



American Society of Clinical Oncology

Making a world of difference in cancer care

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

Introduction

- The American Society of Clinical Oncology (ASCO) first published evidence-based clinical practice guidelines for the use of chemotherapy and radiotherapy protectants in 1999 and a previous update was published in 2002
- ASCO guidelines are updated at intervals by an Update Committee of the original Expert Panel
- For the 2008 update, the ASCO Update Committee expanded the scope of the guideline to include a new agent, palifermin, and a section on radiation – associated esophagitis

Guideline Methodology: Systematic Review

- The panel completed a review and analysis of the medical literature available from 2002 to June 2007 on the use of chemotherapy and radiotherapy protectants. There was no date limit on the search regarding palifermin.
 - ✓ Medline
 - ✓ PreMedline
 - ✓ Cochrane Collaboration Library

Guideline Methodology: Panel Members

•Martee L. Hensley, MD, Co-Chair	•Memorial Sloan Kettering Cancer Center
•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 (GBMC)
•Bahman Emami, MD	•Loyola Medical Center
•William J. Gradishar, MD	•Northwestern University
•Daniel M. Green, MD	•Roswell Park Cancer Institute

Guideline Methodology: Panel Members (continued)

•Tarun Kewalramani, MD	•Memorial Sloan-Kettering Cancer Center
•Neal J. Meropol, MD	•Fox Chase Cancer Center
•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	•Arizona Cancer Center
•Todd H. Wasserman, MD	•Mallinckrodt Institute of Radiation

Medications covered by Guideline Update 2008:

- Dexrazoxane
- Amifostine
- Palifermin - new
- Mesna

Clinical Questions New to Update

1. Role of Amifostine regarding radiation therapy-associated toxicity esophagitis
2. Palifermin
 - a. Autologous Hematopoietic Stem Cell Transplantation
 - b. Allogeneic Hematopoietic Stem Cell Transplantation
 - c. Dose and Administration of Palifermin With Hematopoietic Stem Cell Transplantation
 - d. Non-Stem Cell Transplantation and Solid Tumors

Use of Dexrazoxane in Breast Cancer

- Not recommended for routine use for patients with metastatic breast cancer receiving initial doxorubicin-based chemotherapy.
- Consider using for patients with metastatic breast cancer who have received more than 300 mg/m² of doxorubicin in the metastatic setting and who may benefit from continued doxorubicin-containing therapy. Management of patients who received more than 300 mg/m² 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.
- The use of dexrazoxane in the adjuvant setting is not suggested outside of a clinical trial.

Use of Dexrazoxane in Other Malignancies

- Adults – Consider the use of dexrazoxane in adult patients who have received more than 300 mg/m² of doxorubicin-based therapy. Exercise caution in the use of dexrazoxane in settings in which doxorubicin-based therapy has been shown to improve survival.
- Pediatric patients - Insufficient evidence to make a recommendation for the use of dexrazoxane in the treatment of pediatric malignancies.

Use of Dexrazoxane - Other Anthracycline Doses and Schedules

- Based on 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.
- Limited data for using dexrazoxane with epirubicin for treatment of other cancers. Insufficient data to make a recommendation regarding the use of dexrazoxane with other potentially cardiotoxic agents.

Use of Dexrazoxane - Other Anthracycline Doses and Schedules (cont'd)

- High-dose anthracyclines: No new data address 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.
- Insufficient evidence on which to base a recommendation for the use of dexrazoxane in patients with cardiac risk factors or underlying cardiac disease .

Use of Dexrazoxane – Monitoring Therapy

- After termination of anthracycline therapy: Patients receiving dexrazoxane need continued cardiac monitoring. After cumulative doxorubicin doses of 400 mg/m², cardiac monitoring should be frequent. Repeat the monitoring study after 500 mg/m² and subsequently after every 50 mg/m² of doxorubicin is suggested. Strongly consider the termination of dexrazoxane/doxorubicin therapy in patients who develop a decline in LVEF to below institutional normal limits or who develop clinical congestive heart failure.
- Dose: Suggested dexrazoxane dose - 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.

Use of Amifostine in Chemotherapy-Associated Toxicities

- Amifostine may be considered for the prevention of nephrotoxicity in patients receiving cisplatin-based chemotherapy.
- While using 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.

Use of Amifostine in Chemotherapy-Associated Toxicities (cont'd)

- Use of amifostine for protection against thrombocytopenia in patients receiving chemotherapy or radiotherapy not recommended.
- Present data are insufficient to support the routine use of amifostine for the prevention of platinum-associated neurotoxicity or ototoxicity.
- Data are insufficient to support the routine use of amifostine for the prevention of paclitaxel-associated neuropathy.

Use of Amifostine in Chemotherapy-Associated Toxicities (cont'd)

The current FDA-approved dose is 910 mg/m² intravenously over 15 minutes, 30 minutes prior to chemotherapy.

- Familiarity with the package insert and close patient monitoring during the infusion are required.
- Common toxicities: acute hypotension, nausea, and fatigue.

Use of Amifostine in Radiotherapy-Associated Toxicities

- May be considered to decrease the incidence of acute and late xerostomia in patients undergoing fractionated radiotherapy 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.
- Data are insufficient to recommend amifostine to prevent mucositis associated with radiation therapy for head and neck cancer.
- Data are insufficient to recommend the routine use of amifostine to prevent esophagitis in patients receiving concurrent chemoradiotherapy for non-small cell lung cancer.

Use of Amifostine in Radiotherapy-Associated Toxicities (cont'd)

- With radiation therapy, the recommended amifostine dose is 200 mg/ m²/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.

Use of Palifermin – Autologous hematopoietic stem cell transplantation

- Palifermin is recommended for use for patients undergoing autologous hematopoietic 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.

Use of Palifermin – Autologous hematopoietic stem cell transplantation (cont'd.)

- Dose: 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.

Use of Palifermin - Allogeneic HSCT and other

- Palifermin may be considered for use in patients undergoing myeloablative allogeneic hematopoietic stem cell transplant with a TBI-based conditioning regimen.
- Insufficient data to recommend its use in myeloablative conditioning regimens consisting of chemotherapy alone in this setting.
- Insufficient data to recommend the use of palifermin in the non-stem cell transplant setting, or for use in the treatment of solid tumors.

Use of Mesna - Ifosfamide

- Mesna recommended to decrease the incidence of ifosfamide-associated urothelial toxicity.
- Suggested daily dose: 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/m²/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.

Use of Mesna – Ifosfamide (cont'd)

- There is insufficient evidence on which to base a recommendation for the use of mesna with ifosfamide doses in excess of 2.5 g/m²/d. 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.

Use of Mesna – Ifosfamide

(cont'd)

- United States Food and Drug Administration (FDA) approved Mesna tablets to prevent hemorrhagic cystitis in patients receiving ifosfamide chemotherapy.
- Recommended dose and schedule: 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.
- For patients who vomit within 2 hours of taking oral mesna - repeat the dose or receive IV mesna. Repeat dosing schedule on each day that ifosfamide is administered.

Use of Mesna - Cyclophosphamide

- 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.
- 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.

Additional ASCO Resources

- The full text of the guideline, this slide set, and additional clinical tools and resources can be found at:
<http://www.asco.org/guidelines/protectants>
- A patient guide on chemotherapy and radiation therapy protectants can be found at <http://www.cancer.net>



ASCO Guidelines

It is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because 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.