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## Use of Dexrazoxane as a Cardioprotectant in Patients Receiving Doxorubicin or Epirubicin Chemotherapy for the Treatment of Cancer Practice Guideline Report #12-5

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ORIGINAL GUIDELINE: November 16, 1998

NEW EVIDENCE ADDED TO THE GUIDELINE REPORT: June 2002

MOST RECENT LITERATURE SEARCH: January 2004

This summary integrates the original practice guideline report with the most current information (labeled Update).

### SUMMARY

#### Guideline Questions

- Should dexrazoxane be used routinely in patients with advanced or metastatic cancer who are at risk of developing cardiotoxicity when receiving chemotherapy containing doxorubicin or epirubicin?
- Do the available data support the use of dexrazoxane in the adjuvant setting for patients at risk of developing cardiotoxicity?

#### Target Population

These recommendations apply to adult patients with non-hematologic malignancies who are receiving anthracycline-containing chemotherapy.

#### Recommendations

- The evidence supports the use of dexrazoxane to protect against the cardiotoxicity associated with conventional-dose doxorubicin in patients with advanced but anthracycline-sensitive cancer, in whom the continued use of anthracycline-containing chemotherapy is indicated in the opinion of the treating physician, and who have received 300 mg/m<sup>2</sup> or more of doxorubicin.
- The evidence supports the use of dexrazoxane to protect against the cardiotoxicity associated with conventional-dose epirubicin in patients with advanced but anthracycline-sensitive cancer, in whom the continued use of anthracycline-containing chemotherapy is indicated in the opinion of the treating physician. There are no data indicating the optimal cumulative dose of epirubicin at which dexrazoxane should be instituted. For doxorubicin, use of dexrazoxane is recommended after the cumulative dose reaches 300 mg/m<sup>2</sup> (i.e. 55% of the recommended maximum). A similar formula could be used for epirubicin; that is, institution of dexrazoxane when the cumulative dose of epirubicin reaches 550mg/m<sup>2</sup>, as the recommended maximum cumulative dose in Canada is 1000mg/m<sup>2</sup>.
- Preclinical studies did not show any cardioprotectant effect for dexrazoxane when used with mitoxantrone, and no clinical studies have been done. Therefore, dexrazoxane is not recommended for use with mitoxantrone.

## Qualifying Statements

- There is no evidence to support or refute the use of dexrazoxane in the adjuvant setting for any tumour type. Because of concerns that dexrazoxane may reduce the efficacy of anthracyclines, and because data are not yet available on long-term toxicities, further studies should be performed before the drug is used in this setting.
- The majority of published studies of dexrazoxane have been performed on patients with breast cancer. Two trials in patients with other tumour sites (small-cell lung cancer and pediatric sarcoma) report beneficial effects on cardiotoxicity consistent with those for breast cancer. These results lend support to the use of the drug in conjunction with doxorubicin in patients with other tumour sites, although further studies should be performed to confirm these benefits. There are no data on the use of dexrazoxane in patients with hematologic malignancies.
- There are no data on the use of dexrazoxane in patients with pre-existing cardiac disease or anthracycline-induced cardiotoxicity; further studies should be performed in these settings.
- There are no data available regarding interaction between dexrazoxane and chemotherapeutic agents other than doxorubicin, epirubicin, cyclophosphamide, 5-fluorouracil or vincristine, and care should be exercised before using dexrazoxane with regimens that contain drugs other than these.

## Methods

Entries to MEDLINE (through January 2004), EMBASE (through January 2004), and Cochrane Library (through Issue 4, 2003) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology have been searched for evidence relevant to this practice guideline. The most recent literature search was performed in January 2004.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative's Systemic Treatment Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Systemic Treatment Disease Site Group, which comprises medical oncologists, pharmacists and one patient representative.

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

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

## Key Evidence

Seven randomized controlled trials, two with placebo control, were reviewed. Clinical cardiotoxicity data from six trials were pooled (n=1070). The meta-analysis indicated that the risk of experiencing clinical cardiotoxicity was significantly reduced by dexrazoxane (odds ratio, 0.21; 95% confidence interval, 0.08 to 0.51; p=0.0006). There was no significant benefit shown in individual trials for objective response or survival.

One of the randomized controlled trials revealed a significantly lower objective response rate in the dexrazoxane arm. However, a meta-analysis of objective response across five trials of breast cancer patients (n=818) did not confirm this effect (odds ratio, 0.80; 95% confidence interval, 0.61 to 1.06; p=0.12). The use of dexrazoxane increased the incidence of myelosuppression and other noncardiac toxicities, but these were generally mild.

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## **PREAMBLE: About Our Practice Guideline Reports**

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

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

### Reference:

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

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