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ASCO SPECIAL ARTICLE

American Society of Clinical Oncology 2008 Clinical Practice Guideline Update: Use of Chemotherapy and Radiation Therapy Protectants

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
To update a clinical practice guideline on the use of chemotherapy and radiation therapy protectants for patients with cancer.

Methods
An update committee reviewed literature published since the last guideline update in 2002.

Results
Thirty-nine reports met the inclusion criteria: palifermin and dexrazoxane, three reports (two studies) each; amifostine, 33 reports (31 studies); and mesna, no published randomized trials identified since 2002.

Recommendations
Dexrazoxane is not recommended for routine use in breast cancer (BC) in adjuvant setting, or metastatic setting with initial doxorubicin-based chemotherapy. Consider use with metastatic BC and other malignancies, for patients who have received more than 300 mg/m^2 doxorubicin who may benefit from continued doxorubicin-containing therapy. Cardiac monitoring should continue in patients receiving doxorubicin. Amifostine may be considered for prevention of cisplatin-associated nephrotoxicity, reduction of grade 3 to 4 neutropenia (alternative strategies are reasonable), and to decrease acute and late xerostomia with fractionated radiation therapy alone for head and neck cancer. It is not recommended for protection against thrombocytopenia, prevention of platinum-associated neurotoxicity or ototoxicity or paclitaxel-associated neuropathy, prevention of radiation therapy–associated mucositis in head and neck cancer, or prevention of esophagitis during concurrent chemoradiotherapy for non–small-cell lung cancer. Palifermin is recommended to decrease severe mucositis in autologous stem-cell transplantation (SCT) for hematologic malignancies with total-body irradiation (TBI) conditioning regimens, and considered for patients undergoing myeloablative allogeneic SCT with TBI-based conditioning regimens. Data are insufficient to recommend use in the non-SCT setting.

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INTRODUCTION

The American Society of Clinical Oncology (ASCO) first published evidence-based clinical guidelines for the use of chemotherapy and radiation therapy protectants in 1999. ASCO guidelines are updated periodically by a subset of the original expert panel, and in 2002, the first update to the protectants guideline was published. For the 2008 guideline update, an update committee of the panel met to review the literature published since the 2002 report.

Since 2002, a new protectant has been approved by the US Food and Drug Administration. Palifermin, a recombinant keratinocyte growth factor, was approved for prophylaxis against severe mucositis associated with hematopoietic stem-cell transplantation in hematologic malignancies. The updated guideline includes a new section on palifermin; in addition, given the growing body of evidence on amifostine use in the prevention of esophagitis, the panel decided to add a new section on amifostine use for the prevention of esophagitis in the setting of chemoradiotherapy for non–small-cell lung cancer. For the 2008 update, the update committee considered literature on the three agents discussed in the 2002 update (dexrazoxane, amifostine, and mesna), and

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with the exception of palifermin, did not broaden the scope of agents in the update.

A summary of the recommendations contained in this guideline update is contained in Table 1. ASCO's practice guidelines and technology assessments reflect expert consensus based on clinical evidence and literature available at the time they are written, and are intended to assist physicians in clinical decision making and identify questions and settings for further research. Due to the rapid flow of scientific information in oncology, new evidence may have emerged since the time a guideline or assessment was submitted for publication. Guidelines and assessments are not continually updated and may not reflect the most recent evidence. Guidelines and assessments cannot account for individual variation among patients, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge of the patient, to determine the best course of treatment for the patient. Accordingly, adherence to any guideline or assessment is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. ASCO guidelines and assessments describe the use of procedures and therapies in clinical practice and cannot be assumed to apply to the use of these interventions in the context of clinical trials. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of ASCO's guidelines or assessments, or for any errors or omissions.

UPDATE METHODOLOGY

The 2008 update committee consisted of experts in clinical medicine, clinical research, health services, and related disciplines (biostatistics, medical decision making, patient-physician communication), and a patient representative. Update committee members are listed in Appendix A1.

The panel met once; additional work on the guideline was completed through teleconferences and electronic mail. The purposes of the panel meeting were to review the evidence relating to each clinical question and to make writing assignments for the respective sections. All members of the panel participated in the preparation of the draft guideline update, which was then disseminated for review by the entire panel. Feedback from external reviewers was also solicited, and the manuscript was submitted to *Journal of Clinical Oncology* for independent review. The content of the guideline and the manuscript were reviewed and approved by the ASCO Health Services Committee and reviewed and adopted by the Board of Directors before dissemination.

Literature Review and Analysis

For the 2008 update, the following electronic databases were searched from January 2002 to June 2007: MEDLINE, preMEDLINE, and the Cochrane Collaboration Library. The searches for articles on palifermin and on the effect of amifostine on esophagitis was not limited by date, as these topics are both new to the guideline. Results were supplemented with hand searching of systematic reviews and contributions from panel members' personal files. Search terms included the names of each of the protectants considered in the guideline ("dexrazoxane," "mesna," "amifostine," and "palifermin") as well as all of the identified brand names (US and European). These search terms were combined with "neoplasms," "cancer," "malignancies," and "tumors." Searches were limited by study type to randomized controlled trials (phase II or III), meta-analyses, and systematic reviews. Other study designs, including prospective or retrospective cohort studies and phase I or phase I/II randomized trials, were excluded. English-language studies available in full text and published in peer-reviewed journals were eligible.

Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria: participants received chemotherapy and/or radiation therapy for treatment of malignancy; participants were randomly assigned to a protectant arm or a control arm (control arm could consist of no protectant, a placebo, the same protectant at an alternate dose/route, or a different protectant); and outcomes reported included at least one of the following: primary treatment toxicities (eg, hemorrhagic cystitis or other urothelial toxicity, neurotoxicity, ototoxicity, nephrotoxicity, neutropenia, thrombocytopenia, xerostomia, mucositis, esophagitis, cardiotoxicity); toxicity of chemo- or radioprotectant (including ability to protect tumor); compliance with planned dose/intensity of primary therapy (radiation dose/schedule and chemotherapy dose/schedule); compliance with chemo- or radioprotectant dose/schedule delivery; breaks in treatment; quality of life, or patient-reported outcome (PRO)/symptom tool; cost effectiveness; and disease-free survival, overall survival, or local control rate. The primary outcome of interest was chemotherapy- or radiation therapy–induced toxicity.

An initial article abstract screen was performed by two ASCO staff, who independently reviewed each abstract for inclusion criteria. Disagreements were resolved by consensus. The ASCO panel cochairs reviewed the title lists of included and excluded abstracts, and full-text articles were obtained for each included abstract. Full-text review was undertaken by two ASCO staff, who independently reviewed each article for the inclusion criteria. Again, disagreements were resolved by consensus. Each article meeting the inclusion criteria underwent data extraction for patient characteristics, study design and quality, intervention, and outcomes, including adverse events. Evidence summary tables were developed based on data extracted from studies meeting the criteria for inclusion.

RESULTS

Literature Search

Preliminary searches identified 744 potential randomized controlled trials. The abstract screen eliminated 643 abstracts that failed to meet any of the inclusion criteria or were duplicates resulting from searching across more than one database. The remaining 101 reports were reviewed in full for the interventions and outcomes described above. Sixty-two reports were excluded at the full-text review stage; the most common reasons for exclusion included nonrandomized study designs or no report of original data (ie, the report was a review of previously reported trials). Thirty-nine reports met the inclusion criteria and underwent data extraction.

Of these 39 reports, three articles reported on two studies of palifermin; three articles reported on two studies of dexrazoxane, and 33 articles reported on 31 studies in amifostine. No randomized controlled trials of mesna published since 2002 were identified.

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Table 1. Summary of Updated Recommendations for Use of Chemo- and Radioprotectants

Recommendation Category	2008 Recommendation
Use of dexrazoxane	
Breast cancer	
Initial use in patients with metastatic breast cancer	No change from 2002; it is recommended that dexrazoxane not routinely be used for patients with metastatic breast cancer receiving initial doxorubicin-based chemotherapy
Delayed use in patients with metastatic breast cancer who have received more than 300 mg/m^2 of doxorubicin	No change from 2002; it is suggested that the use of dexrazoxane be considered for patients with metastatic breast cancer who have received more than 300 mg/m^2 of doxorubicin in the metastatic setting and who may benefit from continued doxorubicin-containing therapy; treatment of patients who received more than 300 mg/m^2 in the adjuvant setting and are now initiating doxorubicin-based chemotherapy in the metastatic setting should be individualized, with consideration given to the potential for dexrazoxane to decrease response rates as well as decreasing the risk of cardiac toxicity; these patients were not included in the clinical trials of dexrazoxane
Use in patients receiving adjuvant chemotherapy for breast cancer	No change from 2002; the use of dexrazoxane in the adjuvant setting is not suggested outside of a clinical trial
Other malignancies	
Use in adult patients with other malignancies	No change from 2002; the use of dexrazoxane can be considered in adult patients who have received more than 300 mg/m^2 of doxorubicin-based therapy; caution should be exercised in the use of dexrazoxane in settings in which doxorubicin-based therapy has been shown to improve survival
Use in pediatric malignancies	No change from 2002; there is insufficient evidence to make a recommendation for the use of dexrazoxane in the treatment of pediatric malignancies
Other anthracycline doses and schedules	
Use in patients receiving other anthracyclines or other anthracycline dose schedules	No change from 2002; on the basis of the available data and extrapolations from the experience with doxorubicin plus dexrazoxane, the use of dexrazoxane may be considered for patients responding to anthracycline-based chemotherapy for advanced breast cancer and for whom continued epirubicin therapy is clinically indicated; data for using dexrazoxane with epirubicin for treatment of other cancers are limited; data are insufficient to make a recommendation regarding the use of dexrazoxane with other potentially cardiotoxic agents
Use in patients receiving high-dose anthracycline therapy	There are no new data addressing the use of dexrazoxane, and there are no new data regarding the clinical use of high-dose anthracyclines; thus, the panel has elected to delete this particular guideline statement, since its clinical relevance appears limited
Use in patients with cardiac risk factors	No change from 2002; there is insufficient evidence on which to base a recommendation for the use of dexrazoxane in patients with cardiac risk factors or underlying cardiac disease
Monitoring therapy	
Termination of anthracycline therapy for patients receiving dexrazoxane	No change from 2002; patients receiving dexrazoxane should continue to undergo cardiac monitoring; after cumulative doxorubicin doses of 400 mg/m^2, cardiac monitoring should be frequent; the panel suggests repeating the monitoring study after 500 mg/m^2 and subsequently after every 50 mg/m^2 of doxorubicin; the panel suggests that the termination of dexrazoxane/doxorubicin therapy be strongly considered in patients who develop a decline in LVEF to below institutional normal limits or who develop clinical congestive heart failure
Dose of dexrazoxane	No change from 2002; it is suggested that patients who are being treated with dexrazoxane receive dexrazoxane at a ratio of 10:1 with the doxorubicin dose, given by slow IV push or short IV infusion, 15 to 30 minutes before doxorubicin or epirubicin administration; a ratio of 10:1 with the epirubicin dose may be reasonable; however, it should be noted that the optimal dose ratio has not been determined
Use of amifostine	
Chemotherapy-associated toxicities	
Nephrotoxicity	No change from 2002; amifostine may be considered for the prevention of nephrotoxicity in patients receiving cisplatin-based chemotherapy
Neutropenia	While the use of amifostine may be considered for reduction of the incidence of grade 3 and 4 neutropenia associated with chemotherapy, the clinician may reasonably consider alternative strategies such as the use of myeloid growth factor support or chemotherapy dose reduction to ameliorate neutropenia
Thrombocytopenia	The panel recommends against the use of amifostine for protection against thrombocytopenia in patients receiving chemotherapy or radiation therapy
Neurotoxicity and ototoxicity	Present data are insufficient to support the routine use of amifostine for the prevention of platinum-associated neurotoxicity or ototoxicity
Paclitaxel-associated neurotoxicity	Data are insufficient to support the routine use of amifostine for the prevention of paclitaxel-associated neuropathy
Dose and administration of amifostine with chemotherapy	The current FDA-approved dose of amifostine is 910 mg/m^2 IV over 15 minutes, 30 minutes prior to chemotherapy; familiarity with the package insert and close patient monitoring during the infusion are required; common toxicities include acute hypotension, nausea, and fatigue
Radiation therapy-associated toxicities	
Xerostomia	The use of amifostine may be considered to decrease the incidence of acute and late xerostomia in patients undergoing fractionated radiation therapy alone for head and neck cancer; current data do not support the routine use of amifostine with concurrent platinum-based chemoradiotherapy for head and neck cancer
Mucositis	Data are insufficient to recommend amifostine to prevent mucositis associated with radiation therapy for head and neck cancer
Esophagitis*	Data are insufficient to recommend the routine use of amifostine to prevent esophagitis in patients receiving concurrent chemoradiotherapy for non–small-cell lung cancer
Dose and administration of amifostine with radiation therapy	No change from 2002; when given with radiation therapy, the recommended amifostine dose is 200 mg/m^2/day, given as a slow IV push over 3 minutes, 15 to 30 minutes before each fraction of radiation therapy; administration of amifostine requires close patient monitoring, but adverse effects are fewer at this lower dose; many patients require antiemetics; blood pressure should be measured just before and immediately after the 3-minute amifostine infusion; the hypotension associated with amifostine at this dose is less frequent but still requires close monitoring

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Table 1. Summary of Updated Recommendations for Use of Chemo- and Radioprotectants (continued)

Recommendation Category	2008 Recommendation
Use of palifermin*	
Autologous hematopoietic stem-cell transplantation	Palifermin is recommended for use in patients undergoing autologous stem-cell transplantation for a hematologic malignancy with a total body irradiation conditioning regimen to decrease the incidence of severe mucositis; there are insufficient data to recommend the routine use of palifermin for patients undergoing autologous stem-cell transplantation for a hematologic malignancy where the conditioning regimen is chemotherapy only
Allogeneic hematopoietic stem-cell transplantation	Palifermin may be considered for use in patients undergoing myeloablative allogeneic hematopoietic stem-cell transplantation with a total body irradiation–based conditioning regimen; there are insufficient data to recommend its use in myeloablative conditioning regimens consisting of chemotherapy alone in this setting
Dose and administration of palifermin with hematopoietic stem-cell transplantation	Palifermin should be administered intravenously at 60 μg/kg daily for 3 days preceding the start of the conditioning regimen and 60 μg/kg daily for 3 days beginning on the day of stem-cell infusion; it should not be administered within 24 hours of the initiation of the conditioning regimen
Non–stem-cell transplantation and solid tumors	There are insufficient data to recommend the use of palifermin in the non–stem-cell transplantation setting, or for use in the treatment of solid tumors
Use of mesna	
With ifosfamide	
Mesna dosing with standard-dose ifosfamide	No change from 2002; it is suggested that the daily dose of mesna be calculated to equal 60% of the total daily dose of ifosfamide, administered as three bolus doses given 15 minutes before and 4 and 8 hours after administration of each dose of ifosfamide, when the ifosfamide dose is less than 2.5 g/m^2/day administered as a short infusion; for use with continuous-infusion ifosfamide, mesna may be administered as a bolus dose equal to 20% of the total ifosfamide dose followed by a continuous infusion of mesna equal to 40% of the ifosfamide dose, continuing for 12 to 24 hours after completion of the ifosfamide infusion
Mesna dosing with high-dose ifosfamide	No change from 2002; there is insufficient evidence on which to base a recommendation for the use of mesna with ifosfamide doses in excess of 2.5 g/m^2/day; the efficacy of mesna for urothelial protection with very high-dose ifosfamide has not been established; given the longer half-life of ifosfamide in these dosages, more frequent and prolonged mesna dosage regimens may be necessary for maximum protection from urotoxicity
Mesna administration by the oral route	No change from 2002; mesna tablets have been approved by the FDA to prevent hemorrhagic cystitis in patients receiving ifosfamide chemotherapy; the recommended dose and schedule is to administer mesna as an IV bolus injection in a dosage equal to 20% of the ifosfamide dosage (weight/weight) at the time of ifosfamide administration; mesna tablets are given orally in a dosage equal to 40% of the ifosfamide dose at 2 and 6 hours after each dose of ifosfamide; the total daily dose of mesna is 100% of the ifosfamide dose; patients who vomit within 2 hours of taking oral mesna should repeat the dose or receive IV mesna; the dosing schedule should be repeated on each day that ifosfamide is administered
Mesna use with cyclophosphamide	No change from 2002; mesna plus saline diuresis or forced saline diuresis is recommended to decrease the incidence of urothelial toxicity associated with high-dose cyclophosphamide in the setting of stem-cell transplantation
Surveillance of patients receiving ifosfamide and/or cyclophosphamide and mesna	No change from 2002; there are insufficient data to make a recommendation regarding specific monitoring for hemorrhagic cystitis in patients receiving mesna to ameliorate ifosfamide or high-dose cyclophosphamide–associated urothelial toxicity; recommendations for monitoring reflect the design of clinical trials involving mesna use and the opinion of the panel

Abbreviations: LVEF, left ventricular ejection fraction; IV, intravenous; FDA, US Food and Drug Administration.
*This topic is new to the guideline.

Limitations of the Literature

Overall, the quality of the published literature was limited. Many trials failed to adequately document allocation concealment or the conduct of an intention-to-treat analysis, and the majority of trials lacked a placebo in the control arm. Due to the subjective nature of many of the end points studied, placebo control is critical for reliable results. Many trials also measured end points repeatedly over time, and different instruments or assessment tools were used for assessing the same outcome across trials.

GUIDELINES FOR THE USE OF DEXRAZOXANE

All but one of the recommendations concerning the use of dexrazoxane remain unchanged from the previous update, and can be found in Table 1. The one minor change consisted of deleting the guideline statement pertaining to dexrazoxane use in patients receiving high-dose anthracycline therapy, as no new data addressing the use of dexrazoxane in this setting were identified; further, also not identified were new data regarding the clinical use of high-dose anthracyclines. Therefore, the panel elected to delete this particular guideline statement.

GUIDELINES FOR THE USE OF AMIFOSTINE

Amifostine Use in Chemotherapy-Associated Toxicity

Nephrotoxicity: 2008 recommendation. Amifostine may be considered for the prevention of nephrotoxicity in patients receiving cisplatin-based chemotherapy. No change from 2002.

Literature update and discussion. There are no new data on which to base a change in the prior recommendation. None of the studies identified since 2002 examined the occurrence of nephrotoxicity in patients receiving amifostine.

Neutropenia: 2008 recommendation. While the use of amifostine may be considered for reduction of the incidence of grade 3 and 4 neutropenia associated with chemotherapy, the clinician may reasonably consider alternative strategies such as the use of myeloid growth factor support or chemotherapy dose reduction to ameliorate neutropenia. [This represents a change from the 2002 recommendation.]

Literature update and discussion. Since the 2002 update, 11 randomized controlled trials have reported outcomes for neutropenia in studies examining amifostine use with chemotherapy or chemoradiotherapy (Table 2).[1-11] Ten of these trials were performed in an adult

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Table 2. Randomized Controlled Trials of AMF Use in CT or CRT Reporting Neutropenia As an Outcome

Reference	No. of Patients	Malignancy Planned Primary Therapy	Assessment	Neutropenia Criteria/Outcomes Assessed	Results
Antonadou, 2002[1]	50	Head and neck CRT: carboplatin	Weekly for 7 weeks; at 4 weeks and 8 weeks follow-up	ANC (grades 0-4)	All NS For weeks 2, 3, 4, 5, 6, 7, and follow-up at weeks 4 and 8, respectively, $P = .119$, .455, .381, .948, .491, .869, .443, and .511
Antonadou, 2003[2]	73	NSCLC (stages IIIA-B) CRT: paclitaxel or carboplatin (as radiosensitizer)	Weekly	ANC $< 1.3 \times 10^9$/L	All NS XRT + paclitaxel, $P = .391$ (n = 2 AMF arm; n = 4 control arm) XRT + carboplatin, $P = .287$ (n = 6 AMF arm; n = 9 control arm)
Bernstein, 2006[3]*	69	Ewing sarcoma or PNET CT: ifosfamide, etoposide alternated with vincristine, doxorubicin, cyclosphosphamide	Weeks 6, 12, 18	Days (mean) ANC less than 500/uL	All NS AMF arm, weeks 6, 12, and 18, respectively: 4.80, 6.30, 6.03 Control arm, weeks 6, 12, and 18, respectively: 4.41, 6.23, 6.69
Gold, 2003[4]	30	Mixed gynecological, ACUPS (majority ovarian) CT: topotecan	Every 3 to 4 days during weeks 2 and 3 of each cycle	All treatment cycles, grade 4 neutropenia All treatment cycles, grade 3 and 4 neutropenia ANC nadir (mean)	AMF, 17%; control, 37%; $P = .02$ AMF, 38%; control, 67%; $P = .003$ AMF, 1,763; control, 844; $P = .0003$
Hwang, 2004[5]	60	Mixed hematologic Allo-HSCT CT: busulfan, cyclophosphamide; some patients received CyTBI or etoposide; cyclosporine and methotrexate for GVHD prophylaxis	Daily until white cell (ANC > 500/uL) and platelet recovery	Grades 3-4 neutropenia Days to neutrophil engraftment (neutrophil count of $> 500/mm^3$) Note: all patients received G-CSF until ANC $> 500/cm^3$	NS; all patients in both arms had grade 3-4 AMF group, median 20 days (range, 14-21 days) Control group, median 17 days (range, 11-27 days; P = NS)
Kanat, 2003[6]	38	NSCLC (stages IIIA-IV) CT: paclitaxel, carboplatin	Weekly during treatment	Grades 3-4 neutropenia (no. of cycles) Note: CSF used for ANC < 500/uL or neutropenic fever	AMF arm, 19 cycles (16.6%); control arm, 11 cycles (9.6%); $P = .16$
Komaki, 2004[7]	62	NSCLC (stages II, IIIA, IIIB) CRT: etoposide, cisplatin	Weekly CBC during treatment; at 1 month and 3 months post-treatment; every 3 months for 2 years; then every 6 months	Granulocytopenia Neutropenic fever	AMF, 10%; control, 23%; $P = .167$ AMF, 16%; control, 39%; $P = .046$
Leong, 2003[8]	60 (placebo control)	NSCLC (stage IIIA-IIIB) CRT: carboplatin, paclitaxel	Not clear	Grade 3-4 neutropenia	AMF, 52%; control, 44%; P = NS
Lorusso, 2003[9]	187	Ovarian cancer CT: carboplatin, paclitaxel	Weekly	Grade 3-4 neutropenia, all cycles Note: G-CSF allowed only in patients developing prolonged grade 4 neutropenia or febrile neutropenia	AMF, 31.3%: control, 37.9%; $P = .03$
Movsas, 2005[10] (RTOG 98-01)	243	NSCLC (stage II to IIIA/B) CRT: carboplatin, paclitaxel	NR	Infection or FN, induction CT Infection or FN, ≤ 90 days from start of CRT	Grade 3-4: AMF, 1%; control, 4%; P = NS AMF, grades 1, 2, 3, 4, 5, respectively: 2%, 8%, 9%, 2%, 1% Control, grades 1, 2, 3, 4, 5, respectively: 1%, 3%, 3%, 0%, 1% (favors control arm, $P = .03$)
Spencer, 2005[11]	90	Multiple myeloma Auto-SCT CT: melphalan	NR	Days to neutropenia ($< 0.5 \times 10^9$/L) Count recovery Median duration (days) of severe neutropenia Note: filgrastim from day +1 post–stem-cell re-infusion until ANC exceeded 1.0×10^9/L	AMF, median, 5% (range, 4%-6%) Control, median, 5% (range, 3%-8%; P = NS) AMF, median, 10% (range, 5%-22%) Control, median, 10% (range, 8%-57%; P = NS) AMF, 3; control, 5; P = NS

Abbreviations: AMF, amifostine; CT, chemotherapy; CRT, chemoradiotherapy; ANC, absolute neutrophil count; NS, no significant difference; NSCLC, non–small-cell lung cancer; XRT, radiation therapy; PNET, primitive neuroectodermal tumor; ACUPS, adenocarcinoma of unknown primary site; Allo-HSCT, allogeneic hematopoietic stem-cell transplantation; G-CSF, granulocyte colony-stimulating factor; CyTBI, cyclophosphamide/total body irradiation; GVHD, graft versus-host disease; NR, not reported; FN, febrile neutropenia; Auto-SCT, autologous stem-cell transplantation; RTOG, Radiation Therapy Oncology Group.

*Pediatric study.

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population; one studied the use of amifostine in a pediatric population.[3] Most of these trials did not have neutropenia as a primary end point, but data on neutropenia were available in the published results. The majority of trials (n = 9) enrolled fewer than 100 patients. Two trials[9,10] enrolled 187 and 243 patients, respectively.

Neutropenia was generally defined in these studies by the National Cancer Institute Common Toxicity Criteria (CTC) grade. Other neutropenic end points included the number of days absolute neutrophil count (ANC) was less than 500/uL, ANC nadir, time to neutropenia, time to count recovery, or median duration of severe neutropenia. Other outcomes reported included rates of infection or febrile neutropenia.

The majority of studies reported no significant differences in rates of neutropenia, but most included small numbers of participants. In the largest study reporting data on grades 3 to 4 neutropenia,[9] conducted in 187 patients with ovarian cancer, a significant difference in grades 3 to 4 neutropenia across all chemotherapy cycles was found, in favor of amifostine ($P = .03$). In this study, granulocyte colony-stimulating factor was allowed only in patients developing prolonged (ANC $<$ 500/uL for $\geq$ 3 days) grade 4 neutropenia or febrile neutropenia. Among the trials enrolling fewer than 100 patients, one other study conducted in patients with predominantly ovarian cancer receiving topotecan also showed a significant difference in grades 3 and 4 neutropenia ($P = .003$) across all chemotherapy treatment cycles.[4] Additionally, the mean ANC nadir was significantly lower in patients in the control arm ($P = .0003$).

The one other large trial,[10] RTOG 98-01, enrolled 243 patients with non–small-cell lung cancer receiving chemotherapy plus hyperfractionated radiation. This trial reported no significant difference in infection or febrile neutropenia between study arms during induction chemotherapy, but noted a significant ($P = .03$) difference in favor of the no-amifostine arm in these parameters at 90 days or less from the start of chemoradiotherapy.

Across all studies considered, reports of benefit, specifically lower frequencies of grades 3 to 4 neutropenia were inconsistent. However, because the eight small trials reporting no difference in rates of neutropenia were all limited by sample size (range, 38 to 90), and the one large trial reporting rates of grade 3 to 4 neutropenia showed a significant difference, the Panel continues to recommend that amifostine may be considered for reduction of the incidence of grade 3 and 4 neutropenia associated with chemotherapy. Alternative strategies, including myeloid growth factor support and chemotherapy dose reduction, are also reasonable options, particularly in light of the potential negative effect amifostine may have on platelets.

Thrombocytopenia: 2008 recommendation. The panel recommends against the use of amifostine for protection against thrombocytopenia in patients receiving chemotherapy or radiotherapy. [This represents a change from the 2002 recommendation.]

Literature update and discussion. Since the 2002 update, 10 randomized controlled trials have reported outcomes for thrombocytopenia in studies examining amifostine use with chemotherapy, combined chemoradiotherapy or radiation therapy (Table 3).[2-6,8,9,11-13] While not all of these trials reported thrombocytopenia as a primary end point, information provided on thrombocytopenia was collected for each trial reporting. Outcomes assessed in these trials included thrombocytopenia (defined by various platelet counts), percent of treatment cycles with thrombocytopenia, mean platelet nadir for all cycles, mean percent decrease from baseline in each cycle, median time to platelet recovery, or time to thrombocytopenia.

Seven of these trials reported no significant differences in thrombocytopenia between patients receiving or not receiving amifostine.[2,3,5,6,8,11,13] Two reported a mix of nonsignificant outcomes and outcomes significantly favoring the control arms without amifostine.[4,12] The remaining study[9] reported an outcome favoring the control group.

The study by Gold et al,[4] which randomly assigned patients with gynecologic malignancies (the majority with ovarian cancer) receiving topotecan plus amifostine or topotecan alone, found no significant differences between arms in mean platelet nadir for all cycles, or for frequency of grades 3 to 4 thrombocytopenia. However, the rate for grades 1 to 4 thrombocytopenia was 78% in the amifostine arm, compared with 55% in the control arm ($P = .02$). In the study by De Vos et al,[12] patients with ovarian cancer were randomly assigned to receive paclitaxel and carboplatin, with or without amifostine. There was no significant difference between arms in mean percent decrease of platelet count from baseline. The study found a significant difference in the percent of cycles with thrombocytopenia grade 0 versus grades 1 to 2 versus grades 3 to 4 (overall, $P < .01$) favoring the no-amifostine arm.

The remaining study, the largest trial identified,[9] reported higher rates of grades 3 to 4 thrombocytopenia in patients receiving amifostine ($P = .001$).

The results of these studies led the panel to strengthen its recommendation against use of amifostine for the prevention of thrombocytopenia associated with chemotherapy. The panel expanded its recommendation to encompass chemotherapy generally, and added a recommendation against use of amifostine with radiation therapy for prevention of thrombocytopenia.

Neurotoxicity and ototoxicity: 2008 recommendation. Present data are insufficient to support the routine use of amifostine for the prevention of platinum-associated neurotoxicity or ototoxicity. [This represents a change from the 2002 recommendation.]

Literature update and discussion. Since the 2002 update, five randomized controlled trials that reported amifostine use for the prevention of neurotoxicity, ototoxicity, or both, as outcomes in patients receiving platinum drugs were identified.[6,8,12,14,15] Table 4 provides details on the study characteristics and outcomes reported.

A study in 90 patients with ovarian cancer receiving paclitaxel and carboplatin showed mixed results.[12] Neurologic parameters that showed no difference with the use of amifostine included freedom from neurotoxicity and neurotoxicity scores derived from patient quality of life questionnaires. A difference was seen in sensory neurotoxicity across all cycles, with grade 1 toxicity reported in 48% of the amifostine arm and 45% of the control arm, and grade 2 toxicity reported in 2% of the amifostine arm and 12% of the control arm (overall, $P < .001$). However, there was no significant difference in the frequencies of grade 1, 2, or 3 neurotoxicity at the end of six cycles of therapy (grade 1: amifostine, 69%, control, 55%; grade 2: amifostine, 7%, control, 27%; grade 3: amifostine, 7%, control, 4%).

In another small study,[6] 38 patients with non–small-cell lung cancer receiving paclitaxel and carboplatin were randomly assigned to amifostine or control, with neurologic and audiologic tests performed at baseline and after the sixth treatment cycle; audiologic tests were also performed after the third treatment cycle. The neurologic and audiologic assessments comprised a battery of tests (Table 4), but

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Table 3. Randomized Controlled Trials of AMF Use in CT or CRT Reporting Thrombocytopenia As an Outcome

Reference	No. of Patients	Planned Primary Therapy	Malignancy	Assessment	Thrombocytopenia Criteria/Outcomes Assessed	Results
Antonadou, 2003[2]	73	CRT: paclitaxel or carboplatin (as radiosensitizer)	NSCLC (stages IIIA-B)	Weekly	Platelets $< 100 \times 10^9$/L	XRT + paclitaxel, $P = .216$ (n = 0 AMF arm; n = 2 control arm) XRT + carboplatin, $P = .075$ (n = 5 AMF arm; n = 10 control arm)
Bernstein, 2006[3*]	69	CT: ifosfamide, etoposide alternated with vincristine, doxorubicin, cyclophosphamide	Ewing's sarcoma or PNET	Weeks 6, 12, 18	Platelets < 50,000/uL	Weeks 6, 12, and 18, respectively: AMF, 2.77, 6.42, 7.43; control, 2.84, 7.33, 10.27; P = NS
De Vos, 2005[12]	90	CT: paclitaxel and carboplatin	Ovarian cancer (stages IC-III)	Days 1 and 14 of each cycle	% of cycles with grades 0 *v* 1-2 *v* 3-4 thrombocytopenia	Grade 0, 1-2, 3-4, respectively: AMF, 46, 50, 4; control, 72, 27, 1; overall $P < .01$
					Mean % decrease from baseline in each cycle	Cycles 2, 3, 4, 5, 6, respectively: AMF, 28, 30, 31, 35, 32; control, 27, 25, 31, 32, 28; P = NS
Gold, 2003[4]	30	CT: topotecan	Mixed gynecological, ACUPS (majority ovarian)	Every 3 to 4 days during weeks 2 and 3 of each cycle	Mean platelet nadir for all cycles	$P = .16$ (no other statistics reported)
					Grade 3-4 thrombocytopenia	AMF, 11%; control, 16%; P = NS
					Grade 1-4 thrombocytopenia	AMF, 78%; control, 55%; odds ratio, 0.35; 95% CI, 0.13 to 0.89; $P = .02$
Hwang, 2004[5]	60	Allo-HSCT CT: busulfan, cyclophosphamide; some pts received CyTBI or etoposide; cyclosporine and methotrexate for GVHD prophylaxis	AML, ALL, MDS, CML, SAA, lymphoma	Daily until platelet count recovery (> 20,000/uL)	Median time to platelets $> 20{,}000/mm^3$	AMF, 23 (range, 10-33); control, 20 (range, 10-41; P = NS); all patients in both arms had thrombocytopenia requiring transfusion support
Kanat, 2003[6]	38	CT: paclitaxel, carboplatin	NSCLC (stages IIIA-IV)	Weekly during treatment	Grades 3-4 thrombocytopenia	NS; no grade 3-4 in either arm
Leong, 2003 (placebo-control) [8]	60	CRT: carboplatin, paclitaxel	NSCLC (stage IIIA-IIIB)	Not clear	Grade 3-4 thrombocytopenia	NS; no grade 3-4 in either arm
Lorusso, 2003[9]	187	CT: carboplatin, paclitaxel	Ovarian cancer	Weekly	Grade 3-4 thrombocytopenia, all cycles	AMF: 3.3%; control: 0.6%; $P = .001$, in favor of control group
Spencer, 2005[11]	90	Auto-SCT	Multiple myeloma	NR	Median duration of severe thrombocytopenia (days)	AMF, 4; control, 5; P = NS
						AMF, 7 (range, 1-11); control, 8 (range, 0-12); P = NS
					Time to thrombocytopenia (days)	For platelets $> 20 \times 10^9$: AMF, 13 (range, 9-36); control, 11 (range, 9-54); P = NS
		CT: melphalan			Recovery of counts (days)	For platelets $> 50 \times 10^9$: AMF, 15 (range, 10-47); control, 14.5 (range, 7-49); P = NS
Veerasarn, 2006[13]	67	XRT	Head and neck cancer	NR	Grades 3-4 hematologic toxicity	NS; none in either arm

Abbreviations: AMF, amifostine; CT, chemotherapy; CRT, chemoradiotherapy; NSCLC, non–small-cell lung cancer; XRT, radiation therapy; PNET, peripheral neuroectodermal tumor; NS, no significant difference; ACUPS, adenocarcinoma of unknown primary site; Allo-HSCT, allogeneic hemotopoietic stem-cell transplantation; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; MDS, myelodysplastic syndrome; CML, chronic myelogenous leukemia; SAA, severe aplastic anemia; CyTBI, cyclophosphamide/total body irradiation; GVHD, graft-versus-host disease; Auto-SCT, autologous stem-cell transplantation; NR, not reported.

*Pediatric study.

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Table 4. Randomized Controlled Trials of AMF Use in CT or CRT Reporting Neurotoxicity/Ototoxicity (platinum-based treatment) As an Outcome

Reference	Study Characteristics	Assessment Criteria/Outcomes Assessed	Results (*P*)
De Vos, 2005[12]	AMF *v* no AMF N = 90 CT: paclitaxel and carboplatin Ovarian cancer (stages IC-III)	Sensory neurotoxicity, all cycles: grade 1: AMF, 48%; control, 45%; grade 2: AMF, 2%; control, 12%	Overall, < .001
		Freedom from neurotoxicity, all cycles: AMF, 49%; control, 40%	NS
		Per individual patient after 6 tx cycles: grade 1: AMF, 69%; control, 55%; grade 2: AMF, 7%; control, 27%; grade 3: AMF, 7%; control, 4%	Overall, NS
		Neurotoxicity scores (moderate and severe, respectively) from QOL questionnaires: fatigue: AMF, 28% and 10%; control, 31% and 22%; paresthesia: AMF, 28% and 22%; control, 41% and 15%; weakness: AMF, 21% and 6%; control, 18% and 12%; difficulty writing: AMF, 3% and 6%; control, 13% and 9%; difficulty walking: AMF, 9% and 9%; control, 19% and 13%	All NS
Glover, 2003[14]	AMF *v* no AMF N = 94 CT: cisplatin (120 mg/m^2 in control arm, 150 mg/m^2 in AMF arm) Melanoma (metastatic)	Severe or worse neurological events: grade 3: AMF, n = 8; control, n = 3; grades 4 or 5, 0 in both arms	NR
		Of 11 patients with grade 3, seven suffered severe hearing loss or required a hearing aid: DTRs diminished: AMF, 29%; control, 33%; vibratory sensation diminished: AMF, 22%; control, 25%; position sensation diminished: AMF, 11%; control, 10%; other abnormal neurological signs: AMF, 25%; control, 21%; paresthesia: AMF, 33%; control, 21%; motor function diminished: AMF, 13%; control, 6%	
Kanat, 2003[6]	AMF *v* no AMF	Audiologic tests* performed at baseline and after 3rd and 6th treatment cycle; neurologic tests† performed at baseline and after 6th treatment cycle	
	N = 38	Grade 1 or 2 paresthesia after 6th cycle: AMF, 8/19; control, 18/19	.018
	CT: paclitaxel, carboplatin	Grade 2 sensory motor impairment during treatment: AMF, 2/19; control, 9/18	.029
	NSCLC (stages IIIA-IV)	Audiologic testing and other tests (repeated after 3rd and 6th cycles)	NS
		Nerve conduction studies pre-and post-treatment: AMF, no difference in any motor or sensory parameter; control, significant decrease in mean motor conduction velocity of right peroneal nerve	AMF, NS control, .04 for right peroneal; NS for all else
		Grade 3 or 4 clinical neurotoxicity not observed in any patient; no patient reported vertigo, tinnitus, or hearing loss	
Hilpert, 2005[15]	AMF *v* placebo	Assessment performed at registration, after each cycle, and at 3- and 6-month follow-up	
	N = 72	Max VPT, hands: AMF, 3.18 μm, after 5 cycles; placebo, 3.83 μm, after 6 cycles	.0114‡
	Paclitaxel, carboplatin ± epirubicin		
	Ovarian cancer	Max VDT, hands: AMF, 2.75 μm, after 6 cycles; placebo, 2.93 μm, at 3-month follow-up	.0038
		Recovery of threshold values to baseline: AMF 6-month follow-up; placebo persisted with pathological values	
		Max VPT, feet: AMF, 5.25 μm, after 6 cycles; placebo, 11.88 μm, after 3-month follow-up	.0015
		Max VDT, feet: AMF, 5.42 μm, after 6 cycles; placebo, 8.61 μm, after 6 cycles	.0012
		Recovery of threshold values to baseline at 6-month follow-up reached in AMF group but not placebo group	
		TPD 1.5 cm, back of hand	.0094
		TPD, all other§	NS
		Sensory neuropathy (NCI CTC): grade 1: AMF, 49%; control, 44%; grades 2-4: AMF, 30%; control, 47%	.0103
		Patient questionnaire on cumulative incidence of motor activity disorders‖ (percent of cycles) to 6-month follow-up	All NS
		Patient questionnaire on cumulative incidence of sensory neuropathic symptoms** (percent of cycles) to 6-month follow-up	All NS, except loss of skillfulness (*P* = .04 in favor of AMF)
Leong, 2003[8]	AMF *v* placebo	Nerve conduction tests performed before and after treatment††	NS
	N = 60	Overall, 72 neurophysiologic parameters before and after treatment	NS
	CRT: paclitaxel, carboplatin NSCLC (stage III)		

Abbreviations: AMF, amifostine; CT, chemotherapy; CRT, chemoradiotherapy; NS, no significant difference; NR, not reported; DTRs, deep tendon reflexes; NSCLC, non–small-cell lung cancer; VPT, vibration perception threshold; VDT, vibration disappearance threshold; TPD, two-point-discrimination; NCI CTC, National Cancer Institute Common Toxicity Criteria.

*Pure-tone audiometry, short increment sensitivity index, tone decay, speech discrimination, tympanogram, stapes reflex, bi-thermal caloric test, positional tests, and cerebellar tests.

†ENMG laboratory: motor distal latencies and proximal motor conduction velocities measured for bilateral peroneal nerves, right median and left ulnar nerves. Sensory distal latencies and distal sensory conduction velocities and sensory nerve amplitudes were obtained for right median and left ulnar nerves, and right sural nerve with a surface electrode.

‡Multivariate analysis for VPT and VDT; protective effect of AMF.

§Back of hand (10, 5, and 3 cm) and tibia (4 and 10 cm).

‖Walking, walking in the dark, downstairs, upstairs, writing, button on/button up, astereognosis.

**Paresthesia, deafness, prickle, pruritus, pain in extremities, twinges, burning pain, loss of skillfulness.

††Bilateral motor and sensory: median, ulnar, peroneal; bilateral motor tibial; bilateral sensory, sural. Recorded proximal and distal latency, nerve conduction velocity, and motor and sensory action potential amplitude.

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significant differences favoring amifostine were seen only in grade 2 sensory motor impairment during chemotherapy ($P = .029$) and in one element of the nerve conduction studies. In the nerve conduction studies (four motor, three sensory), pre- and post-treatment for both groups showed no significant changes over the course of treatment, with the exception of right peroneal nerve conduction velocity in the control group, which decreased during treatment ($P = .04$). Grade 1 or 2 paresthesia after the sixth cycle of chemotherapy occurred in eight of 19 patients in the amifostine group, and 18 of 19 patients in the control group ($P = .018$). Audiologic testing showed no significant difference at any point in time, and no patient reported vertigo, tinnitus, or hearing loss. Grade 3 or 4 clinical neurotoxicity was not observed in any patients.

In one of the two placebo-controlled trials identified since the 2002 update, 72 patients with ovarian cancer receiving paclitaxel and carboplatin were randomly assigned to receive epirubicin or no third chemotherapy agent, and randomly assigned to receive amifostine or placebo.[15] The effect of amifostine treatment on neurotoxicity was assessed with objective testing and subjective patient questionnaires. While this study reported mixed results, consistent differences in vibration thresholds on the hands and feet were seen. Other assessments showed little or no difference with the use of amifostine. Significant differences in favor of amifostine were reported for maximum vibration perception thresholds and maximum vibration disappearance thresholds for both the hands and feet. Also statistically significant was two-point discrimination on the back of the hand (1.5 cm). However, two-point discrimination for all other areas and distances (back of hand, 10, 5, and 3 cm; tibia, 10 and 4 cm) showed no difference between amifostine and placebo arms. Grade 1 sensory neuropathy was reported in 49% of the amifostine group and 44% of the control group; grades 2 to 4 were reported in 30% and 47% of the amifostine and control groups, respectively ($P = .0103$). A patient questionnaire on sensory neuropathy symptoms addressed eight domains, and all showed nonsignificant differences with the exception of "loss of skillfulness," which favored amifostine ($P = .04$). Another questionnaire on motor activity disorders found no significant difference in seven domains.

The second placebo-controlled trial was conducted in 60 patients with unresectable stage III non–small-cell lung cancer.[8] This study found no difference between patients randomly assigned to amifostine or placebo in nerve conduction studies conducted before and after treatment, or overall in 72 neurophysiologic parameters measured.

The publication by Glover et al,[14] conducted in 94 patients with metastatic melanoma, did not provide statistical analysis of the results reported. Moreover, patients in the control arm (without amifostine) received cisplatin at a dose of 150 mg/m^2, while patients in the amifostine arm received cisplatin at a dose of 120 mg/m^2. Grade 3 neurological events occurred in eight patients in the amifostine group, and in three of the control group. Of these 11 patients, seven suffered severe hearing loss or required a hearing aid. No patients experienced grades 4 or 5 neurological toxicity. Other reported outcomes were mixed with respect to amifostine effectiveness: more patients in the control group experienced diminished deep tendon reflexes and vibratory sensation, while more patients in the amifostine group experienced diminished joint position sense and motor function, other abnormal neurological signs, and paresthesias.

A meta-analysis published in 2007[16] examined the efficacy of chemoprotective agents, including amifostine, to prevent or limit the neurotoxicity of cisplatin and related compounds. Of the five (n = 541) amifostine trials reviewed, one used quantitative sensory testing and demonstrated a favorable outcome for amifostine use. However, this result was based on only 14 patients receiving amifostine. The authors concluded that data were insufficient to conclude if amifostine prevented or limited platinum-associated neurotoxicity.

The trials published since the 2002 update, while showing some evidence of improvement in certain areas, have inconsistent results, and the clinical significance of these findings is unclear. One placebo-controlled trial showed maximum vibration perception and disappearance thresholds to be significantly improved with amifostine, but reported no difference in 14 of 15 PROs, and a significant difference in only one of six two-point discrimination tests. The second randomized, placebo-controlled trial reported no difference in 72 neurophysiologic measures tested. Overall, these studies do not support a change to the existing recommendation, which does not support the routine use of amifostine to prevent cisplatin-associated neurotoxicity or ototoxicity. The data do, however, warrant generalizing the recommendation to include carboplatin-associated neurotoxicity and ototoxicity, since four of five trials identified since the 2002 update utilized carboplatin instead of cisplatin. Current data do not support routine use of amifostine to prevent neurotoxicity and/or ototoxicity associated with platinum-based therapy.

Paclitaxel-associated neurotoxicity: 2008 recommendation. Data are insufficient to support the routine use of amifostine for the prevention of paclitaxel-associated neuropathy. [This represents a change from the 2002 recommendation.]

Four studies have been reported since the 2002 update that examine the use of amifostine to ameliorate paclitaxel-associated neurotoxicity. All of these studies used a combination of platinum and paclitaxel, and all four are discussed in detail in the Neurotoxicity and Ototoxicity section.[6,8,12,15]

As noted earlier, these studies gave inconsistent results, and one of the two placebo-controlled studies reported negligible differences in patient-reported neurotoxicity outcomes, while the other reported no difference in neurophysiologic parameters, including before- and after-treatment nerve conduction testing. Therefore, the panel concluded that data are insufficient to support routine use of amifostine to prevent taxane-associated neuropathy.

Dose and Administration of Amifostine With Chemotherapy

2008 recommendation. The current US Food and Drug Administration–approved dose of amifostine is 910 mg/m^2 intravenously over 15 minutes, 30 minutes before chemotherapy. Familiarity with the package insert and close patient monitoring during the infusion are required. Common toxicities include acute hypotension, nausea, and fatigue. [This recommendation remains essentially unchanged from the 2002 recommendation.]

Literature update and discussion. This recommendation remains essentially unchanged. The dose and route described in the US Food and Drug Administration–approved label continues to be recommended by the panel, as no new studies comparing different doses or routes of amifostine administration in patients treated with chemotherapy alone were identified.

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Amifostine Use in Radiation Therapy-Associated Toxicities

Xerostomia: 2008 recommendation. The use of amifostine may be considered to decrease the incidence of acute and late xerostomia in patients undergoing fractionated radiation therapy alone for head and neck cancer. Current data do not support the routine use of amifostine with concurrent platinum-based chemoradiotherapy for head and neck cancer. [This represents a change from the 2002 recommendation.]

Literature update and discussion. This recommendation was changed slightly to reflect that amifostine is recommended for consideration in the setting of radiation therapy alone, but not in the setting of concurrent platinum-based chemoradiotherapy. Three new studies were identified that used intravenous (IV) amifostine in the setting of radiation therapy alone in head and neck cancer;[13,17,18] an additional three studies examined IV amifostine use in the setting of platinum-based chemoradiotherapy in head and neck cancer (Table 5).[1,19,20]

All three of the studies conducted in the setting of radiation therapy alone showed significant reductions in grade 2 or greater acute or late xerostomia. PROs also showed significant improvement. For the two studies reporting on saliva production, the smaller study (n = 67) showed no difference in the collection of whole saliva, but the larger study (n = 303) showed a significant increase in the proportion of patients with unstimulated saliva production. In the smaller study, scintigraphy at 1 year showed improved parotid gland function in patients in the amifostine arm. Although none of these trials were placebo controlled, all showed some significant differences in subjective and objective end points. The 2002 guideline update recommended that amifostine be considered to decrease xerostomia in patients undergoing fractionated radiation therapy for head and neck cancer, and results from these three additional studies were felt to warrant a continuation of this consideration in the setting of fractionated radiation therapy alone.

Two additional studies comparing different doses/routes of amifostine in the setting of radiation therapy alone in head and neck cancer are discussed in the Relevant Dose and Administration section.

In the setting of platinum-based chemoradiotherapy, two of three identified studies[1,20] (n = 41, 50) reported significant differences in xerostomia at various time points during the study (Table 5). The largest study (n = 132), however, was the only study with a placebo control, and found no difference in grade 2 or greater acute or late xerostomia.[19] An additional study,[21] published as a preliminary report, used paclitaxel with radiation therapy, and is discussed in the section on mucositis. This study found no effect of amifostine on xerostomia visual analog scores or whole saliva at 3 months postradiotherapy.

Due to the subjectivity of many of the outcome measures employed, interpretation of results from non–placebo-controlled trials should be undertaken with caution. Because the largest trial testing amifostine in the setting of platinum-based chemoradiotherapy was also the only trial that used a placebo in the control group, and it reported no difference between study arms, the panel felt that the weight of the data was not sufficient to recommend the routine use of amifostine in this setting.

Mucositis: 2008 recommendation. Data are insufficient to recommend amifostine to prevent mucositis associated with radiation therapy for head and neck cancer. [This represents a narrowing of the 2002 recommendation.]

Literature update and discussion. This recommendation was changed slightly to specify clearly that data do not support routine use of amifostine for the prevention of mucositis specifically in the setting of radiation therapy for treatment of head and neck cancer. The 2002 guideline stated that data were insufficient to recommend amifostine for prevention of mucositis associated with radiation therapy, without specifying the setting of head and neck cancer. Since 2002, six studies have been published that examined amifostine in the setting of radiation therapy or chemoradiotherapy and reported mucositis as an outcome (Table 6).[1,13,17,19-21]

Of the two studies in the setting of radiation therapy alone, one showed no beneficial effect of amifostine on grade 2 or greater mucositis, and the other showed mixed results, depending on the timing of the assessment.[13,17] Of the four studies examining amifostine use with radiochemotherapy (three platinum-based, one with paclitaxel), three showed no beneficial effects of amifostine on mucositis.[1,19-21] The remaining study, with 50 patients, did show a significant effect of amifostine.[1] The largest study (n = 132), which was also the only placebo-controlled study, showed no difference in grade 3 or greater acute mucositis.[19]

A meta-analysis conducted by Stokman et al[22] included seven randomized trials of amifostine use in the prevention of mucositis. Neither of the radiation therapy–only trials discussed earlier[13,17] were included in the analysis. Pooling of results from all seven studies showed a significant effect of amifostine in the prevention of grades 3 and 4 mucositis. Of the seven trials analyzed, one was conducted in patients receiving chemotherapy only and one was conducted in patients receiving chemotherapy and bone marrow transplant. The remaining five trials were conducted in patients receiving either radiation therapy or chemoradiotherapy. Of the total, five trials were published before 2002, and two were published during or after 2002—the study by Antonadou et al[1] is discussed earlier, and the study by Lorusso et al[9] was conducted in patients with ovarian cancer. The meta-analysis plot reflects that for three of the seven trials, an odds ratio could not be estimated.

A Cochrane meta-analysis[23] identified seven randomized controlled trials of amifostine use in head and neck cancer treated with radiation therapy. Due to the publication date, this meta-analysis did not include the data from the Jellema et al[17] and Veerasarn et al[13] studies. For mild versus moderate to severe mucositis (0 to 1 $v \geq 2$), the pooling of five trials produced a relative risk of 0.84 (95% CI, 0.75 to 0.95) in favor of amifostine; for moderate versus severe mucositis (0 to 2 $v \geq 3$), the pooling of six trials gave a relative risk of 0.60 (95% CI, 0.37 to 0.97). The authors concluded that amifostine provided minimal benefit in preventing moderate and severe mucositis.

A third meta-analysis,[24] which comprised only phase III studies without a placebo control arm, examined the use of amifostine during radiation therapy or chemoradiotherapy in patients with head and neck cancer, thoracic cancer, and pelvic tumors. For the subset of head and neck cancer trials, pooling of five trials (n = 439) showed a significant effect of amifostine on reduction of grade 3 or greater mucositis.

Due to the subjective nature of mucositis end points, and the difficulty of measurement, blinded, placebo-controlled study designs are critical for fair assessment of the efficacy of any intervention to decrease mucositis. With a few exceptions, almost all of the

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Table 5. Randomized Controlled Trials of IV AMF Use in Head and Neck Cancer Reporting Xerostomia As an Outcome

Reference	Arms	No.	Chemotherapy	Results	
				Xerostomia	VAS Average Scores
Radiation therapy					
Jellema, 2006[17]	No AMF	91		Grade 2 or higher (late): 6 months: AMF 0, 74%; AMF 3, 67%; AMF 5, 52%; $P = .03$; 12 months: AMF 0, 68%; AMF 3, 59%; AMF 5, 56%; $P = .24$; 18 months: AMF 0, 65%; AMF 3, 50%; AMF 5, 57%; $P = .59$; 24 months: AMF 0, 58%; AMF 3, 57%; AMF 5, 73%; $P = .81$; patient-reported xerostomia deteriorated significantly more in no-AMF group at later follow up ($P = .016$)	
	200 mg/m^2 IV, 3 times/wk				
	200 mg/m^2 IV, 5 times/wk				
Veerasarn, 2006[13]	200 mg/m^2 IV	67		Incidence of acute: week 2: AMF, 3%; control, 0%; $P = .325$; week 3: AMF, 16%; control, 31%; $P = .176$; week 4: AMF, 17%; control, 48%; $P = .013$; week 5: AMF, 18%; control, 79%; $P = < .001$; week 6: AMF, 19%; control, 76%; $P = < .001$; end: AMF, 39%; control, 82%; $P = .001$; 1 month: AMF, 16%; control, 40%; $P = .061$; 2 month: AMF, 18%; control, 17%; $P = .387$; 3 month: AMF, 8%; control, 33%; $P = .032$	Acute: week 2: AMF, 1.58; control, 2; $P = .442$; week 3: AMF, 2.61; control, 3.22; $P = .254$; week 4: AMF, 3.06; control, 4.48; $P = .035$; week 5: AMF, 3.08; control, 5.03; $P = .004$; week 6: AMF, 3.44; control, 4.64; $P = .077$; end: AMF, 3.73; control, 6.49; $P < .001$; 1 month: AMF, 2.1; control, 3.5; $P = .076$; 2 month: AMF, 1.57; control, 3.04; $P = .015$; 3 month: AMF, 1.04, control, 2.46; $P = .015$. Late phase: 6 months: AMF, 0.77; control, 2; $P = .007$; 12 months: AMF, 0.57; control, 1.12; $P = .439$; 18 months: AMF, 0.22; control, 1.55; $P = .011$; 24 months: AMF, 0.5; control, 0.72; $P = .757$
	No AMF				
Wasserman, 2005[18]	200 mg/m^2 IV	303		Incidence of late: 6 month: AMF, 4%; control, 24%; $P = .065$; 12 month: AMF, 5%; control, 30%; $P = .047$; 18 month: AMF, 6%; control, 12%; $P = .577$; 24 month: AMF, 0; control, 34%; $P = .039$	
	No AMF				
Platinum-based chemoradiotherapy					
Antonadou, 2002[1]	300 mg/m^2 IV	50	Carboplatin, 90 mg/m^2 once/week before XRT	Incidence of xerostomia grade 0-4, respectively (P for grade 2 or greater): 3 months: AMF 18.2%, 54.5%, 27.2%, 0, 0; control 0, 17.4%, 73.9%, 8.7%, 0; $P = .0001$; 6 months: AMF 9.1%, 54.5%, 27.3%, 9.1%, 0; control 0, 17.4%, 69.6%, 13.0%, 0; $P = .0023$; 9 months: AMF, 13.6%, 68.2%, 9.1%, 9.1%, 0; control, 0, 21.7%, 65.2%, 13.0%, 0; $P = .0001$; 12 months: AMF, 18.2%, 72.7%, 9.1%, 0, 0; control, 4.3%, 34.8%, 56.5%, 4.3%, 0; $P = .0004$; 18 months: AMF, 18.2%, 77.3%, 4.5%, 0, 0; control, 8.7%, 60.9%, 30.4%, 0, 0; $P = .0470$; no difference in grade 3, no grade 4 observed	
	No AMF				
Buentzel, 2006[19]	300 mg/m^2 IV (days 1-5 and 21-25), 200 mg/m^2 IV (before XRT on other days)	132	Carboplatin, 70 mg/m^2	Incidences of $\geq$ grade 2 acute xerostomia: AMF, 39%; placebo, 34%; $P = .715$	
	Placebo			Incidences of $\geq$ grade 2 late xerostomia: AMF, 39%; placebo, 24%; $P = .235$	
Vacha, 2003[20]	250 mg IV	41	Carboplatin, 70 mg/m^2	Significant reduction in acute xerostomia at weeks 2 and 4 (no patient numbers provided, $P = .002$, $P = .0021$, respectively), and in salivary gland toxicity for all treatment weeks ($P = .024$)	
	No AMF				

Abbreviations: IV, intravenous; AMF, amifostine; VAS, visual analog scale; XRT, radiation therapy.

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Table 6. Randomized Controlled Trials of AMF Use in Head and Neck Cancer Reporting Mucositis As an Outcome

Reference	Arms	No.	Results
Radiation therapy			
Jellema, 2006[17]	No AMF	91	No difference in grade 2 or greater acute mucositis; $P = .22$
	200 mg/m^2 IV, 3 times/wk		
	200 mg/m^2 IV, 5 times/wk		
Veerasarn, 2006[13]	200 mg/m^2 IV	67	Grade 2-3 acute mucositis: week 2: AMF, 0; control, 7%; $P = .147$; week 3: AMF, 26%; control, 28%; $P = .937$; week 4: AMF, 14%; control, 45%; $P = .01$; week 5: AMF, 18%; control, 83%; $P < .001$; week 6: AMF, 19%; control, 75%; $P < .001$; end: AMF, 36%; control, 75%; $P = .002$; 1 month: AMF, 4%; control, 8%; $P = .533$; 2 months: AMF, 0; control, 6%; $P = .239$; 3 months: AMF, 0; control, 0; 6 months: AMF, 5%, control, 6%; $P = .804$; 12 months: AMF, 0; control, 16%; $P = .057$; 18 months: AMF, 0; control, 12%, $P = .145$; 24 months: AMF, 0; control, 0
	No AMF		
Chemoradiotherapy			
Antonadou, 2002[1]	300 mg/m^2 IV	50	Significant reduction in grade 2 or greater acute mucositis assessed weekly for weeks 2-7; range, $P < .0001$ to .0092
	No AMF		Significant reduction remained at follow-up weeks 4 and 8 ($P = .0245$ and $P = .00216$, respectively), effect lost at week 12
	Carboplatin, 90 mg/m^2		
Braaksma, 2002[21*]	500 mg SQ	41	Mean XRT dose at start of mucositis grade 3-4: all patients, 40 Gy; AMF, 44 Gy; control, 35 Gy; $P = .04$
	No AMF		
	Paclitaxel, 60 mg/m^2		Mean duration of acute mucositis grade 3-4: all patients, 53 days; AMF, 58 days; control, 47 days; $P =$ NS
			Mean duration to acute mucositis resolution: All patients, 112 days; AMF, 131 days; control, 93 days; $P = .03$
Buentzel, 2006[19]	300 mg/m^2 IV and 200 mg/m^2 IV†	132	Incidences of acute mucositis $\geq$ grade 3: AMF, 39%; control, 22%; $P = .055$
	Placebo		
	Carboplatin, 70 mg/m^2		
Vacha, 2003[20]	250 mg IV	41	No difference in mean mucositis values between groups; grade 3 occurred only in control group
	No AMF		
	Carboplatin, 70 mg/m^2		

Abbreviations: AMF, amifostine; IV, intravenous; SQ, subcutaneous; NS, no significant difference.
*Preliminary report of then ongoing trial.
†300 mg on days 1-5 and 21-25, 200 mg before XRT on other days.

trials reported to date lack a placebo control. All of the trials in the Sasse et al[24] meta-analysis (those in head and neck cancer and all others) lacked a placebo control, and there was no patient or physician blinding in any of the studies. There is a lack of results from adequately designed studies from which to make recommendations in this area. Based on an assessment of the overall data, the panel felt that the new evidence did not support a significant change to the 2002 recommendation.

Esophagitis: 2008 recommendation. Note: This topic is new to the guideline. Data are insufficient to recommend the routine use of amifostine to prevent esophagitis in patients receiving concurrent chemoradiotherapy for non–small-cell lung cancer.

Literature review and discussion. For this new topic, articles were included for review if they were randomized controlled trials of amifostine use in the setting of chemoradiotherapy for non–small-cell lung cancer. In addition, the panel reviewed two systematic reviews identified in the literature search.[24,25] Five randomized trials conducted in patients with non–small-cell lung cancer receiving chemoradiotherapy and reporting esophagitis as an outcome were identified (Table 7).[2,7,8,10,26] In the meta-analyses reviewed by the panel, two additional studies were reported that were not individually reviewed by the panel to inform this specific recommendation, as these studies[27,28] used radiation therapy only, without chemotherapy. An additional two studies conducted in head and neck cancer patients were identified that reported esophagitis outcomes,[1,17] but because the panel decided to limit any recommendation on amifostine use in the prevention of esophagitis to lung cancer, these studies are not discussed further in this section.

The Sasse et al [24] meta-analysis discussed in the Mucositis section also conducted an analysis of trials of amifostine use for the prevention of esophagitis in patients with thoracic tumors undergoing radiation therapy with or without chemotherapy (concurrent or sequential). Pooling of six trials gave an odds ratio of 0.38 for the prevention of esophagitis with amifostine (95% CI, 0.26 to 0.54), which was statistically significant ($P < .00001$). There was, however, wide variability in the results across the studies in this subset ($P = .0004$), and no placebo-control arms in the studies, which severely limits interpretation of the results.

In the five randomized trials published since 2002 and reviewed by the panel, esophagitis outcome results were mixed. The largest study,[10] Radiation Therapy Oncology Group (RTOG) 98-01 (n = 242), reported no significant difference in grade 3 or greater esophagitis between arms or in physician dysphagia logs. The patient-reported swallowing symptom reported as area under the curve during chemoradiotherapy was, however, significantly lower in those patients receiving amifostine. Patients in the amifostine treatment arm had significantly higher rates of acute nausea, vomiting, infection and febrile neutropenia, and cardiovascular events, compared with the no amifostine treatment group. The cardiovascular events were mostly transient hypotension. Grade 1, 2, and 3 acute cardiovascular toxicities were reported in 11%, 15%, and 4%, respectively, in the amifostine arm, versus 2%, 7%, and 1% in the control arm ($P = .0001$). The only

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Table 7. Randomized Controlled Trials of AMF Use in Non–Small-Cell Lung Cancer Treated With CRT Reporting Esophagitis As an Outcome

Reference	Arms	No.	Chemotherapy	Results
Antonadou, 2003[2]	AMF 300 mg/m^2 IV	73	Paclitaxel or carboplatin (as radiosensitizer)	Assessed once/week during treatment then every 4 weeks for ≥ 3 months or until toxicities resolved
	No AMF			Acute esophagitis ≥ grade 3 during treatment, all patients: AMF, 38.9%; control, 84.4%; $P < .001$
				Acute esophagitis ≥ grade 3 during treatment, XRT + paclitaxel: AMF, 47%; control, 88%; $P = .014$; unplanned subgroup analysis
				Acute esophagitis ≥ grade 3 during treatment, XRT + carboplatin: AMF, 29%; control, 80%; $P = .006$; unplanned subgroup analysis
				Grade ≥ 3 esophagitis, 2 months post-treatment, XRT + paclitaxel: AMF, 12.5%; control, 56%; $P = .023$; unplanned subgroup analysis
				No patients in the XRT + carboplatin group experienced esophagitis at 15 days post-treatment; unplanned subgroup analysis
Komaki, 2004[7]	AMF 500 mg IV	62	Etoposide, cisplatin	Dysphagia: grade 1: AMF, 48%; control, 23%; grade 2: AMF, 35%; control, 42%; grade 3-4: AMF, 16%; control, 35%
	No AMF			Significant reduction in grade 1-2 esophageal toxicity in favor of AMF arm; $P = .021$
Leong, 2003[8]	AMF 740 mg/m^2 IV	60	Carboplatin, paclitaxel	Grade 2-3 esophagitis: AMF, 43%; control, 70%; P = NS
	Placebo (double-blind)			
Movsas, 2005[10]	AMF 500 mg IV	242	Carboplatin, paclitaxel	Acute dysphagia or esophagitis: grade 3: AMF, 28%; control, 31%; grade 4: AMF, 2%; control, 3%; grade 5: AMF, 0; control, 0; $P = .9$ for ≥ grade 3
	None			Average patient swallowing AUC score during CRT: AMF, 2.19; control, 2.34; $P = .025$
				No significant difference based on physician dysphagia logs*
Senzer 2002[26]†	AMF 500 mg IV‡ and 200 mg IV	100	Carboplatin, paclitaxel, gemcitabine, cisplatin	Grade 3-4 esophagitis: AMF, 8.5%; control, 9.4%; P = NS
	No AMF			Grade 3-4 dysphagia: AMF, 2.1%; control, 1.9%; P = NS

Abbreviations: AMF, amifostine; CRT, chemoradiotherapy; IV, intravenous; XRT, radiation therapy; NS, no significant difference; AUC, area under curve.
*A weekly physician-rated dysphagia log assigning an esophagitis grade (based on National Cancer Institute Common Toxicity Criteria).
†Preliminary report, 100 patients available for preliminary analysis of 182 planned.
‡500 mg prior to chemotherapy, 200 mg prior to radiation therapy.

placebo-controlled, double-blind trial[8] (n = 60) reported no significant difference in grades 2 to 3 esophagitis. Another small (n = 63) study[26] also reported no difference in grade 3 or greater esophagitis.

The two remaining studies reported positive outcomes. The first (n = 73) reported a significant reduction in grade 3 or greater esophagitis during primary treatment,[2] and the second[7] (n = 62) reported a significant reduction in the severity of dysphagia with amifostine (ie, more grade 1 to 2 dysphagia in the amifostine arm compared with the control arm). This latter study was designed and powered to detect a reduction in the incidence of grade 3 to 4 esophageal reactions with amifostine use, but results were reported as a "trend toward less severe (grade 1 to 2) esophageal toxicity."[7]

Data support the safety of amifostine in this setting, with a recent meta-analysis[25] showing that amifostine had no effect on tumor response in patients with non–small-cell lung cancer receiving chemotherapy or radiation therapy (see Discussion). However, the extreme statistical heterogeneity in the data evaluated in the meta-analysis of amifostine effects on esophagitis, coupled with the lack of a placebo control in all but one of the studies individually reviewed, makes it difficult to draw firm conclusions as to the efficacy of amifostine. Currently, data are insufficient to recommend the routine use of amifostine in the setting of chemoradiotherapy in lung cancer for the prevention of esophagitis.

Dose and Administration of Amifostine With Radiation Therapy

2008 recommendation. When given with radiation therapy, the recommended amifostine dose is 200 mg/m^2/d, given as a slow IV push over 3 minutes, 15 to 30 minutes before each fraction of radiation therapy. Administration of amifostine requires close patient monitoring, but adverse effects are fewer at this lower dose. Many patients require antiemetics. Blood pressure should be measured just before and immediately after the 3-minute amifostine infusion. The hypotension associated with amifostine at this dose is less frequent but still requires close monitoring. [No change from 2002.]

Literature update and discussion. There are no new compelling comparative data to show preserved efficacy with subcutaneous or other routes or doses. Three studies published since 2002 compared different doses or routes of administration of amifostine,[17,29,30] and one study compared intrarectal dosing to no amifostine (Table 8).[31] Two of the studies were conducted for prevention of xerostomia in patients with head and neck cancer, while the other two were conducted in patients with prostate, cervical, and endometrial cancer for the prevention of acute lower gastrointestinal toxicity. Of the two studies for prevention of xerostomia, one was a preliminary report[29] of an ongoing trial, and the other showed less effect of amifostine three times per week versus five times per week, on grade 2 or greater xerostomia at 6 months by RTOG criteria.

The two trials examining the protective effect of amifostine on lower gastrointestinal toxicity found no grade 3 or 4 toxicity in any patient. The first trial, which compared intrarectal amifostine to none, reported a significant difference in grade 0 versus grades 1 to 2 proctitis in patients with prostate cancer receiving amifostine intrarectally; the second trial reported a significant difference in grade 0 versus grades 1 to 2 acute lower gastrointestinal toxicity in

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Table 8. Randomized Controlled Trials Comparing Different Dose/Routes of AMF for Prevention of Radiation-Associated Toxicity

Reference	Arms	No.	Malignancy	Primary Outcome Results
Bardet, 2003[29*]	200 mg/m^2 IV; short 3-minute infusion 15-30 minutes before each XRT fraction 500 mg/d SQ; two slow 1.25 mL injections at 2 sites 20-60 minutes before each XRT fraction	54	Head and neck	Xerostomia, acute ≥ grade 2: 23% in IV group, 19% in SQ group
Jellema, 2006[17]	No AMF 200 mg/m^2 IV, 3 times/week 200 mg/m^2 IV, 5 times/week	91	Head and neck	Xerostomia ≥ grade 2: 6 months: AMF 0, 74%; AMF 3, 67%; AMF 5, 52%; P = .03; 12 months: AMF 0, 68%; AMF 3, 59%; AMF 5, 56%; P = .24; 18 months: AMF 0, 65%; AMF 3, 50%; AMF 5, 57%; P = .59; 24 months: AMF 0, 58%; AMF3, 57%; AMF5, 73%; P = .81
Kouloulias, 2004[31]	1,500 mg in 40 mL saline, IR No AMF	67	Prostate	Acute (rectal) mucositis: grade 0: AMF, 85%; control, 56%; grade 1: AMF, 15%; control, 38%; grade 2: AMF, 0; control, 6% P = .026 (pooled over grade) P = .015 (grade 0 *v* 1-2) No grade 3 or 4 toxicity
Kouloulias, 2005[30]	1,500 mg in 40 mL saline, IR 500 mg SQ	53	Prostate, cervical, endometrial	Lower GI toxicity: grade 0: IR, 89%; SQ, 58%; grade 1: IR, 11%; SQ, 38%; grade 2: IR, 0; SQ, 4% P = .04 (pooled over grade) P = .014 (grade 0 *v* 1-2) No grade 3 or 4 toxicity

Abbreviations: AMF, amifostine; IV, intravenous; SQ, subcutaneous; XRT, radiationtherapy; IR, intrarectal.
*Preliminary findings of Groupe Oncologie Radiotherapie Tête et Cou 2000-02; data for 54 of a planned 292 patients reported.

patients given amifostine intrarectally, compared with patients receiving amifostine via the subcutaneous route.

One additional study[32] was identified that compared different IV doses of amifostine. The study was stopped early due to a high rate of serious adverse effects of amifostine leading to discontinuation of study drug. Rades et al[32] reviewed the literature for studies of amifostine during radiation therapy in head and neck cancer, and combined the results of three studies with their own. They reported a total amifostine discontinuation rate of more than 25%, which was significantly influenced by whether patients were receiving concurrent chemotherapy with radiation, but not by amifostine dose received.

GUIDELINES FOR THE USE OF PALIFERMIN

Note: This topic is new to the guideline. Mucositis of the oral cavity and the oropharynx (oral mucositis) is a frequent complication of high-dose chemotherapy and radiation therapy. In its least severe form, mucosal erythema and ulceration are associated with few or no symptoms. More commonly, oral mucositis is characterized by mouth and oropharyngeal pain and impaired swallowing significant enough to be considered by patients to be the worst complication of autologous hematopoietic stem-cell transplantation (auto-HSCT).[33] Infrequently, oral mucositis is severe enough to cause significant mucosal bleeding or tissue inflammation and edema that requires endotracheal intubation to protect a compromised airway. Palliation of pain generally requires intravenous narcotics, and the consequential inability to tolerate solids and liquids may necessitate the administration of parenteral nutrition. Oral mucositis is frequently accompanied by mucositis of the gastrointestinal tract, which can result in nausea, vomiting, diarrhea, abdominal pain, and bleeding. The severity of oral mucositis among patients undergoing HSCT directly correlates with the duration of febrile neutropenia, the duration of narcotic usage, the duration of hospitalization, and the cost of hospitalization.[34]

A number of scoring systems are available to grade the severity of oral mucositis, although none is universally accepted. Most scoring systems incorporate both subjective (eg, pain) and objective (eg, number and extent of ulcers) criteria to arrive at a final score.[35-37] The WHO scale rates mucositis from 0 to 4 depending on the presence of oropharyngeal erythema and ulcers and the ability to tolerate solids and liquids (Table 9).[35]

WHO grades 3 and 4 mucositis are considered "severe" and are usually characterized by pain that requires intravenous narcotics. Patients with WHO grades 0 to 2 oral mucositis often require minimal or no intravenous narcotics and generally do not require extensive nutritional support.

Severe oral mucositis occurs in virtually all patients undergoing HSCT with myeloablative conditioning regimens that include total-body irradiation (TBI).[38,39] In addition, severe mucositis of the oral cavity, oropharynx, and/or esophagus universally occurs when conditioning regimens include involved-field radiotherapy that involves these sites. The incidence of severe mucositis among recipients of conditioning regimens consisting of high-dose chemotherapy alone is variable and depends on the doses and number of

Table 9. WHO Mucositis Scale

Grade	Criteria
0	No subjective or objective evidence of mucositis
1	Soreness with or without erythema; no ulcers
2	Erythema and ulceration; can swallow solids
3	Erythema and ulceration; cannot swallow solids
4	Erythema and ulceration; alimentation not possible

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mucositis-inducing agents included in a given regimen, inter-patient variability in drug pharmacokinetics, and inter-observer inconsistencies in grading mucositis. A systematic review has estimated that the risk of severe mucositis among patients undergoing transplantation with high-dose chemotherapy alone is approximately 31% (95% CI, 27% to 35%).[40] There are no reliable and validated prognostic models to determine which patients undergoing chemotherapy-only conditioning will develop severe oral mucositis. Etoposide, melphalan, and thiotepa are drugs commonly used in conditioning regimens for hematologic malignancies whose dose-limiting extramedullary toxicity includes mucositis.

Palifermin (Kepivance; Amgen Manufacturing Ltd, Thousand Oaks, CA) is a recombinant truncated form of human keratinocyte growth factor (KGF),[41] a member of the fibroblast growth factor family, that acts on epithelial tissue in a paracrine fashion to exert a net cytoprotective effect against chemotherapy- and radiation therapy–induced mucosal injury.[42,43] Palifermin is the only agent approved by the US Food and Drug Administration for prophylaxis against severe mucositis among patients undergoing auto-HSCT or allogeneic (allo) -HSCT for hematologic malignancies.

Auto-HSCT

2008 recommendation. Palifermin is recommended for use in patients undergoing autologous stem-cell transplantation for a hematologic malignancy with a TBI conditioning regimen to decrease the incidence of severe mucositis. There are insufficient data to recommend the routine use of palifermin for patients undergoing autologous stem-cell transplantation for a hematologic malignancy where the conditioning regimen is chemotherapy only.

Literature review and discussion. Auto-HSCT. A multicenter double-blind, placebo-controlled, randomized study was conducted to evaluate the efficacy of palifermin to reduce the incidence of WHO grades 3 and 4 mucositis in patients with hematologic malignancies undergoing auto-HSCT with a TBI-containing conditioning regimen.[38] The conditioning regimen consisted of TBI (12 Gy administered in 6, 8, or 10 fractions), etoposide 60 mg/kg on the day after completing TBI, and cyclophosphamide 100 mg/kg 2 days after etoposide. Peripheral blood progenitor cells were infused 2 days after cyclophosphamide. Palifermin 60 μg/kg or placebo was administered daily for the 3 days preceding TBI and for 3 days beginning on the day of stem-cell infusion. Two hundred twelve patients who received at least one dose of palifermin (106 patients) or placebo (106 patients) were evaluated for efficacy and safety. Patients with non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma comprised 87% of the patients. WHO grade 3 or 4 oral mucositis developed in 63% of the palifermin-treated patients and 98% of the placebo-treated patients ($P < .001$). Among patients who developed grade 3 or 4 oral mucositis, its median duration was 3 days in the palifermin group and 9 days in the placebo group ($P < .001$). Palifermin was also effective at reducing the incidence of grade 4 oral mucositis (20% *v* 62%; $P < .001$) and its duration (2 days *v* 6 days; $P = .004$). Patient-reported mouth and throat soreness was significantly lower in the palifermin-treated patients ($P < .001$), and palifermin was also associated with improved swallowing, drinking, eating, talking, and sleeping ($P < .001$ for all).[44]

Based on these data, palifermin is recommended for use in patients undergoing auto-HSCT with a conditioning regimen that includes TBI in order to decrease the frequency of severe mucositis. Because the incidence of severe mucositis is also high with auto-HSCT conditioning regimens that include involved-field radiotherapy to the oral cavity, oropharynx, and/or esophagus, palifermin may be considered. The panel cautions, however, that data are lacking from randomized controlled trials to support this extrapolation for palifermin use to the involved-field radiation conditioning regimen setting. There are no randomized, controlled trials of palifermin to prevent grade 3 or 4 mucositis in patients treated with chemotherapy-only conditioning regimens. In addition, there is variability in the incidence of grade or 4 mucositis with chemotherapy-only conditioning regimens. Thus, data are currently insufficient to make a recommendation regarding the general use of palifermin in patients receiving chemotherapy-only conditioning regimens.

Allo-HSCT

2008 recommendation. Palifermin may be considered for use in patients undergoing myeloablative allogeneic HSCT with a TBI-based conditioning regimen. There are insufficient data to recommend its use in myeloablative conditioning regimens consisting of chemotherapy alone in this setting.

Literature review and discussion: Allo-HSCT. Injury to the gastrointestinal epithelium in patients undergoing allo-HSCT may be induced by the conditioning regimen and/or acute graft-versus-host disease (GVHD). Because the severity of regimen-induced oral mucositis is dependent on the conditioning regimen and not the source of hematopoietic stem cells, the ability of palifermin to reduce the incidence of severe regimen-induced oral mucositis in patients undergoing allo-HSCT is not expected to be different than in patients undergoing auto-HSCT, although this has not been directly evaluated in randomized studies.

A phase I/II randomized placebo-controlled study was conducted to evaluate the efficacy of palifermin to prevent GVHD after allo-HSCT.[45] The conditioning regimen consisted of cyclophosphamide and TBI in 54 patients or busulphan and cyclophosphamide in 46 patients. The conditioning regimen used was based on institutional and investigator preference and not stipulated by the study design. Hematopoietic stem cells consisted of either bone marrow or filgrastim-stimulated peripheral blood progenitor cells from six of six human leukocyte antigen–matched sibling donors. GVHD prophylaxis included methotrexate given on days 1, 3, 6, and 11 post–stem-cell infusion. Patients received either placebo (n = 31) or palifermin (n = 69) in one of four dosing schemas. While this study design precludes definitive statements regarding the effects of palifermin on severe oral mucositis or acute GVHD, it is notable that the incidence of severe mucositis among palifermin-treated patients in the cyclophosphamide and TBI group was significantly lower than among placebo-treated patients (100% *v* 81% l $P = .05$). There was no difference in the incidence of severe mucositis in the palifermin- and placebo-treated patients who received busulphan and cyclophosphamide (50% *v* 44%). There was no significant difference in the incidence of grades 2 to 4 or grades 3 to 4 acute GVHD in the two groups.

Dose and Administration of Palifermin With Hematopoietic Stem-Cell Transplantation

2008 recommendation. Palifermin should be administered intravenously at 60 μg/kg daily for 3 days preceding the start of the

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conditioning regimen and 60 μg/kg daily for 3 days beginning on the day of stem-cell infusion. It should not be administered within 24 hours before or after the initiation of the conditioning regimen.

Literature review and discussion. Administration of palifermin should follow the protocol used in the randomized controlled trial and in the US Food and Drug Administration–approved label. Common toxicities of palifermin include rash and/or erythema (55% to 95% of patients), pruritus, edema, sensation of increased tongue thickness, and alteration of taste.[38,45] The severity of the rash or skin reaction, though it has varied somewhat across trials, has generally been mild to moderate.

There is considerable interest in the testing of more convenient schedules for delivery of palifermin, including the investigation of a single dose of 180 μg/kg given 72 or 48 hours before initiation of TBI conditioning, with palifermin 60 μg/kg daily for 3 days beginning the day of stem-cell infusion. While data from a small randomized trial are potentially encouraging,[46] further efficacy data are needed before these alternative dosing schedules are adopted.

Non–Stem-Cell Transplantation Setting and in Treatment of Solid Tumors

2008 recommendation. There are insufficient data to recommend the use of palifermin in the non–stem-cell transplantation setting, or for use in the treatment of solid tumors.

Literature review and discussion. One phase I/II randomized trial was identified that examined palifermin in the setting of solid tumors.[47] Although trials that were solely phase I were excluded from the systematic review of the literature for this guideline update, it should be noted that this study followed on the promising results of an earlier randomized phase I trial that showed a lower rate of grade 2 to 4 mucositis in patients with colorectal cancer treated with palifermin compared with placebo.[48] In the phase I/II multicenter study, Rosen et al[47] randomly assigned 64 patients with metastatic colorectal cancer receiving fluorouracil/leucovorin to palifermin or placebo, given for 3 consecutive days before each of two consecutive chemotherapy cycles. They reported a lower incidence of grade 2 or worse oral mucositis in patients who received palifermin, compared with placebo (29% *v* 61% in cycle 1; 11% *v* 47% in cycle 2).

This small phase I/II study is the only one identified to date in the non–stem-cell transplant setting. Currently, data are insufficient to recommend the use of palifermin in the non–stem-cell transplant setting, or for use in the treatment of solid tumors.

GUIDELINES FOR THE USE OF MESNA

No studies examining mesna use in the setting of a randomized controlled trial were identified in the update search. There is, therefore, no evidence on which to base changes to any of the recommendations contained in the 2002 update. These recommendations are listed in Table 1, and form part of the 2008 update.

DISCUSSION

Concern has been raised that chemotherapy and radiation therapy protectant agents may compromise tumor response and survival. In all of the studies reviewed, for those studies reporting overall survival, disease-free survival, progression-free survival, or local control rate, no significant differences were found between patients receiving these agents and those not receiving them. A recent meta-analysis[25] designed to determine the effect of amifostine on response rates in patients with locally advanced non–small-cell lung cancer (treated with radiation therapy or chemoradiotherapy) found no effect of amifostine on tumor response. Tebbi et al[49] reported an increase in second malignancies in children receiving dexrazoxane, and this guideline does not recommend the routine use of dexrazoxane in the pediatric setting. Few studies of chemotherapy and radiation therapy protectants have been conducted in pediatric populations. The Tebbi et al study highlights the need for assessment of longer-term outcomes in patients treated with chemotherapy and radiation therapy protectants, particularly when these agents are used in the treatment of potentially curable malignancies.

Patients should be apprised of the risks and benefits of these chemotherapy and radiation therapy protectant agents, and should understand that these agents have not been shown to increase disease-free or overall survival. It is reassuring that these agents have not been shown to have a detrimental effect on progression-free or overall survival. There was a trend toward higher objective response rates among patients with metastatic breast cancer initiating anthracycline treatment compared with those assigned to anthracycline plus dexrazoxane. Such a trend toward higher response rates was not observed among patients in studies where dexrazoxane treatment was delayed until after cumulative doxorubicin doses of 300 mg/m^2. Patients should be informed that the intended effect of using a chemotherapy or radiation therapy protectant agent is to decrease the risk of developing certain specific toxicities of primary therapy, but the use of these agents has not clearly been shown to allow greater doses to be delivered or a longer time course of treatment. The short-term adverse effects of the chemotherapy and radiation therapy protectant agents have generally been well-characterized (eg, hypotension and nausea with amifostine; rash/erythema with palifermin), and in some studies have led to high rates of protectant discontinuation. The economic costs of these agents varies and, while a formal cost-effectiveness analysis is beyond the scope of this guideline, Table 10 provides estimated costs for each, based on data from Centers for Medicare and Medicaid Services (Rockville, MD).[50]

Quality of life is a clinical trial end point that may be particularly relevant for clinical trials assessing the efficacy of chemotherapy and radiation therapy protectants, since the goal of using protectants is to minimize the adverse experiences of cancer treatment. However, since quality of life is a particularly subjective end point, studies that include quality of life as an assessment end point must include a placebo control group. Lacking a placebo control, there is a chance that patients assigned to receive the protectant agent will report better outcomes, even if there is no such actual effect. For example, in RTOG 98-01 trial,[10] 243 patients were randomly assigned to receive two cycles of paclitaxel plus carboplatin followed by concurrent weekly chemotherapy plus hyperfractionated radiation with or without amifostine during chemoradiotherapy. There was no difference in the primary, objective end point of grade 3 or worse esophagitis (30% with amifostine, 35% without amifostine), and no difference in overall quality of life scores. However, more patients assigned to

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Table 10. Estimated Costs for Protectant Agents Discussed in Guideline[50]

Protectant	Usual Dose/Delivery Schedule	Estimated Costs/Unit
Dexrazoxane	Dexrazoxane at a ratio of 10:1 with the doxorubicin dose, given by slow IV push or short IV infusion, 15 to 30 minutes before doxorubicin or epirubicin administration; a ratio of 10:1 with the epirubicin dose may be reasonable	$180.94/250 mg
Amifostine	With radiation therapy: 200 mg/m^2/day given as slow IV push over 3 minutes, 15 to 30 minutes before each fraction of radiation therapy With chemotherapy: 910 mg/m^2 IV over 15 minutes, 30 minutes prior to chemotherapy	$511.22/500 mg
Palifermin	60 μg/kg daily for 3 days preceding the start of the conditioning regimen and 60 μg/kg daily for 3 days beginning on the day of stem-cell infusion†	$11.36/50 μg
Mesna	With standard-dose ifosfamide, when ifosfamide dose is $<$ 2.5 g/m^2/day administered as short infusion: calculate mesna daily dose to equal 60% of ifosfamide total daily dose, administered as 3 bolus IV doses given 15 minutes before and 4 and 8 hours after each dose of ifosfamide With standard-dose ifosfamide, continuous-infusion: administer mesna IV as a bolus dose equal to 20% of total ifosfamide dose followed by continuous infusion of mesna equal to 40% of the ifosfamide dose, continuing for 12 to 24 hours after completion of ifosfamide infusion Oral route: administer mesna as IV bolus injection, with dose equal to 20% of ifosfamide dose (weight/weight) at the time of ifosfamide administration; give mesna tablets orally in a dose equal to 40% of ifosfamide dose at 2 and 6 hours after each dose of ifosfamide; total daily dose of mesna is 100% of the ifosfamide dose; patients who vomit within 2 hours of taking oral mesna should repeat the dose or receive IV mesna; the dosing schedule should be repeated on each day that ifosfamide is administered	$7.87/200 mg (injection)

NOTE. Drug costs were estimated from a third-party payer perspective, based on reimbursement rates from the Centers for Medicare and Medicaid Services that are widely accepted by providers, computed at the manufacturer's average sales price plus 6%. Other treatment-related direct and indirect costs were not considered. Actual treatment costs and reimbursement will vary considerably across regions, payers, institutions, and practices, as well as over time, and the reader should consult current local cost information specific to their practice setting.
Abbreviations: IV, intravenous.
†Palifermin should not be administered within 24 hours of the initiation of the conditioning regimen.

receive amifostine reported improvement on the pain subscale and in swallowing difficulty diary reports than did patients who did not receive amifostine. Such differences might easily be explained by the lack of a placebo control.

Because chemotherapy and radiation therapy protective agents are designed to prevent or ameliorate toxicities, studies should be designed with reliable, reproducible, and clinically meaningful end points. Since the assessment of the end points is often, at least partly, subjective, it is critical that trials are blinded and placebo controlled. Trials that lack these key design elements limit the ability to use the data to write a guideline. For example, while data from several trials suggest that amifostine may have a potential role in preventing severe esophagitis associated with radiation for lung cancer, the variability in the measurement of the outcome and the lack of placebo control in the positive studies made it difficult to determine whether there was meaningful activity of the drug. Thus, these data were considered insufficient to recommend routine use of amifostine to prevent esophagitis. In contrast, the trial design to assess the efficacy of palifermin on oral mucositis used an accepted mucositis scale and was double blind and placebo controlled. These data were considered compelling, and support the panel's recommendation for use of palifermin to prevent severe mucositis in the stem-cell transplantation setting.

The development of palifermin as a mucositis-prevention agent since the time of the last chemotherapy and radiation therapy protectant guideline update is an advance for the field. The panel looks forward to seeing further studies of the current agents (some areas of interest include dosing schedules, assessment of efficacy with newer chemotherapy agents, and efficacy in ameliorating clinically important end points such as esophagitis) and to seeing development of other novel protectants.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Table A1. Update Committee Panel Members

Panel Member	Institution
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Lynn M. Schuchter, MD, Co-Chair	University of Pennsylvania
Gail Broder	Patient Representative
Gary I. Cohen, MD	The Cancer Center at Greater Baltimore Medical Center
Bahman Emami, MD	Loyola University Medical Center
William J. Gradishar, MD	Northwestern University
Daniel M. Green, MD	St Jude Children's Research Hospital
Tarun Kewalramani, MD	Memorial Sloan-Kettering Cancer Center
Neal J. Meropol, MD	Lahey Clinic
R. Brian Mitchell, MD	Virginia Cancer Institute
J. Tate Thigpen, MD	University of Mississippi
Andy Trotti, III, MD	H. Lee Moffitt Cancer Center
Daniel Von Hoff, MD	Translational Genomics Research Institute
Todd H. Wasserman, MD	Washington University in St Louis School of Medicine

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