the two arms in the occurrence of grade 3 or 4 neutropenia or thrombocytopenia, or the number of infectious episodes, bleeding, platelet transfusions or red blood cell transfusions.

In a small randomized trial published as an abstract, Rudolph et al (10u) reported less grade II/III leucopenia (1.3% versus 9.8% of all cycles) and less thrombocytopenia (0 versus 4 patients) for patients in the amifostine arm compared with patients in the control arm however, statistical significance was not reported.

Bildat et al (11u), reported abstract data on 51 patients randomized to carboplatin and etoposide with or without amifostine. Changes in leucocyte, thrombocyte, and hemoglobin levels were not significantly different between the two treatment groups.

Table 2. Reported outcomes for hematological toxic effects in ten amifostine trials.

Poplin et al,1994 (5)
• Incidence of thrombocytopenia (grades 3 and/or 4); mean platelet nadirs count (x 1,000/mm^3); percent decrease from baseline platelet count to the nadir; mean hemoglobin levels (g/dl); and mean granulocyte count (cells/mm^2).
Betticher et al, 1995 (6)
• Median days to platelet recovery (>100 x 10^9 l^{-1}); platelet transfusion requirement (units/course); and median hemoglobin (g l-1), neutrophil (x 10^9 l^{-1}) and platelet (x 10^9 l^{-1}) count levels.
Kemp et al, 1996 (7) and Rose, 1996 (8)
• Cumulative incidence of grade 4 neutropenia associated with fever and/or infection requiring antibiotic therapy; failure to recover from grade 4 neutropenia (≥1,500/µL by day 22); incidence of discontinued treatment due to toxic adverse effects; total days patients were on antibiotics; total days patients were in hospital.
Budd et al, 1997 (9)
• Median platelet nadir and neutrophil nadir counts (x 10^9 l); incidence of thrombocytopenia (grades 3 or 4) after the 1st cycle; percent decrease from baseline platelet count to the nadir after the 1st cycle; incidence of grade 4 thrombocytopenia over all courses of chemotherapy.
Anderson et al, 1998 (10)
• Incidence of grade 4 thrombocytopenia (over all courses); incidence of platelet transfusions; median platelet nadir counts (x 1,000/mm^3); mean days to platelet recovery to 100,000/mm^3; mean days to platelet recovery to 50,000/mm^3; incidence of grade 4 neutropenia over all courses of treatment.

Planting et al, 1999 (4u)
• Incidence of anemia, leucopenia, neutropenia, thrombocytopenia; total number of weeks delayed because of hematologic toxicity.
Gelmon et al, 1999 (5u)
• Incidence of grade 4 neutropenia; nadir white blood cell count; incidence of anemia.
Jost et al, 1999 (6u)
• Incidence of grades 3 and 4 neutropenia and thrombocytopenia (over all cycles and cycles 1-3).
Petrilli et al, 1999 (7u)
• Incidence of neutropenia, leucopenia and thrombocytopenia.
Johnson et al, 2001 (8u)
• Incidence of grade 3/4 neutropenia and thrombocytopenia (any cycle); incidence of grade 3/4 neutropenia in cycle 1.
Rudolph et al, 2001 (10u) abstract
• Incidence of leucopenia and thrombocytopenia.
Bildat et al, 2001 (11u) abstract
• Changes in leucocyte, thrombocyte, and hemoglobin levels.

Protection Against Nephrotoxicity

Nephrotoxicity is a specific side effect of cisplatin, and to a much lesser extent, carboplatin. The value of amifostine in protecting against cisplatin-induced nephrotoxic effects was measured by Kemp, Rose and colleagues (7,8). Several parameters of renal function were studied.

Hypomagnesemia was reduced in both incidence and severity in patients on amifostine by the last cycle of treatment (p=0.001). Fewer patients in the amifostine group experienced treatment delays due to creatinine elevations than did patients in the control group (5% v. 15%; p=0.014). Furthermore, fewer patients on amifostine required early discontinuation of treatment because of failure of creatinine to normalize by day 35 (2 v. 15; p=0.001).

Renal function differences were pronounced, especially in the later cycles of treatment. By cycle six, a lower percentage of patients receiving amifostine had a delay or discontinuation of therapy, compared with patients in the control group (10% v. 36%; p=0.003). Renal toxic effects were also assessed by changes in creatinine clearance from baseline. Using the Cockroft-Gault formula, which accounts for the effect of age and body surface area on serum creatinine levels, fewer patients in the amifostine arm than in the control arm experienced a relative reduction of 40% or more from baseline in creatinine clearance (13% v. 30%; p=0.001). Amifostine also protected the kidneys from the combined assault of cisplatin and nephrotoxic antibiotics. In this subset, control patients were five times more likely to suffer a 40% or greater relative reduction in creatinine clearance (p =0.032).

Update

Four trials located in the update searches measured the value of amifostine in protecting against nephrotoxicity (4u,6u,7u,9u). In the trial by Planting and colleagues (4u), no significant differences were seen between the two treatment groups for nephrotoxicity of any grade, based on serum creatinine levels. Grade 2 or 3 hypomagnesemia was observed in six patients in the amifostine group versus 14 patients who received cisplatin alone (p=0.04).

Jost and colleagues (6u) measured creatinine clearance, the minimum creatinine clearance during cycle three of chemotherapy and overall measures of renal toxicity in patients receiving cisplatin and 5-FU with or without amifostine. There was no difference in the mean creatinine clearance between the two treatment arms. Ninety-four percent of patients in the amifostine group experienced no renal toxicity, compared with 78% of patients in the control group (p=0.007).

Petrilli and colleagues (7u) observed that renal toxicity, measured by creatinine clearance, was significantly less severe among the group of patients that received amifostine (p<0.001; no values reported).

Hartmann and colleagues (9u) reported a relative reduction in the glomerular filtration rate of 11% for patients treated with amifostine, versus 30% for control patients. The excretion of NAG at day five was significantly lower in the amifostine group compared to control patients (8 v. 14 U/g creatinine; p=0.005), as was the excretion of albumin at day three (16 v. 50 mg/g creatinine; p=0.01). In addition, the incidence of hypomagnesemia during treatment was 6% in the amifostine-treated patients versus 69% in control patients (no p value reported).

Protection Against Neurotoxicity (including ototoxicity)

Only the study by Kemp, Rose (7,8) and colleagues addressed the question of the effects of amifostine on neurotoxicity. By cycle five, the incidence of peripheral neuropathy was lower in the amifostine group than in the control group (p=0.015). Over the six cycles, there was a statistically significant reduction in the severity of peripheral neuropathy (p=0.029). No patients in the amifostine group and only two patients in the control group required cessation of therapy because of neurotoxicity. A smaller proportion of patients in the amifostine group experienced clinical hearing loss or tinnitus requiring dose reduction or discontinuation of therapy than patients in the control group (9% v. 16%; p=0.108). Since neurotoxicity may appear after the cessation of chemotherapy, these data may underestimate the protective effects of amifostine. Overall, fewer patients in the amifostine arm discontinued treatment prematurely due to the renal, neurologic or otologic toxic effects of chemotherapy than in the control arm (10% v. 26%;p=0.001).

Update

Four trials addressed the question of the effects of amifostine on neurotoxicity (4u,5u,7u,10u). In the trial by Planting and colleagues (4u), clinical grade 1 neurotoxicity was reported in four patients receiving cisplatin and amifostine and five patients receiving cisplatin alone. Neurotoxicity was analyzed by serial vibration perception thresholds in the left hand, and showed a diminished incidence in the amifostine arm versus the control arm (p=0.03). There was no difference between the two study arms in the incidence of ototoxicity of any grade.

Gelmon and colleagues (5u) used a self-administered cumulative symptom score, that combined paresthesia, numbness and pain of hands and feet, as well as a number of other measures, to assess neurotoxicity in patients receiving paclitaxel with or without amifostine. No differences were found between the amifostine and the control arm for any of the various measures of neurotoxicity.

Petrilli and colleagues (7u) reported no differences between the two study groups in the incidence of ototoxicity in patients receiving a combination of cisplatin, carboplatin, doxorubicin and ifosfamide with or without amifostine. The incidence of neurotoxicity was not assessed.

Rudolph et al (10u) reported abstract data on 31 patients randomized to chemotherapy with or without amifostine. Patients who received amifostine had significantly less peripheral neurotoxicity (p=0.048) than patients who received no further treatment.

Tumour Protection

None of the studies provide any evidence of tumour protection by amifostine. In the trial of ovarian cancer patients by Kemp, Rose and colleagues (7,8), tumour response was assessed at second-look laparotomy. One-third of the patients in each arm did not undergo this procedure and they were considered non-responders in this intent-to-treat analysis. There was no significant difference in either complete response (CR) rate (43.3% v. 36.5%; p=NS), or pathological CR plus clinical partial response (75% v. 65.4%; p=NS) between amifostine-treated and control patients, respectively.

The limited data available do not appear to indicate that amifostine is providing tumour protection. However, these data should be interpreted with caution. Based on a 95% confidence interval around a difference in response rate of 6.8%, the data are consistent with a range of outcomes, from an 11.3% worse response rate for cisplatin plus amifostine compared with cisplatin alone, to as much as a 24.9% improvement in response rate for cisplatin plus amifostine. To exclude differences in response rate of 5% and 10% respectively, with a power of 80%, prospective recruitment of approximately 1500 and 400 subjects per group would be required (compared with the approximately 120 recruited to each arm of the Kemp, Rose and colleagues study). However, the study by Detsky and colleagues (11) points out that if the observed effect is small, the risk of a false-negative conclusion (and the sample size required to draw negative or equivalency conclusions) is often much less than that generated by the "prospective" calculation. Similar limitations apply to other outcomes such as survival.

Update

Five trials measured tumour response (4u-6u,8u,11u). There was no significant difference in the objective response rates between the amifostine and the control arms in any of the trials.

Survival

Survival data was reported in four of the five trials, with no statistically significant difference between the amifostine and control groups in any of these trials. Kemp, Rose and colleagues (7,8) reported identical median survival times (31 months) for two groups of patients with ovarian cancer receiving cyclophosphamide and cisplatin with or without amifostine. The survival curves were virtually superimposable. Subgroup analysis according to post-debulking residual tumour bulk also showed no difference.

The study by Betticher and colleagues (6) reported median survivals of 14 and nine months for patients treated with amifostine plus carboplatin and carboplatin alone respectively, but the difference was not statistically significant. Poplin and colleagues (5) reported median survival times of 7.2 and 6.3 months for amifostine and control (both received mitomycin-C); but again, the difference was not statistically significant. The survival data from of a subset of non-small-cell lung cancer patients in the trial by Budd and colleagues (9) showed a nonsignificant improvement for those receiving amifostine (p=0.116).

Update

Jost and colleagues (6u) reported median survival times of 8.3 months for patients receiving amifostine and 6.4 months for patients in the control group, but this difference was not significant.

Johnson and colleagues (8u) reported median survival times of 14 months for patients receiving amifostine and 11 months for patients treated with chemotherapy alone.

Bildat et al (11u) reported median survival times of 11 months for patients receiving amifostine and 9.5 months for patients treated with chemotherapy alone. This difference was not statistically significant (log rank p=0.4).

Quality of Life

Quality of life (QOL) was not directly assessed in any of these trials. However, the number of days in hospital and on antibiotics was measured in the large trial by Kemp, Rose and colleagues (7,8) in patients with ovarian cancer. The number of days in hospital due to neutropenia in patients treated with amifostine compared with control were 89 and 226 respectively (p=0.019). Also, the amifostine group spent fewer days on antibiotics than control patients (111 v. 284; p=0.031). In the trial reported by Betticher and colleagues (6), there was a trend in favour of amifostine in terms of hospitalization rate, mainly for intravenous antibiotics (0/25 v. 6/25 cycles; p=0.06), and infection rate (3/20 v. 10/25 cycles; p=NS).

Adverse Effects

Side effects associated with amifostine are frequent but generally mild and transient. The major concern is hypotension during administration, usually occurring toward the end of the 15-minute infusion. Hypotension is less likely to occur if the patient is adequately hydrated, and can be managed by placing the patient supine or head-down, infusing additional saline and temporarily holding the amifostine infusion. A comprehensive guideline is available which addresses the prevention and management of this complication (4).

The study by Poplin and colleagues (5) reported that amifostine was discontinued because of hypotension in 13 (13%) of 97 cycles, and in 12 (25%) of 48 patients. In most cases, the patients returned to normotension within 10 minutes, and were given reduced dosages of amifostine in subsequent cycles. Betticher and colleagues (6) reported that hypotension occurred in 15 of 20 courses, leading to discontinuation in 12 courses. In the trial by Kemp, Rose and colleagues (7,8), 75 (62%) of 122 patients treated with amifostine had a reduction in systolic blood pressure requiring interruption of the amifostine infusion. In total, over the course of the study, 145 (25%) of 581 amifostine infusions were associated with a reduction in blood pressure. In the study by Budd and colleagues (9), hypotension did not reverse within five minutes of interrupting the amifostine infusion in 14 of 82 cycles, leading to subsequent dose modification. No sequelae were reported.

Nausea and vomiting were reported in four of the five trials. In the study by Kemp, Rose and colleagues (7,8), more patients in the amifostine arm experienced grade 3 or 4 nausea and vomiting than patients in the control arm (30% v. 23%, p=0.22) with an already emetogenic regimen. Betticher and colleagues (6) reported nausea and vomiting in 90% of all patients receiving amifostine compared with 70% of those receiving carboplatin alone. Poplin and colleagues (5) reported vomiting in 15% of those in the control group versus 73% of the amifostine group. In the study by Budd and colleagues (9), nausea was more frequent with amifostine than without (p=0.002), but was almost always mild (grade 1).

Other side effects were reported, including flushing, sneezing, dizziness, hiccoughs and chills (5-8). In the study by Anderson and colleagues (10), amifostine was felt to be well tolerated, being interrupted in four of 24 patients and terminated prematurely in three of 24.

Update

Hypotension during amifostine infusion was reported in 47% of patients in the trial by Planting and colleagues (4u). Dose modification was required in three patients and hypotension did not recur in two patients. In the third patient, hypotension recurred despite dose reduction, and amifostine was withheld. One patient in this trial died shortly after the second administration of amifostine as a result of asphyxia due to mechanical obstruction and pulmonary edema. Petrilli and colleagues (7u) reported hypotension in 14.5% of infusions, with no patient requiring discontinuation of amifostine.

In the trial by Gelmon and colleagues (5u), vomiting was reported in 75% of those receiving amifostine, versus 40% of those in the control group. Nausea was reported in 90% of the amifostine group versus 55% of the control group in this trial. It is noteworthy to mention that the

majority of patients in these trials, including the trials included in the original practice guideline report, did not receive serotonin receptor antagonists. The incidence of nausea and vomiting may be diminished by the co-administration of these drugs, especially in the platinum context.

Hartmann et al (9u) observed rash in 33% of cycles, nausea/vomiting in 13% and hypotension in 3%. All side effects were completely reversible within hours after application of amifostine.

Dosage

It is believed that 740 mg/m^2 of amifostine may offer the same degree of protection as 910 mg/m^2 of amifostine, with a lower incidence of side effects such as hypotension and vomiting (12). While this needs evaluation in randomized controlled trials, one study by Glover and colleagues employed a controlled crossover design in a phase II trial to investigate the myelosuppressive effects of cyclophosphamide with and without amifostine (13). Twenty-one patients with various tumour types received one cycle of cyclophosphamide 1500 mg/m^2 initially without amifostine, and then acting as their own controls, the same dose of cyclophosphamide was administered with 740 mg/m^2 of amifostine three weeks later. The mean nadir white blood cell (WBC) count increased from 1760/ml to 2500/ml ($p<0.0005$) and the mean nadir granulocyte count increased from 541/ml to 1247/ml ($p<0.0005$). Only 14% of the cycles were associated with hypotension, which represents an improvement over the 25% observed in the study by Kemp, Rose and colleagues (7,8).

V. INTERPRETIVE SUMMARY

The use of amifostine in reducing cytotoxic side effects related to several chemotherapy agents, specifically, myelotoxicity, nephrotoxicity, neurotoxicity and ototoxicity is the main focus of this recommendation. The diminution of these side effects is consistent across all studies, clinically important in magnitude and statistically significant where power was adequate. Lower rates of hospitalization for neutropenia, and diminished nephrotoxicity, neurotoxicity and ototoxicity are benefits which impact both short-term and long-term quality of life. The protective effects of amifostine against nephrotoxicity, neurotoxicity and ototoxicity related to cisplatin have been demonstrated in only one RCT. Confirmatory studies are needed.

Can amifostine perform "safely"? First, it does appear to function with manageable toxicity. While the optimal dose is unresolved, (910 mg/m^2 v. 740 mg/m^2, or even less), the lower doses are probably associated with less hypotension. Secondly, the word "safely" implies an absence of tumour protection. In the large trial in patients with ovarian cancer by Kemp, Rose and colleagues (7,8), there was no significant difference in tumour response or survival rate between the two treatment groups. The other trials were unable to assess the effects of amifostine on tumour activity because of an ineffective treatment regimen (5), or small numbers of patients (6,9,10). Based on their results, Kemp, Rose and colleagues (7,8) claimed their results excluded a tumour-protective effect. If the chemotherapy dose-intensity in both arms had been equal, then this conclusion would be warranted. However, the method of reporting does not allow for extraction of this data. Furthermore, although the number of dose reductions for myelosuppression were the same in each arm, there is clear evidence that treatment-limiting toxicity was significantly less frequent in the amifostine arm. The implication is that the overall dose-intensity of the chemotherapy on the amifostine arm was higher compared with the control arm. If this is so, then the lack of difference in efficacy is at least consistent with some degree of tumour protection by amifostine. However, alternative explanations are possible. Nevertheless, for at least an equivalent (if not higher) dose-intensity, the chemotherapy-related toxicity was markedly less in the amifostine arm, without a trade-off in diminished efficacy. Thus it can be concluded, in this tumour type and with this regimen, that amifostine enhanced the therapeutic index of the cytotoxic agents used.

In the study by Kemp, Rose and colleagues (7,8), the doses of cisplatin and cyclophosphamide were somewhat higher than would generally be used in Canada. However, some controversy exists as to the optimal doses of these drugs in this regimen. Furthermore, with the advent of paclitaxel used in combination with cisplatin or carboplatin, the cyclophosphamide/cisplatin regimen is becoming obsolete.

Three of the studies (6,9,10) documented the ability of amifostine to protect against the platelet-suppressive effect of carboplatin. However, this effect appeared to be clinically significant only when higher than standard doses of carboplatin were employed. Caution should be exercised in generalizing these results to other chemotherapy regimens. There is evidence that amifostine and paclitaxel interact pharmaco-kinetically, for example (14). It is, however, acknowledged that new RCTs are unlikely to be done in each disease site with each new regimen, to validate the place of amifostine. Consequently, clinical judgement will continue to be necessary.

Data regarding the use of amifostine after commencement of chemotherapy are not available for analysis; therefore it is recommended that amifostine be given from the beginning of chemotherapy.

Update

Amifostine has been investigated with only a limited number of cytotoxic agents apart from the alkylating agents and platinum analogues. One of these is paclitaxel, for which there is conflicting evidence regarding a pharmacokinetic interaction with amifostine (14,5u). Evidence from a randomized phase II trial (5u) suggests that amifostine does not provide protection from any of the toxicities (including neurotoxicity) of single-agent paclitaxel, despite preclinical evidence that a selective cytoprotective effect for normal cells might exist. This finding is not surprising, given the absence of any plausible biochemical explanation for a protective effect (apart from a pharmacokinetic one) and given the mechanism of action of the taxane. However, the trial indicated no tumour-protective effect either and amifostine should be further investigated as a cytoprotectant in platinum-taxane combinations.

VI. TREATMENT ALTERNATIVES

Alternative strategies are available to deal with the myelosuppressive effects of chemotherapy: dose reduction; substitution of less toxic drugs, (e.g. carboplatin for cisplatin); use of colony-stimulating factor (CSFs), especially G-CSF; use of erythropoietin or thrombopoietin-type factors; or premature cessation of chemotherapy. The costs, risks and benefits of each of these options are likely to vary. Thorough analysis of these alternatives would require that each be studied properly across disease sites.

The options are more limited in dealing with other toxicities related to alkylating agents. Nephrotoxicity is only partially ameliorated by modern hydration regimens. Neurotoxicity and ototoxicity are not predictable in individual patients, and patients cannot be "rescued" from them.

Unlike CSFs, amifostine can be given with concurrent chemotherapy and radiation. Drug substitution (carboplatin for cisplatin) is highly controversial and carboplatin is in fact more myelosuppressive than cisplatin. Premature cessation of treatment is inappropriate in curable tumours, and may be undesirable in palliative chemotherapy. The same comments apply to dose reduction. Furthermore, there is little evidence on the extent to which dose reduction compromises the palliative benefits of chemotherapy.

On the other hand, blanket use of amifostine in all patients on any alkylating regimen is not being advocated. Neurotoxicity, ototoxicity and nephrotoxicity are not major issues in regimens employing relatively low cumulative doses of cisplatin. Routine use of amifostine should only be considered with cisplatin regimens involving moderate to high doses of cisplatin, especially cumulative doses in excess of 300 mg/m^2, after which the incidence of peripheral neuropathy is predicted to rise (12). However, it is recognized that there are occasional individuals who

develop nerve damage at lower doses of cisplatin. Research to prospectively identify these individuals is required.

VII. ONGOING TRIALS

Three randomized trials are currently in progress or planned to begin, and will likely provide more information on the effect of amifostine in various situations. The following provides details of these trials:

NU-97CC4, NCI-G99-1633: Phase III randomized study of amifostine chemoprotection in patients with ovarian epithelial cancer receiving chemotherapy. Patients will be randomized to receive amifostine or placebo in order to compare the incidence of neurotoxicity, myelotoxicity, length of hospital stay due to infections and quality of life. Sixty patients will be accrued for this study. The summary was last modified on the PDQ website in September, 2001.

ALZA-96-007-ii, NCI-V97-1277,URCC-U4796: Phase II Placebo Controlled, Randomized Study of Amifostine in the Prevention of Paclitaxel-Induced Neuropathy. Patients are randomized to receive either paclitaxel alone or paclitaxel with amifostine pretreatment. Patients are also stratified into 2 groups (cisplatin containing regimens and noncisplatin containing regimens). (Summary Last Modified 05/1999)

ALZA-UCMC-971163, NCI-V97-1330, UCMC-971163: Phase III Randomized Study of Amifostine in Reducing Cisplatin Induced Ototoxicity in Cancer Patients. Patients receive either cisplatin alone or with amifostine IV over 15 minutes, administered 30 minutes before cisplatin. . Thirty patients will be accrued for this study (Summary Last Modified 04/2000).

VIII. DISEASE SITE GROUP CONSENSUS PROCESS

Members of the Systemic Treatment Disease Site Group (STDSG) focused their discussion of amifostine on the indications for its use and the evidence from randomized controlled trials.

The group acknowledged that, because of the limited number of trials, indications for the use of amifostine are not clear cut. However the greatest potential benefit seems to be in situations where amifostine may protect against the irreversible toxicities of cisplatin (neurotoxicity, nephrotoxicity, ototoxicity). Weighing the costs and potential harms of its use are also important before making a decision to use the drug. The group felt that the recommendation should advise against the use of amifostine with taxanes and mention that there are treatment alternatives to amifostine.

Concerning the evidence from randomized trials of amifostine, STDSG members discussed the small number of studies and the small numbers of patients in each of these studies. Amifostine has shown statistically significant benefits in reducing a number of toxic effects associated with chemotherapy treatment of cancer patients. However, members of the STDSG noted that the studies lacked statistical power to detect differences in response and survival, and thus could not definitely exclude tumor protection. It was agreed that more trials of sufficient size are needed in order to assess these effects, although realistically these may not be done. However, there might, in the future, be the possibility to perform a meta-analysis across multiple trials addressing the issue of tumor protection.

Update

Further data has subsequently been published on the use of amifostine with paclitaxel (5u) and this bullet of the recommendation has been modified.

IX. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

This section describes the external review activities undertaken for the original guideline report. For a description of external review activities of the new information presented in the updated sections of this report, please refer to Update below.

Draft Recommendations
Based on the evidence contained in the original report, the Systemic Treatment DSG drafted the following recommendations:

There is evidence from randomized controlled trials that amifostine is an effective agent in relieving side effects of chemotherapy. In the treatment of patients with non-leukemic cancer, with conventional doses of alkylating agents and/or moderate or higher doses of cisplatin, the use of amifostine should be guided by the following considerations:

- In patients scheduled to receive high per course doses of cisplatin ($\geq$100 mg/m^2) or high cumulative doses ($\geq$600 mg/m^2), amifostine is a reasonable therapeutic option to reduce the incidence and severity of neurotoxicity, ototoxicity or nephrotoxicity. There are currently no data to determine whether amifostine produces similar benefits at lower per course doses or cumulative doses of cisplatin. However, the incidence of neurotoxicity is predicted to rise at cumulative doses of cisplatin ($\geq$300 mg/m^2) and the use of amifostine could be considered in this setting.
- Amifostine is one of several reasonable therapeutic options to reduce myelosuppression. In assessing the effects on quality of life, particularly when amifostine is used as part of palliative treatment, acute toxicities of amifostine, such as nausea and vomiting and hypotension, need to be weighed against its ability (based on one study) to reduce the morbidity of myelosuppression (episodes of neutropenic fever).
- If the objective is to improve survival by means of dose maintenance, there is no evidence to justify the routine use of amifostine.
- It is strongly recommended that patients be enrolled in randomized controlled trials designed to address the effects of amifostine on survival, health care costs, optimal dose and quality of life.

Practitioner Feedback
Based on the evidence contained in the original report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods
Practitioner feedback was obtained through a mailed survey of 160 practitioners in Ontario. The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Systemic Treatment DSG.

Results
Key results of the practitioner feedback survey of the original draft guideline report are summarized in Table 3. Ninety-seven (61%) surveys were returned. Seventy-nine (81%) respondents indicated that the evidence-based recommendation was relevant to their clinical practice and they completed the survey.

Summary of Written Comments
Forty-three (44%) respondents provided written comments. The main points were:

1. The recommendation for the use of amifostine is largely based on the evidence from one large, randomized controlled trial (Kemp, Rose and colleagues).

2. The chemotherapy regimen used in the Kemp, Rose and colleagues trial is out-dated, since cisplatin-paclitaxel is now regularly used for treating ovarian cancer. There is little mention of interactions between amifostine and other agents, specifically taxanes.
3. There is no indication in the report as to when amifostine is to be started in relation to chemotherapy.
4. Information is lacking for an economic, cost-benefit analysis for the use of amifostine.

Table 3. Practitioner responses to seven items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing this evidence-based recommendation, as stated in the "*Choice of Topic*" section of the report, is clear.	77 (94)	5 (6)	0 (0)
A practice guideline on this topic will be useful to clinicians.	72 (88)	9 (11)	1 (1)
The literature search is relevant and complete.	71 (87)	9 (11)	1 (1)
The summary of the evidence is acceptable to me.	77 (94)	3 (4)	1 (1)
I agree with the evidence-based recommendation as stated.	70 (85)	5 (6)	6 (8)
This recommendation should serve as a practice guideline.	62 (76)	10 (12)	9 (11)
Would you use this practice guideline in your own practice?	**Yes**	**Unsure**	**No**
	63 (77)	5 (6)	8 (10)

NOTE: Some percentages do not add up to 100 because data from some practitioners is missing.

Modifications/Actions

The STDSG made the following changes to the guideline in response to practitioners' comments:

1. The literature search was updated to June 1998; two additional (small) RCTs were found and have been included in the report. A statement was added to the front page of the practice guideline that the evidence for the use of amifostine is based primarily on one large study in patients with ovarian cancer, and on four smaller studies in patients with various malignancies.
2. Statements were added to the practice guideline and to the *Interpretative Summary* section to indicate that there is no evidence from RCTs about the use of amifostine in patients treated with a cisplatin-paclitaxel chemotherapy regimen, and that, because of possible interactions, the use of amifostine is not recommended with taxanes.
3. A statement was added tot he *Interpretive Summary* to address this comment.
4. Two economic analyses of amifostine were incorporated into the *Implications for Policy* section.

Approved Practice Guideline Recommendations

The approved practice guideline recommendations in Section XI reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Systemic Treatment DSG and the Practice Guidelines Coordinating Committee.

Update

New evidence found by update searches since completion of the original guideline is consistent with the original recommendations. A qualifying statement has been added with the emergence

of new data on the use of amifostine with paclitaxel (5u). New evidence from review and updating activities has not been subject to external review at this time

X. IMPLICATIONS FOR POLICY

The pharmaco-economics of amifostine use needs further research. There is potential for cost savings from the health care system and societal perspectives, with respect to avoidance of both short-term (cost of hospitalization and intravenous antibiotics) and long-term toxic effects of chemotherapy (involuntary unemployment in long-term survivors due to neurotoxicity or ototoxicity). Furthermore, the minimal effective dose of amifostine has not been established, and consequently optimal use may be less costly than it now appears.

Two economic studies of amifostine have been reported (15,16). Dranitsaris (15) conducted a Canadian-situated "willingness to pay" study which arrived at an estimate as to what that the Canadian tax-paying public would be prepared to pay in order to avoid febrile neutropenia. The study used the data from the RCT by Kemp, Rose and colleagues (7,8), which included the now obsolete cisplatin/cyclophosphamide regimen for ovarian cancer. In his report, Dranitsaris concluded that at the present price of amifostine its use would be cost neutral; respondents stated that they would be willing to pay an extra $3476 Can. over their lifetimes to avoid febrile neutropenia. The actual cost of amifostine to achieve this is $3826. Net cost is therefore $350 per patient (95% confidence interval is -$850 to +$1551). Importantly, this study indicated that a lower dose of 740 mg/m^2 amifostine would be a better buy than G-CSF. Furthermore, this study did not consider other social benefits such as the avoidance of neurotoxicity, ototoxicity or nephrotoxicity. The methodology of this study is a variant of cost-benefit analysis, and is thought to avoid some pitfalls inherent in cost effectiveness analysis. Methodological controversies are discussed by the author in this publication, together with a justification of his approach, which captured values from all relevant groups (future patients as well as non-users).

Fishman and colleagues (16) conducted a cost-utility analysis based on American cost data. Their study also employed the obsolete cisplatin/cyclophosphamide data from the study by Kemp, Rose and colleagues (7,8). They concluded that amifostine is within the range of generally accepted cost-effective therapies for the United States. These data are of marginal relevance in Ontario.

Amifostine retails in Canada at approximately $0.50/mg, or $250 Can. per 500-mg vial. Based on a dosage rate of 910 mg/m^2, administered once per cycle, for an average individual of 70 kg or 1.7 m^2, amifostine costs about $780 per cycle. At a dose of 740 mg/m^2 per cycle, the cost falls to approximately $640 per cycle. The assumption has been made that the complete contents of the vial are used and not discarded. Carboplatin is currently less expensive than cisplatin overall, with an approximate additional cost per cycle for the platinum component of $122 for 350 mg/m^2 of carboplatin for an average individual of 1.7 m^2. G-CSF currently costs approximately $2000 per cycle (1 vial/day for 14 days).

XI. PRACTICE GUIDELINE

This practice guideline reflects the most current information and integrates the new evidence with evidence from the original guideline report.

Target Population

These recommendations apply to patients with non-leukemic cancer using conventional doses of alkylating agents and/or moderate or higher doses of cisplatin.

Recommendations

Key Recommendations

- In patients scheduled to receive high per cycle doses of cisplatin (≥100 mg/m^2) or high cumulative doses (≥ 600 mg/m^2), amifostine is a reasonable therapeutic option to reduce the

incidence and severity of neurotoxicity, ototoxicity or clinically relevant nephrotoxicity. There are currently no data to determine whether amifostine produces similar benefits at lower per cycle doses or cumulative doses of cisplatin. However, the incidence of neurotoxicity is predicted to rise at cumulative doses of cisplatin $\geq$ 300 mg/m^2 and the use of amifostine could be considered in this setting.

- Amifostine is one of several reasonable therapeutic options to reduce myelosuppression. In assessing the effects of amifostine on quality of life, particularly when amifostine is used as part of palliative treatment, acute toxic effects of amifostine, such as nausea and vomiting and hypotension, need to be weighed against its ability (based on one randomized study) to reduce the morbidity of myelosuppression (episodes of neutropenic fever).
- If the objective of treatment with amifostine is to improve survival by means of dose maintenance of chemotherapy, there is no evidence to justify the routine use of amifostine.

Qualifying Statements

- Although the limited number of randomized controlled trials to date indicate no adverse impact of amifostine on tumour response or survival, the lack of a tumour protective effect in all situations should not yet be automatically assumed. Consequently the use of amifostine in the curative or adjuvant setting should preferably take place in the context of a clinical trial.
- There are limited data regarding the potential for interaction between amifostine and some other cytotoxic agents. Use of amifostine with non-platinum non-alkylating cytotoxic agents should preferably take place in the context of a clinical trial.

Future Research

- Data from randomized studies are limited; therefore, it is strongly recommended that patients be enrolled in randomized controlled trials designed to address the effects of amifostine on survival, health care costs, optimal dose, quality of life and pharmacokinetics.

XII. JOURNAL REFERENCE

Vincent M, Bramwell V, Moran LA, Anderson D and the Cancer Care Ontario Practice Guidelines Initiative Systemic Treatment Disease Site Group. Use of amifostine to ameliorate the toxic effects of chemotherapy in the treatment of cancer. *Current Oncology* 2000;7(3):149-61.

XIII. ACKNOWLEDGMENTS

The Systemic Treatment Disease Site Group would like to thank Dr. Mark Vincent, a medical oncologist at the London Regional Cancer Centre, Dr. Vivien Bramwell, Ms. Lea Anne Moran, and Mr. Dale Anderson for taking the lead in drafting and revising this practice guideline report.

The Systemic Treatment Disease Site Group would like to thank Dr. Mark Vincent, Dr. Vivien Bramwell, Manya Charette, and Tom Oliver for taking the lead in updating this practice guideline report.

For a full list of members of the Cancer Care Ontario Breast Cancer Disease Site Group please visit the website of the Program in Evidence-based Care at http://www.cancercare.on.ca/ccopgi.

REFERENCES

1. Lewis C. A review of the use of chemoprotectants in cancer chemotherapy. *Drug Saf* 1994;11:153-62.
2. Capizzi RL, Oster W. Protection of normal tissue from the cytotoxic effects of chemotherapy and radiation by amifostine: clinical experiences. *Eur J Cancer* 1995;31A(Suppl 1):S8-13.
3. Schiller JH, Storer B, Berlin J, Wittenkeller J, Larson M, Pharo L, et al. Amifostine, cisplatin and vinblastine in metastatic non-small-cell lung cancer: a report of high response rates and prolonged survival. *J Clin Oncol* 1996;14:1913-21.
4. Schuchter LM. Guidelines for the administration of amifostine. *Semin Oncol* 1996;23(Suppl 8):40-3.
5. Poplin EA, LoRusso P, Lokich JJ, Guilo JJ, Leming PD, Schulz JJ, et al. Randomized clinical trial of mitomycin-C with or without pretreatment with WR-2721 in patients with advanced colorectal cancer. *Cancer Chemother Pharmacol* 1994;33:415-9.
6. Betticher DC, Anderson H, Ranson M, Meely K, Oster W, Thatcher N. Carboplatin combined with amifostine, a bone marrow protectant, in the treatment of non-small-cell lung cancer: a randomised phase II study. *Br J Cancer* 1995;72:1551-5.
7. Kemp G, Rose P, Lurain J, Berman M, Manetta A, Rouliet B, et al. Amifostine pretreatment for protection against cyclophosphamide-induced and cisplatin-induced toxicities: results of a randomized control trial in patients with advanced ovarian cancer. *J Clin Oncol* 1996;14:2101-12.
8. Rose PG. Amifostine cytoprotection with chemotherapy for advanced ovarian carcinoma. *Semin Oncol* 1996;23(Suppl 8):83-9.
9. Budd GT, Ganapathi R, Adelstein DJ, Pelley R, Olencki T, Petrus J, et al. Randomized trial of carboplatin plus amifostine versus carboplatin alone in patients with advanced solid tumours. *Cancer* 1997;80:1134-40.
10. Anderson H, Mercer V, Thatcher N. A phase III randomised trial of carboplatin and amifostine versus carboplatin and G-CSF in patients with inoperable non-small cell lung cancer (NSCLC) [Abstract]. *Proc Am Soc Clin Oncol* 1998;17:465a. Abstract 1787.
11. Detsky AS, Sackett DL. When was a negative clinical trial big enough? How many patients you needed depends on what you found. *Arch Intern Med* 1985;145:709-12.
12. Turrisi AT, Glover DJ, Hurwitz S, Glick J, Norfiest AL, Weller C et al, Final Report of the phase I trial of single-dose WR-2721 [S-2-(3-aminopropylamino) ethylphosphorothioic acid]. *Cancer Treat Rep* 1986;70:1389-93.
13. Glover D, Glick JH, Weiler C, Hurowitz S, Kligerman M. WR-2721 protects against the hematologic toxicity of cyclophosphamide: a controlled phase II trial. *J Clin Oncol* 1986;4:584-8.
14. Schüller J, Czejka M, Pietrzak C, Springer B, Wirth M, Schernthaner G. Influence of the cytoprotective agent amifostine (AMI) on pharmacokinetics (PK) of paclitaxel (PAC) and taxotere (TXT) [Abstract]. *Proc Am Soc Clin Oncol* 1997;16:224a. Abstract 785.
15. Dranitsaris G. A pilot study to evaluate the feasibility of using willingness to pay as a measure of value in cancer supportive care: an assessment of amifostine cytoprotection. *Support Care Cancer* 1997;5:489-99.
16. Fishman DA, Calhoun E, Golub R, Weinstein J, Lurain J, Roland P, et al. Cost-utility assessment of amifostine in first-line therapy for ovarian cancer [Abstract]. *Proc Am Soc Clin Oncol* 1998;17:417a. Abstract 1608.

Update

This section includes all references from the review and updating activities.

1u. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The Practice Guidelines Development Cycle: A conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13:502-12.

2u. Hensley ML, Schuchter LM, Lindley C, Meropol NJ, Cohen GI, Broder G, et al. American Society of Clinical Oncology clinical practice guidelines for the use of chemotherapy and radiotherapy protectants. *J Clin Oncol* 1999;17:3333-55.

3u. Schuchter LM, Hensley ML, Meropol NJ, Winer EP. 2002 Update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2002;20(12):2895-903.

4u. Planting AST, Catimel G, de Mulder PHM, de Graeff A, Höppener F, Verweij J, et al. Randomized study of a short course of weekly cisplatin with or without amifostine in advanced head and neck cancer. *Ann Oncol* 1999;10:693-700.

5u. Gelmon K, Eisenhauer E, Bryce C, Tolcher A, Mayer L, Tomlinson E, et al. Randomized phase II study of high-dose paclitaxel with or without amifostine in patients with metastatic breast cancer. *J Clin Oncol* 1999;17:3038-47.

6u. Jost LM, Michel G, Dunkel-de Raad S, Zanni M, Egger HP, Stupp R. Value of amifostine-cytoprotection in cisplatin and fluorouracil (5-FU) chemotherapy in head and neck cancer (HNCA). A randomized open-label trial [Abstract]. *Proc Am Soc Clin Oncol* 1999;18:392a. Abstract 1515.

7u. Petrilli AS, Oliveira DT, Ginani VC, Kechichian R, Dishketchian A, Roque W, et al. Amifostine (AM) in pediatric osteosarcoma (OS) [Abstract]. *Proc Am Soc Clin Oncol* 1999;18:560a. Abstract 2160.

8u. Johnson PWM, Muers MF, Peake MD, Poulter KM, Gurney EM, Napp V, et al. A randomized trial of amifostine as a cytoprotective agent in patients receiving chemotherapy for small cell lung cancer. *Br J Cancer* 2001;84:19-24.

9u. Hartmann JT, Knop S, Fels LM, van Vangerow A, Stolte H, Kanz L, et al. The use of reduced doses of amifostine to ameliorate nephrotoxicity of cisplatin/ifosfamide-based chemotherapy in patients with solid tumors. *Anti-Cancer Drugs* 2000;11:1-6.

10u. Rudolph S, Fahlke J, Kuhn R, Fenchel K, Lippert H, Ridwelski K. Randomised trial with or without amifostine to reduce neurotoxic side effects under chemotherapy with oxaliplatin (L-OHP), FA/5-FU. Proc Am Soc Clin Oncol 2001; Abstract 2958.

11u. Bildat S, von Pawel J, Gatzemeier U, Niederle N, Keilholtz U, Manegold C, et al. Randomized phase-II study of carboplatin/etoposide versus carboplatin/etoposide plus amifostine in extensive disease (ED) small-cell lung cancer (SCLC): a comparison of acute and cumulative toxicities with the D-Auc method. Proc Am Soc Clin Oncol 2001; Abstract 1278.

APPENDIX 1. Treatment regimens used in the randomized controlled trials of amifostine use in patients receiving chemotherapy.

Trial	Drug and Dose	Route	Schedule
Poplin et al, 1994 (5)	1. amifostine, 910mg/m^2 2. mitomycin-C 20 mg/m^2 3. as above, without amifostine	IV, 15 min infusion	15 minutes prior to mitomycin-C
Betticher et al, 1995 (6)	1. amifostine, 910 mg/m^2, 2. carboplatin 600mg/m^2 3. as above, without amifostine	IV, 15 min infusion	20 min before chemo, then 3 hrs and 4 hrs after; 4 weekly intervals X 3 courses
Kemp et al, 1996 (7) Rose, 1996 (8)	1. amifostine, 910 mg/m^2 2. cyclophosphamide, 1000 mg/m^2 3. mannitol, 12.5 g 4. cisplatin, 100 mg/m^2 5. mannitol, 10 g/h 6. as above, without amifostine	IV, 15 min infusion IV, 20 min infusion IV bolus IV, 30 min infusion IV, 6 hr infusion	
Budd et al, 1997 (9)	1. amifostine 910 mg/m^2 2. carboplatin 500 mg/m^2 3. ondansetron 4. dexamethasone 5. as above, without amifostine	IV, 15 min infusion IV, 5-10 min infusion	15-20 min prior to carboplatin, then 2 hrs after; repeated every 4 weeks.
Anderson et al, 1998 (10)	1. amifostine 740 mg/m^2 2. carboplatin (dose not given) 3. G-CSF 263 µg/day 4. as above, without amifostine	Not reported in abstract	pre- and 2 hrs post-carboplatin from days 2-15; chemo repeated every 4 weeks (max. 6 cycles)
Planting et al, 1999 (4u)	1. amifostine 740 mg/m^2 2. cisplatin 70 mg/m^2 3. as above, without amifostine	IV, 15 min infusion IV, 1 hr infusion	15 min prior to cisplatin chemo repeated every week for 6 cycles
Gelmon et al, 1999 (5u)	1. amifostine 910 mg/m^2 2. paclitaxel 250 mg/m^2 3. as above, without amifostine	IV, 15 min infusion IV, 3 hr infusion	before paclitaxel chemo repeated every 3 weeks for 4 courses
Jost et al, 1999 (6u)	1. amifostine 910 mg/m^2 2. cisplatin 100 mg/m^2 3. 5-FU 1000 mg/m^2/d (4-5 days) 4. as above, without amifostine	IV, 15 min infusion IV IV, 24 hr infusion	before cisplatin chemo repeated every 3 weeks
Petrilli et al, 1999 (7u)	1. amifostine (dose not given) 2. cisplatin/ifosfamide 3. ifosfamide/doxorubicin 4. carboplatin/doxorubicin 5. ifosfamide/carboplatin 6. as above, without amifostine	Not reported in abstract	15 min before cisplatin and carboplatin 26 weeks of alternated cycles
Johnson et al, 2001 (8u)	1. amifostine 740 mg/m^2 2. ifosfamide 3 g/m^2 3. carboplatin (GFR+25)x6 mg 4. etoposide 50 mg bd for 7 days 5. as above, without amifostine	IV, 10 min infusion IV IV orally	immediately before IV drugs chemo repeated every 3 weeks
Hartmann et al, 2000 (9u)	1. amifostine 1000 mg 2. etoposide 500 mg/m2 (V) or paclitaxel 174 mg/m2 (T) 3. ifosfamide 4 g/m2 (I) 4. cisplatin 50 mg/m2 (P) 5. G-CSF 5 µg/kg 6. VIP or TIP + G-CSF without amifostine	IV, 15 min infusion	
Rudolph et al, 2001 (10u)	1. amifostine 910 mg/m^2 2. oxaliplatin 85 mg/m^2 3. FA 500 mg/m^2 4. 5-FU 4000 mg/m^2 5. as above, without amifostine	IV, 10 min infusion IV IV IV	immediately before IV drugs
Bildat et al, 2001 (11u)	1. amifostine 740mg/m^2 2. carboplatin 600 mg/m^2 3. etoposide 120 mg/m^2 4. as above, without amifostine	IV, 15 min infusion IV, 15 min infusion	15 min before carboplatin

APPENDIX 2. Comparison between the ASCO and Cancer Care Ontario (CCO) guidelines.

The evidence-based guideline developed by ASCO in 1999 and updated in 2002 (2u,3u) was compared and contrasted with this guideline. Broadly, they are in alignment. The ASCO guideline supports the use of amifostine in the reduction of nephrotoxicity associated with cisplatin, but states that the data are insufficient to recommend the use of amifostine for protection against neurotoxicity or ototoxicity. The guideline does not emphasize amifostine use with high single or cumulative dose cisplatin to the same extent as the CCO guideline, although dose is mentioned as an issue in the body of the ASCO guideline.

The ASCO guideline concludes that data are insufficient to recommend the use of amifostine for protection against thrombocytopenia, whereas, the CCO guideline recommends the use of amifostine as one of several reasonable options to reduce myelosuppression in general. The CCO guideline does mention a reduction in febrile neutropenia as the main benefit of amifostine therapy.

In 1999, the ASCO guideline specifically mentioned that the evidence was insufficient to recommend against the prevention of paclitaxel-associated neurotoxicity. The only mention made in the initial version of this guideline regarding paclitaxel and amifostine is the fact that there is a pharmacokinetic interaction which warrants further exploration. Incidentally, this is also confirmed in the body of the ASCO document, but not in the abstract. A subsequent paper included in the updated CCO guideline and the 2002 update of the ASCO guideline showed no protection from amifostine against hematologic or neurologic toxic effects of paclitaxel. The ASCO guideline authors modified their recommendation based on this additional evidence to state that "there are no data to support the use of amifostine for prevention of paclitaxel-associated neurotoxicity"

The ASCO guideline, in addition, recommends amifostine for use in patients undergoing fractionated head and neck radiotherapy for the protection of acute and late xerostomia. This CCO document was restricted to the use of amifostine with chemotherapy, and did not cover its use in radiation therapy.

The documents are generally in agreement with respect to the need to consider alternatives to amifostine, such as dose reduction, or substitution of carboplatin for cisplatin, or the use of growth factors. Both guidelines agree that dose reduction should be specifically considered in the absence of clear evidence that the maintenance of dose intensity is necessary.