

## 2002 Update of Recommendations for the Use of Chemotherapy and Radiotherapy Protectants: Clinical Practice Guidelines of the American Society of Clinical Oncology\*

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THE AMERICAN SOCIETY of Clinical Oncology (ASCO) published evidence-based clinical guidelines for the use of chemotherapy and radiotherapy protectants in 1999.<sup>1</sup> ASCO guidelines are updated periodically by a subset of the original expert panel. For the 2002 guideline update, the expert panel co-chairs reviewed the data published since 1998. Computerized literature searches of MEDLINE and CancerLIT were performed. The searches of the English-language literature from 1997 to 2001 included each of the protectants (mesna, dexrazoxane, and amifostine) evaluated in the original guideline. The term “mesna” was combined with “cyclophosphamide,” “oral administration,” and “ifosfamide”; the term “dexrazoxane” was combined with “breast cancer” and with “cardiac”; and the term “amifostine” was combined with “nephrotoxicity,” “neutropenia,” “thrombocytopenia,” “radiation therapy,” “paclitaxel-associated neurotoxicity,” and “chemotherapy.” The search was further limited to human studies and review articles or randomized controlled trials.

The co-chairs drafted the update after review of the pertinent, new literature. The draft update was circulated to the full expert panel for review and approval. Each guideline from the 1999 update is listed below, followed by the 2002 update, if applicable, and then by the 2002 recommendation.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations, and they cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. ASCO considers adherence to these guidelines to be voluntary. The ultimate determination regarding their application is to be made by the physician in light of each patient’s individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative and novel therapies for this symptom in which better treatment is of paramount importance. In that guideline development involves a review and synthesis of the latest

literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

### GUIDELINES FOR THE USE OF MESNA

#### Mesna Use With Ifosfamide

*1999 Recommendation:* The use of mesna is recommended to decrease the incidence of ifosfamide-associated urothelial toxicity.

*2002 Recommendation:* No change.

#### 1. Mesna Dosing With Standard-Dose Ifosfamide

*1999 Recommendation:* 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 2.0.5 g/m<sup>2</sup>/d 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.

*2002 Recommendation:* No change.

#### 2. Mesna Dosing With High-Dose Ifosfamide

*1999 Recommendation:* 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<sup>2</sup>/d. The efficacy

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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.

*2002 Recommendation:* No change.

### 3. Mesna Administration by the Oral Route

*1999 Recommendation:* Administration of the first dose of mesna intravenously, at a dose equal to 20% of the total daily ifosfamide dose, followed at 2 and 8 hours by 40% weight/weight of the ifosfamide dose administered orally may be considered an acceptable alternative to the three-dose intravenous (IV) mesna regimen when the total ifosfamide daily dose is less than 2.0 g/m<sup>2</sup>.

*2002 Update:* Previous oral mesna regimens administered the IV formulation orally. Two randomized clinical studies comparing the recommended IV mesna dose to oral mesna regimens demonstrated less than 5% incidence of grade 3 or 4 hematuria in both arms in conjunction with ifosfamide at doses ranging from 1.2 to 2.0 g/m<sup>2</sup> for 3 to 5 days.<sup>2,3</sup> In a meta analysis of four controlled studies, the safety profile of the IV-oral-oral regimen (n = 119) was similar to that of the all-IV regimen (N = 119). Mesna tablets are available in 400-mg tablets.

*2002 Recommendation:* Mesna tablets have been approved by the United States Food and Drug Administration (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

*1999 Recommendation:* 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.

*2002 Recommendation:* No change.

#### Surveillance of Patients Receiving Ifosfamide and/or Cyclophosphamide and Mesna

*1999 Recommendation:* 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.

*2002 Recommendation:* No change.

## GUIDELINES FOR THE USE OF DEXRAZOXANE

### Breast Cancer

#### 1. Initial Use in Patients With Metastatic Breast Cancer

*1999 Recommendation:* It is recommended that dexrazoxane not routinely be used for patients with metastatic breast cancer receiving initial doxorubicin-based chemotherapy.

*2002 Update:* Although the use of dexrazoxane may decrease cardiotoxicity when used at the initiation of doxorubicin-based chemotherapy in breast cancer, the beneficial effects are also seen when the initiation of dexrazoxane is delayed until a cumulative dose of 300 mg/m<sup>2</sup> is reached.<sup>4</sup> Thus, given the potential for increased expense, and possibly increased toxicity, it continues to be reasonable to recommend against the routine use of dexrazoxane at the initiation of doxorubicin-based chemotherapy in patients with metastatic breast cancer.

The 1999 guideline<sup>1</sup> erroneously stated that nausea and vomiting were more frequent among patient receiving dexrazoxane compared with those receiving placebo. The data from the Swain et al<sup>4</sup> study show that the frequency of any-grade nausea and vomiting was higher among placebo patients; however, there was no significant difference between the two groups in terms of grade 3 nausea or vomiting ( $P = .062$ ;  $P = .52$ , respectively).

*2002 Recommendation:* No change.

#### 2. Delayed Use in Patients With Metastatic Breast Cancer Who Have Received More Than 300 mg/m<sup>2</sup> of Doxorubicin

*1999 Recommendation:* It is suggested that the use of dexrazoxane be considered for patients with metastatic breast cancer who have received more than 300 mg/m<sup>2</sup> of doxorubicin in the metastatic setting and who may benefit from continued doxorubicin-containing therapy.

Management of patients who received more than 300 mg/m<sup>2</sup> 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, and to the risk of cardiac toxicity, and because these patients were not included in the clinical trials of dexrazoxane.

*2002 Update:* A meta-analysis<sup>5</sup> of seven randomized, controlled trials, two of which were placebo-controlled,

addressed the question of the efficacy of dexrazoxane in terms of decreasing the risk of clinical cardiotoxicity. Pooled results from the six studies that had been reported fully in the published literature indicated that the dexrazoxane use was associated with decreased risk of clinical cardiotoxicity (odds ratio, 0.21; 95% confidence interval, 0.09 to 0.5;  $P = .00037$ ). One study<sup>6</sup> assessed the costs of using dexrazoxane in combination with doxorubicin-based chemotherapy for patients with metastatic breast cancer. Using data from two previously reported,<sup>4,7</sup> randomized, placebo-controlled trials to build a Markov model, the authors estimated the cost-per-cardiac event prevented by using dexrazoxane. The model demonstrated that use of dexrazoxane costs approximately \$5,600.00 per cardiac event prevented.

*2002 Recommendation:* No change.

### 3. Use in Patients Receiving Adjuvant Chemotherapy for Breast Cancer

*1999 Recommendation:* The use of dexrazoxane in the adjuvant setting is not suggested outside of a clinical trial.

*2002 Update:* There are no reported randomized, controlled studies of dexrazoxane in the adjuvant chemotherapy setting for breast cancer. In the absence of high-quality, randomized, controlled trial data demonstrating efficacy of dexrazoxane and confirming lack of tumor protection, the use of dexrazoxane in the adjuvant setting should only be used in the clinical trial setting.

*2002 Recommendation:* No change.

## Other Malignancies

### 1. Use in Adult Patients With Other Malignancies

*1999 Recommendation:* The use of dexrazoxane can be considered in adult patients who have received more than 300 mg/m<sup>2</sup> 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.

*2002 Update:* There are no new peer-reviewed, published, randomized, controlled trials addressing the efficacy of dexrazoxane for preventing cardiac toxicity in adult patients receiving doxorubicin-based therapy for malignancies other than breast cancer. A randomized trial of 155 patients (105 assessable) with small-cell lung cancer treated with cyclophosphamide, doxorubicin, and vincristine with or without dexrazoxane was reported in abstract and showed that the total number of cardiotoxicity events (both clinical congestive heart failure and subclinical decrease in left ventricular ejection fraction [LVEF]) was lower among the patients treated with dexrazoxane compared with those who

received cyclophosphamide, doxorubicin, and vincristine alone (12% v 29%,  $P = .029$ ).<sup>8</sup> These data are similar to results of the two small randomized trials<sup>9,10</sup> including sarcoma patients that were considered in the formulation of the 1999 guideline.

*2002 Recommendation:* No change.

### 2. Use in Pediatric Malignancies

*1999 Recommendation:* There is insufficient evidence to make a recommendation for the use of dexrazoxane in the treatment of pediatric malignancies.

*2002 Update:* Although several small studies (some with placebo control, others with historical controls) suggest that the use of dexrazoxane may decrease the risk of cardiac toxicity associated with anthracycline treatment in pediatric malignancies, data remain insufficient to make a specific recommendation regarding current use. The Pediatric Oncology Group is conducting an important study (POG-9426) of doxorubicin, bleomycin, vincristine, and etoposide with or without dexrazoxane, followed by low-dose involved-field radiotherapy, for children with newly diagnosed Hodgkin's disease.

*2002 Recommendation:* No change.

## Other Anthracycline Doses and Schedules

### 1. Use in Patients Receiving Other Anthracyclines or Other Anthracycline Dose Schedules

*1999 Recommendation:* The current data regarding the use of dexrazoxane in patients receiving epirubicin-based therapy are insufficient to make a recommendation.

*2002 Update:* Since the publication of the 1999 guideline, epirubicin has received FDA approval for use in the treatment of breast cancer. Previous studies had demonstrated that the risk of cardiac toxicity from epirubicin may be lower than the risk with doxorubicin.<sup>11</sup> However, at cumulative doses exceeding 1,000 mg/m<sup>2</sup>, cardiac toxicity may be observed in 16% to 35% of patients.<sup>12,13</sup> A randomized trial of three different dosing regimens for treatment of metastatic breast cancer (fluorouracil 500 mg/m<sup>2</sup> + epirubicin 75 mg/m<sup>2</sup> + cyclophosphamide 500 mg/m<sup>2</sup> given every 3 weeks for 11 cycles [FEC 75] v fluorouracil 500 mg/m<sup>2</sup> + epirubicin 100 mg/m<sup>2</sup> + cyclophosphamide 500 mg/m<sup>2</sup> given every 3 weeks for four cycles [FEC 100] followed by four additional cycles with the epirubicin reduced to 50 mg/m<sup>2</sup> v FEC 100 for four cycles, with restart of treatment at time of progression of disease) showed that response duration and time to progression were superior with the longer-duration epirubicin-based regimens but that there was no difference in overall survival among the three treatment approaches in 417 chemotherapy-naïve patients.<sup>14</sup>

Twelve patients had a decrease in LVEF: 11 in the two long-duration FEC arms, and one in the shorter-duration FEC arm. The median cumulative dose of epirubicin received by the 11 patients with a decline in LVEF was 600 mg/m<sup>2</sup> (range, 451 to 817 mg/m<sup>2</sup>).

In an additional study,<sup>15</sup> 105 patients with metastatic breast cancer were treated with epirubicin 90 mg/m<sup>2</sup> + paclitaxel 135 to 225 mg/m<sup>2</sup> or epirubicin 90 mg/m<sup>2</sup> + paclitaxel 175 mg/m<sup>2</sup> + gemcitabine 1,000 mg/m<sup>2</sup> on days 1 and 4. Nine patients developed congestive heart failure: four after cumulative epirubicin dose 1,080 mg/m<sup>2</sup>, two after 720 mg/m<sup>2</sup>, one after 630 mg/m<sup>2</sup>, and two after 540 mg/m<sup>2</sup>. All episodes of clinical congestive heart failure occurred 3 to 6 months after completion of epirubicin-based therapy. The cumulative risk of congestive heart failure was estimated to be 7.7% at a cumulative dose of 720 mg/m<sup>2</sup> and 48.7% at a cumulative dose of 1,080 mg/m<sup>2</sup>. In a study reporting the results of the subset of patients with metastatic breast cancer who had not received prior anthracycline therapy and were treated with epirubicin 120 mg/m<sup>2</sup>, with or without dexrazoxane, as first-line therapy (note that these data do not represent a separate clinical trial; they are a subset analysis of the patients who received high-dose epirubicin in the previously reported trial), cardiotoxicity (defined as clinical congestive heart failure or ejection fraction decline to < 45% or > 20% from baseline) occurred in 19% after a median cumulative epirubicin dose of 720 mg/m<sup>2</sup> (range, 120 to 1,440 mg/m<sup>2</sup>). Eighteen of the cardiac events occurred among the women treated with epirubicin alone, and six events occurred among those treated with epirubicin plus dexrazoxane.<sup>16</sup>

There are no new published randomized, controlled trials assessing the efficacy of dexrazoxane in decreasing the risk of epirubicin-associated cardiotoxicity. The results of the two previously published randomized controlled trials were detailed in the 1999 guideline. In the larger of these, 162 patients with advanced breast cancer were treated with cyclophosphamide, epirubicin 60 mg/m<sup>2</sup>, and fluorouracil (CEF) with or without dexrazoxane, or if the patient had never received anthracycline-based therapy, she received epirubicin 120 mg/m<sup>2</sup> with or without dexrazoxane. Sub-clinical cardiotoxicity was less frequent among patients who received dexrazoxane (23% no dexrazoxane v 7.3% dexrazoxane). The cumulative probability of clinical or laboratory evidence of cardiotoxicity was significantly lower with dexrazoxane (odds ratio, 0.29; 95% confidence interval, 0.09 to 0.78). Response rates were similar (46.2% v 47.6%). All cardiotoxicity events were among those patients who received epirubicin 120 mg/m<sup>2</sup>.<sup>17</sup> Although these studies support the conclusion that dexrazoxane decreases cardiotoxicity among patients treated with epirubicin, definitive

trials large enough to confirm that treatment efficacy is equivalent have not been reported. There are no randomized trials comparing initial dexrazoxane use versus delayed use with epirubicin, although it is notable that no cardiotoxicity events occurred among the patients who had received prior anthracycline therapy and then were treated with cyclophosphamide, epirubicin 60 mg/m<sup>2</sup>, and fluorouracil.

There are no new randomized, controlled trials addressing the ability of dexrazoxane to decrease cardiotoxicity of other potentially cardiotoxic agents, such as mitoxantrone, daunorubicin, and liposomal doxorubicin.

**2002 Recommendation:** 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.

## 2. Use in Patients Receiving High-Dose Anthracycline Therapy

**1999 Recommendation:** There is insufficient evidence on which to base a recommendation for the use of dexrazoxane in patients receiving high-dose anthracycline therapy.

**2002 Update:** There are no new randomized, controlled trials addressing the efficacy of dexrazoxane in decreasing the risk of cardiotoxicity associated with high-dose anthracycline therapy. In the previously detailed trial,<sup>17</sup> 67 patients received epirubicin 120 mg/m<sup>2</sup>, and 68 received epirubicin plus dexrazoxane. All cardiotoxicity events occurred among the group of patients who received high-dose epirubicin at 120 mg/m<sup>2</sup>, with 18 events among those treated with epirubicin alone and six events among those treated with epirubicin plus dexrazoxane. In this small subgroup of patients without prior anthracycline exposure who received high-dose epirubicin, dexrazoxane decreased the risk of cardiotoxicity. While response rates were similar, the study was underpowered to detect a moderate difference in response rates. Similarly in the randomized, controlled trial of epirubicin 160 mg/m<sup>2</sup> with or without dexrazoxane for patients with metastatic breast cancer or soft tissue sarcoma, dexrazoxane was used with initial therapy, and dexrazoxane decreased the risk of cardiotoxicity.<sup>10</sup>

**2002 Recommendation:** Since data for superior outcomes with high-dose as compared with standard-dose epirubicin treatment for metastatic breast cancer are lacking, and since there are no new data from randomized trials confirming that efficacy of high-dose epirubicin is preserved

when given with dexrazoxane, the panel considered the current data for high-dose epirubicin plus dexrazoxane insufficient to make a recommendation.

### Patients With Cardiac Risks

#### 1. Use in Patients With Cardiac Risk Factors

*1999 Recommendation:* 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.

*2002 Update:* The role of pre-existing cardiac risk factors and the frequency of congestive heart failure among 105 patients with metastatic breast cancer receiving epirubicin/paclitaxel-based chemotherapy was investigated in a prospective study.<sup>15</sup> In this study, age over 50 years, a history of prior chest wall radiotherapy, hypertension, and diabetes were considered cardiac risk factors. The cumulative probability of developing congestive heart failure was similar among patients with and patients without cardiac risk factors, up to a cumulative epirubicin dose of 990 mg/m<sup>2</sup> (10% and 12%, respectively). Although no significant difference was found in the incidence of congestive heart failure between patients with and patients without cardiac risk factors, after adjusting for cumulative epirubicin dose, the study had limited power to detect such a difference because of the small number of events.

*2002 Recommendation:* No change.

### Monitoring Therapy

#### 1. Termination of Anthracycline Therapy for Patients Receiving Dexrazoxane

*1999 Recommendation:* Patients receiving dexrazoxane should continue to undergo cardiac monitoring. After cumulative doxorubicin doses of 400 mg/m<sup>2</sup>, cardiac monitoring should be frequent. The panel suggests repeating the monitoring study after 500 mg/m<sup>2</sup> and subsequently after every 50 mg/m<sup>2</sup> 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.

*2002 Recommendation:* No change.

#### 2. Dose of Dexrazoxane

*1999 Recommendation:* 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 administration.

*2002 Update:* The randomized, controlled trials evaluating the cardioprotective effect of dexrazoxane used a dexrazoxane to doxorubicin ratio of 10:1, whereas the ratio of dexrazoxane to epirubicin ranged from 10:1<sup>17</sup> to 6.25:1.<sup>10</sup> In a phase I trial,<sup>18</sup> the maximum-tolerated doses of dexrazoxane and epirubicin were 1,200 mg/m<sup>2</sup> and 135 mg/m<sup>2</sup>, respectively. Administration of dexrazoxane doses of 900 mg/m<sup>2</sup> and 1,200 mg/m<sup>2</sup> increased the clearance of epirubicin and decreased the area under the curve. The study was not designed to determine the optimal dexrazoxane to epirubicin ratio for cardioprotection, but it raises the possibility of a pharmacologic interaction between these agents.

*2002 Recommendation:* 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.

## GUIDELINES FOR THE USE OF AMIFOSTINE

### Amifostine Use in Chemotherapy-Associated Complications

#### 1. Nephrotoxicity

*1999 Recommendation:* Amifostine may be considered for the prevention of nephrotoxicity in patients receiving cisplatin-based chemotherapy.

*2002 Update:* There have been no new randomized studies addressing the efficacy of amifostine for preventing nephrotoxicity in patients receiving cisplatin-based chemotherapy. The FDA has approved amifostine to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or non-small-cell lung cancer. Results from these studies, which were reviewed in the original guideline,<sup>19,20</sup> do not suggest that the effectiveness of cisplatin-based chemotherapy is altered by amifostine. The FDA indication further states that there are only limited data on the effects of amifostine on the efficacy of chemotherapy in other settings and that therefore amifostine should not be administered to patients in settings where chemotherapy can produce a significant survival advantage or cure, except in the context of a clinical trial.

*2002 Recommendation:* No change.

#### 2. Neutropenia

*1999 Recommendation:* The panel recommends that amifostine be considered for the reduction of neutropenia-

associated events in patients receiving alkylating-agent chemotherapy. However, in the absence of clinical data supporting maintenance of the chemotherapy dose-intensity, physicians should consider chemotherapy dose reduction as an alternative to the use of amifostine.

*2002 Recommendation:* No change.

### 3. Thrombocytopenia

*1999 Recommendation:* Present data are insufficient to recommend the use of amifostine for protection against thrombocytopenia in patients receiving alkylating-agent chemotherapy or carboplatin.

*2002 Recommendation:* No change.

### 4. Neurotoxicity and Ototoxicity

*1999 Recommendation:* Present data are insufficient to support the routine use of amifostine for the prevention of cisplatin-associated neurotoxicity or ototoxicity.

*2002 Recommendation:* No change.

### 5. Paclitaxel Associated Neurotoxicity

*1999 Recommendation:* Present data are insufficient to support the use of amifostine for the prevention of paclitaxel-associated neurotoxicity.

*2002 Update:* Since the publication of the 1999 guideline, a randomized phase II study of high-dose paclitaxel with amifostine has been published.<sup>20</sup> In this study, 40 patients with metastatic breast cancer were randomized to receive paclitaxel or paclitaxel preceded by amifostine (910 mg/m<sup>2</sup>). The dose of paclitaxel was 250 mg/m<sup>2</sup>, administered over 3 hours. The amifostine was administered over 15 minutes just before the paclitaxel infusion. Patients completed questionnaires for neurologic symptoms and had standardized neurologic examinations, including objective assessments of power and vibration sense. Overall, there was no difference between the treatment arms on any of the measures of neurotoxicity. However, there were some nonsignificant trends in the frequency of grade 2 and 3 neurosensory toxicity in favor of the amifostine arm. Pharmacokinetic studies were also performed on a subset of patients. Paclitaxel plasma levels were determined and found to be comparable in the presence or absence of amifostine. Thus, there was no evidence that amifostine altered the clearance of paclitaxel. The results from this randomized phase II study do not show evidence of amifostine protection against paclitaxel neurotoxicity. However, these results must be interpreted cautiously as the study was a randomized phase II study and may have been underpowered to detect a clinical difference. A larger, phase III clinical trial would be required to more definitively assess the role of amifostine when given with paclitaxel.

*2002 Recommendation:* There are no data to support the use of amifostine for prevention of paclitaxel-associated neurotoxicity.

## Dose and Administration of Amifostine With Chemotherapy

*1999 Recommendation:* In adults, the suggested dose of amifostine with chemotherapy is 910 mg/m<sup>2</sup>. Amifostine is administered intravenously, over 15 minutes, 30 minutes before chemotherapy. Administration of amifostine requires close patient monitoring, and toxicity is clearly dose related. All patients should be treated with antiemetics before the administration of amifostine, and pretreatment with intravenous fluids should also be considered. Blood pressures are taken every 3 to 5 minutes during the 15-minute infusion. Amifostine is discontinued if blood pressure declines significantly or the patient becomes symptomatic. The hypotension associated with amifostine usually occurs at the end of the infusion and is reversed with discontinuation of the amifostine, administration of saline, and placing the patient in the Trendelenburg position. There are insufficient data to recommend redosing of amifostine after chemotherapy.

*2002 Recommendation:* No change.

## Amifostine Use in Radiation Therapy–Associated Complications

### 1. Xerostomia

*1999 Recommendation:* The panel recommends that amifostine may be considered to decrease the incidence of acute and late xerostomia in patients undergoing fractionated radiation therapy in the head and neck region.

*2002 Update:* The most common and clinically significant toxicities arising from head-neck irradiation are acute mucositis and acute and chronic xerostomia. Small clinical trials have suggested that amifostine protects against radiation-induced toxicity.<sup>21</sup> Since the publication of the 1999 guideline, the final results of a phase III randomized trial of amifostine as a radioprotector in head and neck cancer were published. In that study, 315 patients with previously untreated squamous cell cancer of the head and neck were randomized to radiation alone versus radiation plus amifostine 200 mg/m<sup>2</sup> over 15 to 30 minutes before each radiation therapy treatment. This study demonstrated that amifostine reduced acute and chronic xerostomia while preserving antitumor efficacy.<sup>22</sup> Amifostine reduced the overall incidence of grade 2 or higher acute xerostomia from 78% to 51% ( $P < .0001$ ). The radiation dose associated with this side effect in 50% of all patients was higher in those patients receiving amifostine compared with those who did not (60 Gy v 42Gy, respectively,  $P = .001$ ). Chronic xerostomia

(symptoms 1 year after completion of treatment) occurred in 34% of patients who received amifostine versus 57% in those who did not ( $P = .002$ ). Patients who received amifostine also produced more saliva at 1 year compared with those who did not receive treatment. Amifostine was well tolerated. Nausea, vomiting, and allergic reactions were the most common side effects. Hypotension, usually mild and of short duration, was associated with less than 1% of all amifostine dosages. Complications related to venous catheters occurred in 5% of patients treated with amifostine. There was no evidence that amifostine interfered with the antitumor effects of radiation therapy as measured by local/regional control and overall survival.

Further analysis of this study included a patient benefit questionnaire, which assessed areas such as difficulty speaking and eating, sleep problems, and use of oral comfort aids or fluids. Results of this study showed that amifostine-treated patients consistently reported better patient benefit questionnaire scores, which was indicative of improved oral toxicity-related outcomes and improved clinical benefit.<sup>23</sup>

These data are further supported by a small, double-blind, placebo-controlled study in patients with thyroid cancer undergoing treatment with high-dose radioiodine treatment. Fifty patients were randomly assigned to saline or to amifostine 500 mg/m<sup>2</sup> over 15 minutes before radioiodine treatment. Eleven of the 25 control patients developed grade 1 or 2 xerostomia, while none of the patients treated with amifostine developed xerostomia.<sup>24</sup> Finally, a small randomized study demonstrated that amifostine protected against worsening dental health in patients receiving radiation therapy for head and neck cancer.<sup>25</sup>

*2002 Recommendation:* No change.

## 2. Mucositis

*1999 Recommendation:* Present data are insufficient to recommend amifostine to prevent mucositis associated with radiation therapy.

*2002 Update:* As presented above, since the publication of the 1999 guidelines, the final results of a phase III randomized trial of amifostine as a radioprotector in head and neck cancer were published. Three hundred fifteen patients with previously untreated squamous cell cancer of the head and neck cancer were randomized to radiation alone versus radiation plus amifostine 200 mg/m<sup>2</sup> over 15 to 30 minutes before each radiation therapy treatment. Although this study demonstrated that amifostine reduced acute and chronic xerostomia, amifostine did not reduce the incidence of mucositis. Grade 3 or higher mucositis occurred in 35% of the amifostine group and in 39% of the radiotherapy-alone patients ( $P = .48$ ). The median duration of mucositis was also similar in the two groups of patients

(amifostine group, 41 days v radiotherapy-alone group, 38 days;  $P = .685$ ).<sup>22</sup>

In another radioprotector study, the role of amifostine administered subcutaneously was evaluated in a randomized phase II study. In this study, 140 patients with locally advanced cancer were categorized into three separate regions: head and neck, thoracic, and pelvic localization.<sup>26</sup> Randomizations were performed separately for these three different tumor locations. The dose of amifostine was 500 mg, diluted in 2.5 mL of normal saline and injected subcutaneously, daily, 20 minutes before each radiotherapy fraction. Overall, the results from this study showed a reduced severity of symptoms related to mucositis in those patients treated with amifostine. In the patients treated for gynecologic and rectal tumors, less severe skin radiation toxicity was seen in the perineal/vulvar area in patients treated with amifostine. A phase III study will be required to confirm these preliminary results.

Amifostine has also been evaluated in patients receiving accelerated radiation therapy. Clinical trials of accelerated irradiation suggest improvement of tumor control rates when compared with conventional radiotherapy in patients with head and neck cancer.<sup>27</sup> Accelerated radiation is associated with an increased risk of acute reactions. In a small, randomized trial of 26 patients with inoperable stage IV head and neck cancer, patients were randomized to receive or not amifostine 150 mg/m<sup>2</sup> IV 15 to 30 minutes before each radiation therapy session.<sup>28</sup> Radiation therapy (64 Gy) was delivered over 22 to 23 days. Results from this pilot study suggest that amifostine was able to reduce the severity and duration of mucositis as measured by treatment interruptions, duration of grade 3 mucositis (25.1 days v 49.2 days;  $P = .03$ ), and need for a feeding tube. Ongoing studies will further define the role of amifostine in protecting against radiation-induced mucositis.

*2002 Recommendation:* No change.

## Dose and Administration of Amifostine With Radiation Therapy

*1999 Recommendation:* When given with radiation therapy, the recommended amifostine dose is 200 mg/m<sup>2</sup>/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 side 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.

*2002 Update:* There are no data from randomized clinical trials that test different doses of amifostine in conjunction with radiation therapy. Therefore, the recommendation for dose and schedule of amifostine with radiation therapy has not changed. Ongoing trials are evaluating subcutaneous administration of amifostine when given daily with radiation therapy. In one study, amifostine-related

local toxicity included only mild pain at the site of injection and local erythema. Systemic side effects included nausea, vomiting, and cumulative severe asthenia. No hypotension was reported.<sup>26</sup> There are no data from randomized clinical trials that show that the subcutaneous route is as effective as the IV route of administration in protecting against xerostomia.

*2002 Recommendation:* No change.

## APPENDIX

### Conflict of Interest Disclosure Statements

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*Lynn M. Schuchter, MD, Co-Chair* No conflicts noted.

*Gail Broder* No conflicts noted.

*Gary I. Cohen, MD* No conflicts noted.

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*William J. Gradishar, MD* No conflicts noted.

*Daniel M. Green, MD* No conflicts noted.

*Robert M. Langdon, MD* No conflicts noted.

*Celeste Lindley, PharmD* No conflicts noted.

*Neal J. Meropol, MD* No conflicts noted.

*R. Brian Mitchell, MD* No conflicts noted.

*Robert Negrin, MD* No conflicts noted.

*Ted P. Szatrowski, MD* Employed by Roche Laboratories, Inc.

*J. Tate Thigpen, MD* No conflicts noted.

*Daniel VonHoff, MD* No conflicts noted.

*Todd H. Wasserman, MD* Consultant to Medimmunue Oncology for 2 years as well as a member of their Board advisory committee; given various talks for continued medical education organizations and received in excess of \$2,000 per year.

*Eric P. Winer, MD* No conflicts noted.

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