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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

L. Seymour, V. Bramwell, and members of the Systemic Treatment Disease Site Group

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/m² 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/m² (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/m², as the recommended maximum cumulative dose in Canada is 1000mg/m².
- 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.

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

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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.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, 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:

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

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Phone: 905-525-9140, ext. 22055
Fax: 905-522-7681

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FULL REPORT

I. QUESTIONS

1. 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?
2. Do the available data support the use of dexrazoxane when anthracyclines are being used in the adjuvant setting for patients at risk of developing cardiotoxicity?

II. CHOICE OF TOPIC AND RATIONALE

Doxorubicin and epirubicin are often included in adjuvant and palliative regimens, especially in the management of breast cancer. The prolonged or repeated use of these agents, in the case of relapse after anthracycline-containing chemotherapy, is limited by the development of chronic and usually irreversible cardiotoxicity. This is manifested by either a fall in left ventricular ejection fraction (LVEF) or the development of clinical cardiac failure (congestive heart failure: CHF) (1). Cardiomyopathy develops in 5% to 15% of patients at doxorubicin doses of greater than 450 mg/m^2, while sub-clinical changes in LVEF are seen more frequently. Epirubicin may have a lower potential for cardiotoxicity (2,3).

The following potential strategies may minimize cardiotoxicity:
careful monitoring of LVEF, with early discontinuation of the anthracycline and substitution of other agents in the event of change;

- routine discontinuation of the anthracycline and substitution of other agents when a fixed dose is reached (450-550 mg/m^2);
- the use of epirubicin in preference to doxorubicin;
- changes in the scheduling of the drugs (4,5);
- the use of “cardioprotectants” such as dexrazoxane.

Little is known of the impact on antitumour efficacy of the routine discontinuation of doxorubicin at a fixed dose.

It is believed that anthracycline cardiotoxicity is mediated by the formation of doxorubicin-iron complexes and the generation of hydroxyl radicals leading to oxidative damage to myocardial cells. Dexrazoxane (ICRF-187) is an iron-chelating agent that removes iron from doxorubicin-iron complexes in vitro. Although originally developed as an antineoplastic agent (and it is known to inhibit topoisomerase II), further development in this area was abandoned due to lack of efficacy. However, dexrazoxane was also noted to protect against the development of anthracycline-induced cardiac damage (with doxorubicin and epirubicin, but not mitoxantrone) in a variety of models (6) and the drug has subsequently been developed for this indication. Whereas initial preclinical studies suggested a possible synergistic antitumour activity of anthracyclines and dexrazoxane (7), at least two subsequent studies have suggested the potential for antagonism (8,9). Razoxane, a similar agent, has been associated with the development of secondary malignancies, including leukemia (10), and is not considered in this report. Toxicities noted in phase I studies of dexrazoxane included myelosuppression (dose limiting), as well as abnormalities in liver function tests, nausea and alopecia at doses of 1000 mg/m^2 (continuous infusion for 48 hours) and 1250 mg/m^2 (daily for 3 days) (11,12).

Doxorubicin and epirubicin are increasingly used in the management of breast cancer and other cancers, and although acquired anthracycline resistance is the most usual reason for discontinuing the use of these agents, the risk of cardiotoxicity with these agents is an important clinical problem. The use and scheduling of dexrazoxane as a cardioprotectant needs to be carefully examined, particularly in light of concerns regarding reduced efficacy and increased myelotoxicity.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care, using the methods of the Practice Guidelines Development Cycle (1u). Evidence was selected and reviewed by two members of the PGI's Systemic Treatment Disease Site Group (Systemic Treatment DSG) and methodologists. Members of the Systemic Treatment DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of dexrazoxane in patients with non-hematologic malignancies receiving anthracycline-containing chemotherapy, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

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

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

Guideline History

This practice guideline report was originally completed on November 16, 1998 and published in Cancer Prevention and Control 1999;3(2):145-159. The guideline was reviewed monthly from June 1998 to December 1999, quarterly from April 2000 to June 2002 and most recently in January 2004. In this report, information that has emerged from review and updating activities is labeled Update.

Literature Search Strategy

MEDLINE and CANCERLIT searches were performed for the years 1987 to November 1997. The search terms included the following medical subject headings (MeSH): dexrazoxane, neoplasms, practice guidelines, meta-analysis, randomized controlled trials, double-blind and single-blind method; and the following text words: dexrazoxane, randomized controlled trial and random. The search also included the following publication types: practice guideline, meta-analysis and randomized controlled trial. This search was updated in March 1998. The Physician Data Query (PDQ) clinical trials database and the 1995, 1996 and 1997 American Society of Clinical Oncology (ASCO) proceedings were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed, and the reference lists from these sources were searched for additional trials.

Update

The original literature search has been updated using MEDLINE (through January 2004), EMBASE (through January 2004), the Cochrane Library (Issue 4, 2003) and the proceedings of the annual meetings of ASCO, 1998-2003.

Inclusion Criteria
Articles were selected for inclusion in this systematic review of the evidence if they were or included:
1. Randomized controlled trials (RCTs) comparing dexrazoxane with a placebo or no treatment.
2. Patients receiving chemotherapy containing doxorubicin or epirubicin.
3. Trials reporting on clinical or sub-clinical cardiotoxicity, non-cardiac toxicity, response rates or overall survival.
4. Patients with non-hematologic malignancies.
5. Abstracts of trials were also considered.

Exclusion Criteria
1. Phase I and II studies were not considered for inclusion in this report because of the availability of RCTs.
2. Letters and editorials were not considered.
3. Papers published in a language other than English were not considered.

Synthesizing the Evidence
Combining results across trials provided added power to detect the efficacy of a treatment and increased the precision of the estimate. The outcome measures used to report clinical and sub-clinical cardiotoxicity were consistent from trial to trial (CHF, a decrease in LVEF ≥20 from base line, and a fall in resting LVEF to ≤45%), but in some cases these data were reported together. Since the data for clinical cardiotoxicity were reported separately for all but one trial, it was decided to pool the results for this outcome measure to obtain a more precise estimate of the treatment effect of dexrazoxane. Tests of heterogeneity were conducted to assess whether the differences in chemotherapy regimen (doxorubicin or epirubicin), dose ratio of dexrazoxane to chemotherapy agent, or tumour type contributed to the effect. Since there was a question about the contribution of dexrazoxane to the antitumour effect of the chemotherapy agent, the objective response results were also pooled.

The results were pooled using the software package *Metaanalyst 0.988*, provided by Dr. Joseph Lau of Boston, MA.

IV. RESULTS

Literature Search Results
Seven RCTs were identified, six trials reported fully in the published literature (13-19), and one trial reported only in abstract form (20). Five trials were conducted in patients with breast cancer (13-15,17,19) and three enrolled patients with other tumour sites (16,19,20). One trial involved patients with two disease sites (19). The trials are presented in this report by type of cancer (breast cancer or other tumour sites) and according to the type of anthracycline used (doxorubicin or epirubicin). The outcomes are reported in three categories and include outcomes related to: i) cardiotoxicity (clinical and sub-clinical cardiotoxicity), ii) dose of chemotherapy (cumulative dose), and iii) clinical treatment outcomes (objective response [complete response and partial response] and overall survival). See below and Tables 1, 2 and 3 for detailed results of the RCTs. The pooled results of clinical cardiotoxicity and objective response are reported following a description of the results of individual trials. This information appears in Figures 1 and 2.

Update
One evidence-based practice guideline developed in 1999 (2u) and updated in 2002 (3u) was identified and added in June 2002. No new evidence was located in the most recent review of the literature (January 2004).

Advanced Breast Cancer – Doxorubicin

There are three RCTs of dexrazoxane in patients with advanced breast cancer treated with doxorubicin (13,14,17,18). One trial is reported in two papers (13,14), and two trials are reported together in one article (17) and also in a second paper that reports a retrospective analysis using combined data from the same two trials (18). The results of these trials will be described below and in Table 1. Dosage and scheduling information is provided in Appendix 1.

1) Speyer et al published two reports of one RCT of dexrazoxane in advanced breast cancer (13,14). In the first report (13), interim results were reported, and in the second report (14), final results for 150 patients were reported. Women with advanced breast cancer were randomized to receive either 500 mg/m^2 of cyclophosphamide, 50 mg/m^2 of doxorubicin, 500 mg/m^2 of 5-fluorouracil (5-FU) (CAF) (n=74), or CAF plus dexrazoxane (n=76) in a dose ratio of 20:1 (dexrazoxane: doxorubicin). No patients had received prior anthracycline therapy. The doses of dexrazoxane were not modified during the study, and for the first two cycles, 5-FU and cyclophosphamide doses were modified in preference to doxorubicin where feasible.

The results favoured patients in the CAF and dexrazoxane arm in terms of cardiac protection. Two patients receiving dexrazoxane experienced CHF compared with 20 patients in the CAF-alone group ($p<0.0001$). Fewer patients in the CAF and dexrazoxane group, compared with the CAF- alone group, experienced a decrease in LVEF of 20% or more (5 versus [vs.] 32; $p<0.000001$). The CAF and dexrazoxane group was also favoured in the outcomes related to dosage of chemotherapy, having received more cycles of chemotherapy than the CAF-alone group (11 vs. 9; $p<0.01$). They also tolerated a higher cumulative dose of doxorubicin (500 mg/m^2 vs. 441 mg/m^2; $p<0.05$). However, patients in the CAF and dexrazoxane arm received significantly lower projected doses of 5-FU and cyclophosphamide than those in the CAF-alone group. They also had significantly lower white blood cell (WBC) nadirs (2.3 vs. 2.6 x 10^9/L; $p<0.05$) after the second cycle and lower platelet nadirs (190 vs. 225x10^9/L; p=nonsignificant [NS]) after the first cycle. The rest of the toxicity profile was comparable between the two arms. Objective response, progression-free survival and overall survival were similar in the two arms.

2) Swain et al reported the results of two RCTs, both of which enrolled patients with advanced breast cancer (stage IIIB and IV), who had not received prior anthracycline-containing chemotherapy (17). In both trials, patients were randomized to receive 500 mg/m^2 of 5-FU, 50 mg/m^2 of doxorubicin, and 500 mg/m^2 of cyclophosphamide (FAC) with either dexrazoxane or a placebo. The first study (088001) used dexrazoxane at a dose ratio of 20:1 initially, and after observation of increased toxicity, the protocol was amended, reducing the ratio of dexrazoxane to doxorubicin to 10:1. The second study (088006) began 15 months later, with a dose ratio of 10:1 throughout. Twenty months into the first study (in January 1991), the two studies were further amended due to an excess of cases of cardiotoxicity in the placebo arm. This amendment provided for the late introduction of dexrazoxane. All patients receiving a cumulative dose of at least 300 mg/m^2 of doxorubicin would receive dexrazoxane on an open-label basis (18).

The results were presented only for those patients receiving dexrazoxane at a ratio of 10:1 and those randomized prior to the change in protocol to allow the late introduction of dexrazoxane (17). It is important to note that this is a subgroup analysis, with those patients receiving the high-dose ratio omitted from the analysis (see Figure 3). The results are presented here separately for each trial when reported that way in the paper, as some outcomes were combined across both trials. Some outcomes were reported as hazard ratios. A hazard ratio (HR) greater than 1.0 indicates that an event is more likely to occur in the placebo arm than in the dexrazoxane arm, whereas an HR less than 1.0 means that an event is more likely to occur in the dexrazoxane arm.

The second report, which presents a retrospective analysis of the RCT to assess the effectiveness of the late introduction of dexrazoxane, will be discussed below (18).

There were 349 patients analyzed in study 088001 and 185 in study 088006. The two trials were well balanced for all patient characteristics including cardiac risk factors (prior heart disease, hypertension or diabetes requiring therapy, age >65 years, borderline LVEF). Dose reductions were permitted for cyclophosphamide and 5-FU, but were not allowed for doxorubicin or dexrazoxane.

Cardiac events were more frequent in patients randomized to placebo for both studies (study 088001: HR, 2.63; 95% confidence interval [CI], 1.61 to 4.27; p<0.001 by log rank; study 088006: HR, 2.00; 95% CI, 1.01 to 3.96; p=0.038 by log rank). However, neither HR was statistically significant by Wilcoxon tests. In the combined studies, CHF was more common in the placebo group (2/249 vs. 22/285; p=0.0001). Four patients, all in the placebo arm, died of or with CHF, and had received between 450 and 550 mg/m^2 of doxorubicin.

In study 088001, the objective response rate was significantly higher in the placebo arm compared with the treatment arm (61% vs. 47%; p=0.019); objective response rate results were not significantly different in study 088006 (49% vs. 54%, p=0.63). There was also no difference between treatments in time to progression or overall survival in either study. Patients in the FAC and dexrazoxane group had a statistically significantly lower WBC nadir (predominantly grade 3/4), and granulocyte (predominantly grade 4) and platelet (predominantly grade 1) counts compared with the FAC and placebo group, as well as significantly lower platelet counts at recovery. However, this appeared to be of limited clinical significance, as there were no differences in dose modifications, infection, sepsis, or bleeding between the two arms of both studies. Patients receiving dexrazoxane also experienced significantly more nausea and vomiting, and pain at the injection site than patients receiving placebo.

3) Swain et al published a second report, presenting the results of a retrospective analysis to determine whether the “late” introduction of dexrazoxane confers cardioprotection in patients receiving doxorubicin (18). This analysis compared 102 patients, from two separate trials described previously (17), who received six or more cycles of FAC with dexrazoxane, added beginning with the seventh cycle, with 99 patients who received six or more cycles of FAC with a placebo (see Figure 3). The two groups were well balanced for base line demographics (except for weight) and cardiac risk factors, but imbalances were detected in the site, extent and measurability of disease. In addition, more patients in the FAC and placebo group had achieved an objective response by their sixth cycle of FAC. The FAC and dexrazoxane group had significantly fewer cardiac events (25% vs. 60%; HR, 3.5; 95% CI, 2.2 to 5.7). The treatment group also had a significantly longer overall survival, which was expressed as the number of days from the beginning of the seventh course to death or censorship (median survival, 882 vs. 460 days; HR, 2.2; 95% CI, 1.4 to 3.3). The validity of this result is questionable given the nature of the analysis. Pain on injection was significantly more common in the dexrazoxane arm, and hematologic toxicity was not assessable, as nadir counts were not measured.

Table 1. Randomized trials of dexrazoxane (ICRF-187) in patients with breast cancer receiving doxorubicin.

Trial	n/arm (eval)	Treatment allocation	Outcomes related to cardiotoxicity		Outcomes related to dose of chemotherapy			Other clinical outcomes	
			Clinical* n (%)	Subclinica† n (%)	# receiving >700mg dox	# receiving >1000mg dox	Cumulative dose (mg/m^2)	Objective response ‡ n (%)	Overall survival (median)
Speyer et al 1992 (14)	76 (76) 74 (74)	•CAF + dex •CAF alone	2 (3) 20 (27) p<0.0001	5 (7) 32 (43) p<0.000001	30 8	11 0	500 441 p<0.05	7(9) 5(7) p=NS	18.3 months 16.7 months p=NS
Swain et al 1997 (17) 088001	168 (168) 181 (181)	•CAF + dex •CAF + placebo	0 (0) 15 (8) p<0.001	25 (15) ¶ 57 (31) p<0.001	NR	NR	NR	66/141 (47) 99/152 (61) p=0.019	598 days 551 days p=NS
088006	81 (81) 104 (104)	•CAF + dex •CAF + placebo	2 (2) 7 (7) p=0.30	11 (14) ¶ 32 (31) p=0.006	NR	NR	NR	29/54 (54) 34/69 (49) p=0.63	458 days 553 days p=NS
Swain et al 1997 (18)	102 (102) 99 (99)	•CAF + placebo / dex •CAF + placebo	25 (25) 59 (60) p=0.0001	NR	NR	7 1	NR	NR	882 days 460 days

Note: CAF = cyclophosphamide, doxorubicin, 5-fluorouracil; dex = dexrazoxane; dox = doxorubicin; eval = evaluable; n = number of patients; NR = not reported; NS = no statistically significant difference between the two arms
*Clinical cardiotoxicity=congestive heart failure (CHF) rate
† Sub-clinical cardiotoxicity= decrease in left ventricular ejection fraction (LVEF) from baseline ≥20 EF units, or decrease in resting LVEF to ≤45%
§ Objective response = complete response (CR) plus partial response (PR)
¶ Includes all cardiac events

Advanced Breast Cancer – Epirubicin

Two RCTs were reported in patients with advanced breast cancer receiving epirubicin (15,19). Detailed results are presented below and in Table 2, and dosage and schedules are found in Appendix 1.

1) Venturini et al reported an RCT of epirubicin and dexrazoxane in 162 patients (160 evaluable) with advanced breast cancer (15). Patients who had received prior anthracycline-containing adjuvant chemotherapy received 600 mg/m^2 of cyclophosphamide, 60 mg/m^2 of epirubicin, and 600 mg/m^2 of intravenous (IV) fluorouracil every 3 weeks (CEF), whereas anthracycline-naive patients received high-dose epirubicin (HD-Epi, 120 mg/m^2 IV), every three weeks. Patients were randomized to receive either CEF or HD-Epi with or without dexrazoxane

at a dose ratio of 10:1 (dexrazoxane: epirubicin). Cardiac toxicity was defined as either clinical cardiac failure, a decrease in LVEF ≥20% from base line or a fall in LVEF to ≤45%.

There was no significant difference in the number of cycles administered, nor in the cumulative dose of anthracycline administered. The patient groups were well balanced at base line in terms of prior anthracycline use, cardiac risk factors (diabetes, hypertension, age >65 years, chest wall radiation), and base line LVEF. The cumulative probability of developing cardiotoxicity was significantly lower in the dexrazoxane groups than in the HD-Epi-alone group (7.3% vs. 23.1%; odds ratio [OR], 0.29; 95% CI, 0.09 to 0.78; p=0.006). An OR less than 1.0 favours treatment (dexrazoxane), an OR more than 1.0 favours control, and an OR of 1.0 indicates no difference between groups. Of note, cardiotoxicity (either clinical or laboratory) was seen only in patients receiving HD-Epi and cardiotoxicity was more likely to occur in patients with cardiac risk factors, although dexrazoxane appeared equally effective in patients with and without cardiac risk factors. There was no difference between the CEF and dexrazoxane and CEF-alone groups in objective response rate, defined as complete response plus partial response (47.6% vs. 46.2%). No difference between the treatment and control groups was detected in progression-free survival or overall survival.

There was no difference between the groups in non-cardiac toxicity, although a higher incidence of phlebitis, and nausea and vomiting was noted in the dexrazoxane arm compared with the control (12% vs. 4%).

2) Lopez et al reported an RCT of epirubicin with or without dexrazoxane (19). Ninety-five patients with advanced breast cancer were randomized to receive either 160 mg/m^2 of epirubicin plus 1000 mg/m^2 of dexrazoxane (n=45) or epirubicin alone (n=50), with cycles repeated every three weeks. Dexrazoxane was given at a dose ratio of 6:1. Forty-three and 49 patients were evaluable, respectively (one patient was withdrawn due to angina after one cycle, one patient refused further treatment and one patient was lost to follow-up). There were no statistically significant differences detected in objective response or time to progression. Median overall survival in the epirubicin and dexrazoxane arm was 29 months versus 19 months in the standard-treatment arm, but the difference was not statistically significant.

For the purposes of examining toxicity, including cardiotoxicity, pooled results were reported from these 95 patients with breast cancer and an additional 34 patients with soft tissue sarcomas (see below). A total of 62 evaluable patients received epirubicin and 59 evaluable patients received epirubicin plus dexrazoxane. Noncardiac toxicity was similar in the two arms of the study. The median cumulative dose of epirubicin, mean dose intensity and median number of cycles administered were similar in both arms. Patients who received epirubicin alone were more likely to experience CHF (4 vs. 0 patients) or less severe cardiac effects (9 vs. 4 patients), compared with patients who received epirubicin plus dexrazoxane. The group receiving dexrazoxane and epirubicin did not experience a significant reduction in LVEF values, as did the control group. Interestingly, the difference in LVEF values between the two groups became statistically significant at cumulative epirubicin doses of 960 mg/m^2 (p=0.007).

Table 2. Randomized trials of dexrazoxane (ICRF-187) in patients with breast cancer receiving epirubicin.

Trial	n /arm (eval)	Treatment allocation	Outcomes related to cardiotoxicity		Outcomes related to dose of chemotherapy			Other clinical outcomes	
			Clinical * n(%)	Sub-clinical† n(%)	Number receiving >700mg epi	Number receiving >1000mg epi	Cumulative dose (mg/m^2)	Objective response§ n (%) (95%CI)	Overall survival (median)
Venturini et al, 1996 (15)	84 (82)	•CEF or HD-Epi + dex	2 (2)	4 (5)	54	3	702	39 (46.2) (34.9-57.8)	NR p=0.75
	78 (78)	•CEF or HD-Epi alone	4 (5)	14 (18) p=0.006¶	51	3	713	37 (47.6) (36.5-58.8) p=NS	
Lopez et al, 1998 (19)	45 (43)	•Epi + dex	0/59 (0)#	4/59 (7)#	32/63 (51)#	12/63 (19)#	960#	29 (67) (53-81)	29 mo
	50 (49)	•Epi alone	4/62 (8)#	9/62 (15)#	43/66 (65)#	9/66 (14)#	880#	34 (69) (56-82)	19 mo p=0.21

Note: CEF = cyclophosphamide, epirubicin, and intravenous fluorouracil; dex = dexrazoxane; epi = epirubicin; eval = evaluable; HD-Epi = high-dose epirubicin; n = number; NR = not reported; NS = no significant difference between the two arms; STS = soft tissue sarcoma
*Clinical cardiotoxicity=congestive heart failure (CHF) rate
† Sub-clinical cardiotoxicity= decrease in left ventricular ejection fraction (LVEF) from base line ≥20 EF units, or decrease in resting LVEF to ≤45%
§ Objective response = complete response (CR) plus partial response (PR)
¶ Statistical significance measure includes clinical cardiotoxicity (CHF) data
# Pooled data, includes STS

Other Tumour Sites – Doxorubicin or Epirubicin

There are three RCTs involving patients with tumours other than breast cancer. One trial was conducted in patients with small-cell lung cancer (SCLC) (20), and a second trial in children and young adult patients with sarcoma (16). In both of these trials, patients were treated with doxorubicin-containing chemotherapy. A third trial involved patients with sarcoma who were treated with epirubicin (19). The results of these trials are shown in Table 3, and dosages and schedules appear in Appendix 2.

1) Feldmann et al reported, in abstract form, the results of an RCT of dexrazoxane (dose ratio of 10:1) in patients with SCLC (20). One hundred and fifty-five patients were randomized but only 105 were evaluable at the time of the report. Forty-three patients received 750 mg/m^2 of cyclophosphamide, 50 mg/m^2 of doxorubicin, 2 mg of vincristine (CAV) plus dexrazoxane, and 62 patients received CAV alone. There were significantly fewer cardiac events in the CAV and dexrazoxane group (12% vs. 29%; p=0.029), as well as a smaller reduction in LVEF per cumulative dose of doxorubicin up to 600 mg/m^2. Objective response rates (67% vs. 68%; p=NS) and time to progression (183 vs. 183 days; p=NS) were identical in both groups. Hematologic toxicity appeared similar in both arms, but more phlebitis was seen with dexrazoxane, as well as slightly more infection and sepsis.

2) Wexler et al conducted a randomized trial of dexrazoxane (dose ratio 20:1) as a cardioprotective agent in 38 pediatric and young adult patients (age <25 years) receiving

doxorubicin-containing chemotherapy (VAdriaC) (16). Twenty patients were randomized to receive VAdriaC with dexrazoxane and 18 to receive VAdriaC alone. Patients who received VAdriaC with dexrazoxane had significantly less change in LVEF per 100 mg/m^2 of doxorubicin compared with VAdriaC alone, reported as mean decrease in percentage points (1.0 vs. 2.7; p=0.02). The VAdriaC plus dexrazoxane group tolerated a significantly higher mean cumulative dose of doxorubicin compared with the VAdriaC-alone group when dose-limiting cardiotoxicity developed (410 mg vs. 310 mg; $p<0.05$). There were no differences between the two groups in objective response (80% vs. 81%) or progression-free survival (17 vs. 17 months). Median overall survival was 43 vs. 24 months for treatment with dexrazoxane and the control respectively, but this was not statistically significant.

In patients receiving dexrazoxane, there was a significantly higher incidence of grade 1 transaminase elevations after cycles 1 and 2, and significantly more grade 3 thrombocytopenia after cycles 1 and 6. There were also lower platelet nadirs after cycles 4 and 6, and a significantly longer time to neutrophil recovery after cycle 1, but these differences appeared to be of limited clinical significance as dose modifications were similar in the two arms.

3) Lopez et al also conducted a small randomized trial of dexrazoxane (dose ratio 6:1) as a cardioprotective agent in 34 patients with soft tissue sarcoma. Eighteen patients received epirubicin plus dexrazoxane, while 16 patients received epirubicin alone. Whereas overall survival was similar in both arms, time to progression was nine months in patients who received epirubicin alone, compared with seven months in patients receiving the combination treatment (p=0.07); response rates were 37.5% and 11% respectively (p=NS). The toxicity data from this study were pooled with a similar study conducted in patients with advanced breast cancer, which is discussed above.

Table 3. Randomized trials of dexrazoxane (ICRF-187) in patients with other tumour sites receiving doxorubicin or epirubicin.

Trial	n /arm (eval)	Treatment allocation	Outcomes related to cardiotoxicity		Outcomes related to dose of chemotherapy			Other clinical outcomes	
			Clinical* n (%)	Sub-clinical† n (%)	Number receiving >700mg anthracycline	Number receiving >1000mg anthracycline	Cumulative dose (mg/m^2)	Objective response§ n (%) (95%CI)	Clinical* n(%)
Feldmann et al, 1992 (20) (SCLC)	(43) (62)	•CAV + dex •CAV alone	2 (5) 5 (8)	9 (12) ¶ 24 (29) ¶ p=0.029	NR	NR	NR	29 (67) 42 (68) p=NS	NR
Wexler et al, 1996 (16) (Ped Sarcoma)	20 (18) 18 (15)	•dox + dex •dox alone	NR	4 (22) 10 (67) p<0.01	0 0	0 0	410 310 p<0.05	(at wk 12) 16/20 (80) 13/16 (81) p=NS	43 mo 24 mo
Lopez et al, 1998 (19) (STS)	18 (18) 16 (16)	•epi + dex •epi alone	0/59 (0)# 4/62 (8)#	4/59 (7)# 9/62 (15)#	32/63 (51)# 43/66 (65)#	12/63 (19)# 9/66 (14)#	960# 880#	2 (11) (0-26) 6 (37.5) (14-61)	15 mo 15.5 mo

Note: CAV = cyclophosphamide, doxorubicin, vincristine; dex = dexrazoxane; dox = doxorubicin; epi = epirubicin; eval = evaluable; mo = months; n = number; NR = not reported, NS = no significant difference between the two arms; Ped = pediatric; SCLC = small cell lung cancer; STS = soft tissue sarcoma; wk = week
*Clinical cardiotoxicity=congestive heart failure (CHF) rate
† Sub-clinical cardiotoxicity= decrease in left ventricular ejection fraction (LVEF) from base line ≥ 20 EF units, or decrease in resting LVEF to ≤ 45%
§ Objective response = complete response (CR) plus partial response (PR)
¶ any cardiac event
# Pooled data, includes breast

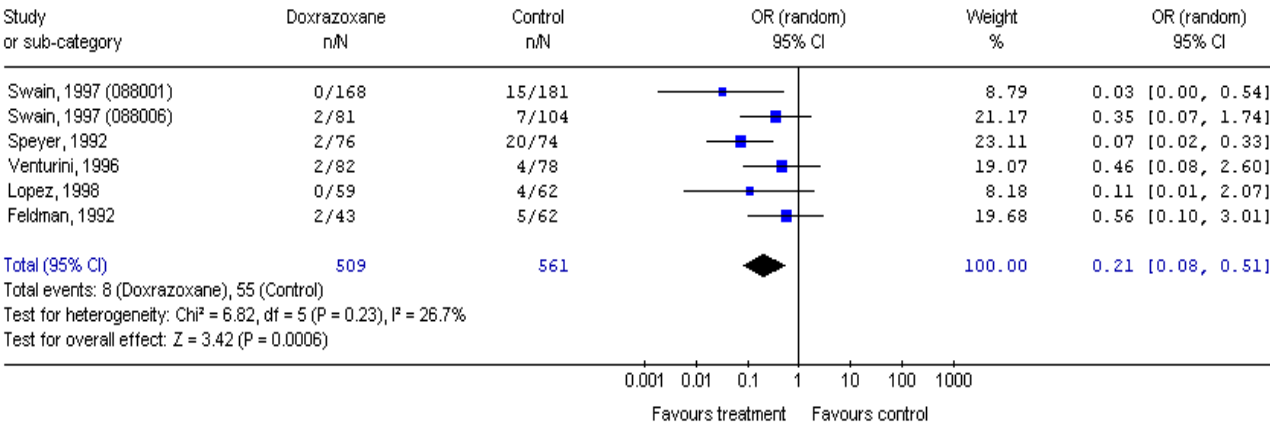
Pooling Results Across Trials

Six papers reported the proportions of patients with clinical cardiotoxicity (13,15,17-20). One trial is reported in two papers (13,14). Two separate trials by Swain et al are reported in one paper (17), and again in another paper (18) that provides a subgroup analysis of these two trials. The sub-group analysis was excluded from the meta-analysis, because there were no new patients added. This provides six comparisons with a total of 1070 patients. The largest trial randomized 349 patients (17) and the smallest randomized 105 patients (20). Due to suspected statistical heterogeneity across studies related to differences in methodological quality, dose ratio, chemotherapy regimen, and tumour type, a random effects model was used for the meta-analysis.

Clinical Cardiotoxicity

When the data from the six trials were combined, there was an observed benefit for dexrazoxane in protecting against clinical cardiotoxicity (CHF) (13,15,17,19,20). Note that two trials were reported in one paper (17). Figure 1 shows graphically the results of the meta-analysis of the six comparisons. The overall effect is expressed as an OR with a 95% CI. For the six comparisons involving 1070 patients, the OR was 0.21 favouring dexrazoxane (95% CI, 0.08 to 0.51; p=0.0006). The risk ratio (RR) was also calculated (RR, 0.23; (95% CI, 0.10 to 0.54; p=0.0006). This translates into a relative risk reduction (RRR) of 0.77 or 77% (RRR=1-RR).

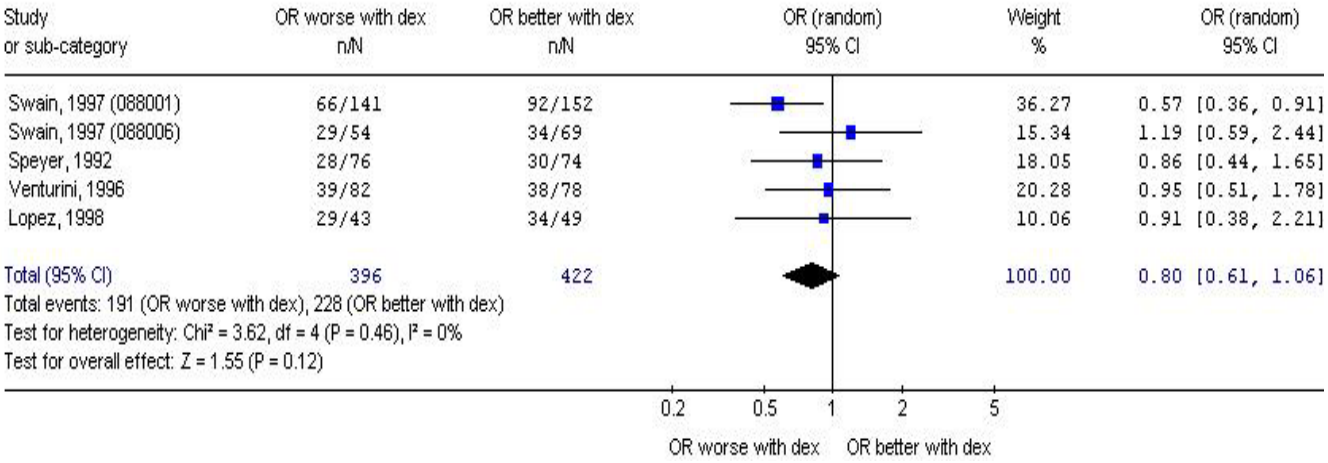
Figure 1. The effect of dexrazoxane on clinical cardiotoxicity (CHF).



Objective Tumour Response

Five trials involving patients with breast cancer provided data to determine the effect of dexrazoxane on the objective response to chemotherapy (13,15,17,19). Two trials were reported in one paper (17). Only trials of patients with breast cancer reported objective tumour response. When the data from these five trials were combined, the meta-analysis did not demonstrate a statistically significant difference between the treatment and control groups. For the five comparisons involving 818 patients with breast cancer shown in Figure 2, the OR is 0.80 (95% CI, 0.61 to 1.06; p=0.12). The RR was also calculated (RR, 0.90; 95% CI, 0.79 to 1.03; p=0.13). This translates into a relative risk reduction (RRR) of 0.10 or 10%. This analysis suggests that dexrazoxane does not adversely influence the antitumour effect of chemotherapy.

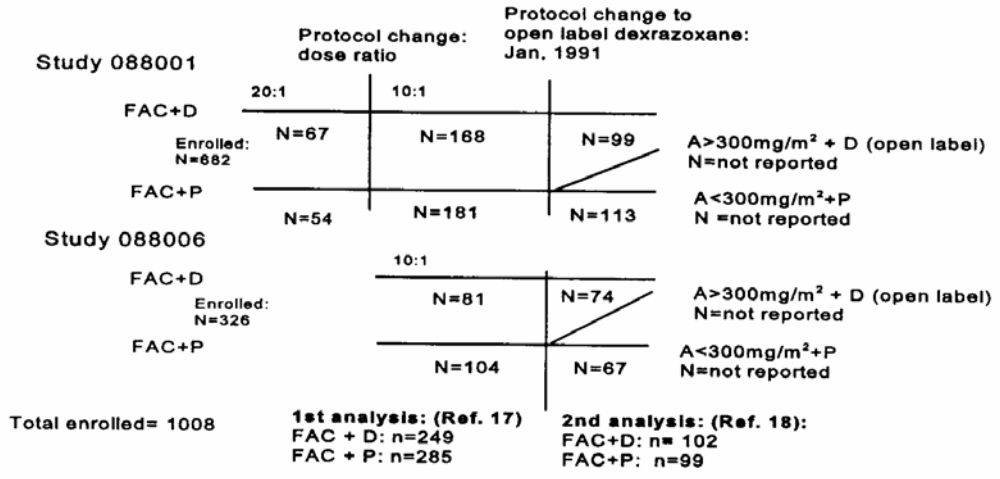
Figure 2. Odds ratio of trials analyzing the effect of dexrazoxane on objective tumour response rate.



Adverse Effects

Noncardiac toxicities were reported in the studies. There were trends noted toward increased hematologic toxicity for chemotherapy plus dexrazoxane compared with chemotherapy alone, including the incidence of thrombocytopenia, lower platelet and WBC nadirs, and greater median time to recovery of an absolute neutrophil count (ANC) 1000mL (see Table 4 for detailed results). Other toxicities associated with dexrazoxane were pain at the injection site, stomatitis and phlebitis.

Figure 3. Study design of two studies of dexrazoxane in patients with advanced breast cancer. From Swain et al (17,18).



Practice Guideline

Update

An evidence-based guideline on the use of chemotherapy and radiotherapy protectants was developed by ASCO in 1999 (2u) and was updated in 2002 (3u). The relevant literature was identified primarily through a search of MEDLINE and CANCERLIT (1966 through 2001) and reviewed by an expert panel. Recommendations developed through a process of consensus are very similar to this guideline report. The expert panel developed the following recommendations for the use of dexrazoxane as a cardioprotectant:

- It is recommended that dexrazoxane not routinely be used for patients with metastatic breast cancer receiving initial doxorubicin-based chemotherapy.
- 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.
- The use of dexrazoxane in the adjuvant setting is not suggested outside of a clinical trial.
- 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.
- There is insufficient evidence to make a recommendation for the use of dexrazoxane in the treatment of pediatric malignancies.
- 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.
- 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.

- 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.
- 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.
- 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.

V. INTERPRETIVE SUMMARY

Cardiotoxicity, especially sub-clinical, is a not uncommon sequela of anthracycline therapy. It is not clear whether the continued use of anthracyclines (i.e. above the maximum recommended cumulative doses) is associated with demonstrable benefits to the patient. Many patients with advanced disease discontinue treatment due to disease progression rather than because of cardiotoxicity. Potential alternative strategies to the use of a “cardioprotective” agent in patients in whom continued anthracycline therapy is indicated include the use of less cardiotoxic analogues, routine discontinuation of the anthracycline at a predetermined dose, or changes in the scheduling of the agents.

Table 4. Toxicities associated with dexrazoxane in the trials.

Trials	Ratio Ratio Dexrazoxane : Anthracycline	Side Effect	Cycle	Results		Statistical Significance (p)
				Dexrazoxane group	Control group	
Breast Cancer: Doxorubicin						
Speyer et al, 1992 (13)	20:1	WBC nadir (median) platelet count nadir (median) hematocrit nadir (median)	2 1 1	2.3 190 33.7	2.6 225 34.9	<0.05 <0.05 p=NS
Swain et al, 1997 (17)	20:1 then 10:1	Thrombocytopenia Platelet counts at recovery WBC count nadir Grade 4 granulocytopenia	2 NR NR NR	47% NR NR 75%	29% NR NR 64%	NR 0.003 0.012 0.009
Swain et al, 1997 (18)	10:1	Pain on injection Dysphagia (No nadir counts done)	NR NR	13% 5%	0% 0%	0.001 NR
Breast Cancer: Epirubicin						
Venturini et al, 1996 (15)	10:1	Phlebitis Stomatitis (grade 3) Leukopenia (grade 4)	NR NR NR	12.2% 8.5% 4.9%	3.8% 5.2% 3.8%	0.053 NR p=NS
Lopez et al, 1998 (19)	6:1	Neutropenia (grade 4)	NR	95%*	91%*	p=NS
Other tumour sites: Doxorubicin						
Feldman et al, 1992 (20)	20:1	Phlebitis Pain on injection Sepsis Infection	NR NR NR NR	6% 7% 23% 27%	1% 4% 15% 23%	NR NR NR NR
Wexler et al, 1996 (16)	20:1	Thrombocytopenia n (%)	1 5 6	11 (47) 13 (72) 9 (64)	3 (16) 2 (18) 1 (11)	<0.05 <0.001 <0.001
		Anemia Time to recovery of ANC[3] 1000/mL	3 1	17 (21) 10.5 days	7 (4) 9 days	0.04 <0.05
		Platelet nadirs	4 5 6	42000 24000 26000	112000 112000 99000	<0.001 <0.001 <0.05

Note: ANC=absolute neutrophil count, NR= not reported, NS= not statistically significant, WBC=white blood cell
*pooled with data from soft tissue sarcoma patient group

Dexrazoxane appears consistently effective in reducing the incidence of both sub-clinical and clinical doxorubicin- or epirubicin-induced cardiotoxicity in patients with advanced breast cancer when used at a dose ratio of 10:1. Similar beneficial effects on cardiotoxicity have been observed in trials of patients with other tumour sites, specifically SCLC and pediatric sarcoma.

The results of the meta-analysis combining trials of patients with different tumour sites treated with doxorubicin or epirubicin confirms this effect. These beneficial effects on cardiotoxicity are apparent when dexrazoxane is added at the initiation of therapy with doxorubicin or epirubicin, but they are also achieved when dexrazoxane is added after a cumulative dose of 300 mg/m^2 of doxorubicin is reached. Similarly, the beneficial effects of dexrazoxane on epirubicin-induced cardiotoxicity are most apparent at higher cumulative doses (>960 mg/m^2).

The use of dexrazoxane is associated with more adverse effects including myelosuppression, nausea, pain on injection and alopecia, but these may be of limited clinical importance. Nonetheless, patients should be carefully monitored for the development of myelosuppression.

Of concern is the documented reduction in response rates in one of three reported studies in breast cancer, although this did not translate into a significant effect on time to progression or overall survival in these small studies in the advanced setting. This effect is observed when results of all the trials are pooled, but to a much lesser degree, and the results are not statistically significant (see Figure 2). The issues of reduced efficacy and increased toxicity are of particular concern in settings where this class of agents is likely to be most beneficial: in adjuvant therapy, in pediatric patients, and in patients treated with curative intent (for example hematologic malignancies). There are no data available on the use of dexrazoxane in these settings.

There are no data available on the use of dexrazoxane with higher doses of doxorubicin, nor in patients with pre-existing cardiac disease or anthracycline-induced cardiotoxicity. The use of dexrazoxane should be limited to patients with advanced cancer treated with doxorubicin or epirubicin until data are available on its impact on efficacy and toxicity in the adjuvant setting. Given concerns regarding the potential negative impact of dexrazoxane on antitumour efficacy and the likelihood that many patients will discontinue doxorubicin or epirubicin because of lack of efficacy before receiving cumulative doses associated with cardiotoxicity, it seems reasonable to recommend initiation of dexrazoxane only in patients who have received 300 mg/m^2 or more of doxorubicin, or approximately 550 mg/m^2 or more of epirubicin. The effectiveness of this strategy has been demonstrated in an RCT, and the strategy appears to be cost-effective.

VI. ONGOING TRIALS

The Systemic Treatment DSG is aware of the following ongoing trials evaluating dexrazoxane:

CLB-49808, CTSU: Phase III randomized study of doxorubicin and cyclophosphamide with or without dexrazoxane, followed by paclitaxel with or without trastuzumab (Herceptin), followed by surgery and radiotherapy with or without trastuzumab in women with HER-2+ stage IIIA or IIIB or regional stage IV breast cancer. A total of 396 women will be accrued and randomized to one of eight treatment arms. The summary was last modified in June, 2001.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

The Systemic Treatment DSG noted that most trials of dexrazoxane were conducted in patients with advanced breast cancer, and discussed the use of dexrazoxane in tumour sites other than the breast. There were two trials that demonstrated an effect on cardiotoxicity in patients with other tumour sites that was consistent with that in breast cancer patients. It was decided to recommend dexrazoxane for use in tumour sites other than advanced breast cancer, with a statement that further research should be undertaken to assess the effects in other tumour sites.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

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

Draft Recommendations

Based on the evidence contained under the Original subtitles throughout this report, the Systemic DSG drafted the following recommendations:

- The evidence supports the use of dexrazoxane in conjunction with conventional-dose doxorubicin in patients with advanced but anthracycline-sensitive cancer, in whom the continued use of anthracycline-containing chemotherapy is indicated, but who have or are expected to receive more than 300 mg/m^2 of doxorubicin.
- The evidence supports the use of dexrazoxane in conjunction with conventional-dose epirubicin in patients with advanced but anthracycline-sensitive cancer in whom the continued use of anthracycline-containing chemotherapy is indicated.
- There is no evidence to support or refute the use of dexrazoxane in the adjuvant setting. However, because of concerns that dexrazoxane may reduce efficacy of anthracyclines, and data are not yet available on long-term toxicities, further studies should be performed before the drug is used routinely 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 in breast cancer. These results support the use of the drug in conjunction with doxorubicin in patients with other tumour sites. Further studies should be performed to confirm these benefits.

Practitioner Feedback

Based on the evidence contained under the Original subtitles in this report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 168 practitioners in Ontario (130 medical oncologists, 34 pharmacists, two radiation oncologists and two hematologists). The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Systemic Treatment DSG.

Results

Key results of the practitioner feedback survey of the original draft guideline report are summarized in Table 5. One hundred and twelve (67%) surveys were returned. Ninety-six (86%) respondents indicated that the evidence-based recommendation was relevant to their clinical practice and they completed the survey. An additional practitioner indicated that the evidence-based recommendation was not relevant to his clinical practice, but went on to complete the questionnaire. This practitioner has been included in the analysis, for a total of 97.

Summary of Written Comments

Forty-one (42%) respondents provided written comments. The main points were:

1. Some practitioners questioned the rationale of using anthracyclines beyond six cycles, as there are no data demonstrating a benefit in terms of quality of life or survival.

2. Some practitioners felt that the concerns regarding reduced efficacy with dexrazoxane should be emphasized.
3. There were queries regarding data supporting the use of dexrazoxane in patients with pre-existing cardiac conditions.
4. Practitioners questioned whether data were available to support a recommended cumulative epirubicin dosage at which dexrazoxane should be administered.
5. It was felt that the recommendation should specify that dexrazoxane should be administered when a dose of 300 mg/m^2 had been reached, as opposed to starting dexrazoxane when more than a total dose of 300 mg/m^2 of doxorubicin is planned.
6. The alternatives to the use of dexrazoxane should be emphasized.

Table 5. Practitioner responses to seven items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	94 (97)	1 (1)	2 (2)
A practice guideline on this topic will be useful to clinicians.	87 (90)	5 (5)	2 (2)
The literature search is relevant and complete.	92 (95)	5 (5)	0 (0)
The summary of the evidence is acceptable to me.	91 (94)	5 (5)	1 (1)
I agree with this evidence-based recommendation as stated.	82 (85)	7 (7)	8 (8)
In your opinion, this recommendation should serve as a practice guideline.	74 (76)	13 (13)	10 (10)
If this evidence-based recommendation were to become a practice guideline, would you make use of it in your own practice?	**Yes**	**Unsure**	**No**
	73 (75)	6 (6)	10 (10)

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

Modifications/Actions

A statement was added to the Interpretive Summary to emphasize that dexrazoxane should be used only in patients for whom the continued use of anthracyclines beyond 300 mg/m^2 (six cycles) is indicated.

1. The Systemic Treatment DSG felt that the second point listed above had been addressed in the report. A statement was added to the Interpretive Summary to outline the settings where there are no data to support the use of dexrazoxane.
2. A statement was added to the Interpretive Summary and to the recommendation indicating that there are no data on patients with pre-existing cardiac disease.
3. A statement was added to the recommendation to indicate that there are no data on the optimal cumulative dose of epirubicin at which dexrazoxane should be administered.
4. The wording of the recommendation was changed to clarify that dexrazoxane should be administered only once the 300 mg/m^2 dose of doxorubicin had been reached.
5. A statement was added to the Interpretive Summary that listed the alternatives to dexrazoxane.

IX. IMPLICATIONS FOR POLICY

One article was identified that reports the results of an economic assessment of dexrazoxane in patients with stage IIIB or IV carcinoma of the breast receiving FAC (21). This economic analysis is a modeling study, based on the patients in the two trials reported by Swain et al described earlier (17,18). The patients received six cycles of FAC without dexrazoxane at which point they received open-label dexrazoxane. It should be noted again that the reporting of these trials is flawed, with a number of patients omitted from the analyses. In addition, this analysis is based on modeling, rather than on actual data collected during the study. Therefore, the results should be considered with caution.

Two cost-effectiveness analyses were done. In the first analysis, the cost of each cardiac event prevented was calculated over a one-year period. The model included costs of tests and procedures associated with chemotherapy and cardiac events (CHF and declines in LVEF) as well as the cost of dexrazoxane. The analysis resulted in a cost of Can$5745 for each cardiac event prevented by using dexrazoxane. In addition, the cost of preventing one CHF event was calculated to be Can$13,182. A second cost-effectiveness study was done, but the assumptions used in the model were so extreme that the information was not credible to the guideline developers.

Dexrazoxane is sold in Canada at approximately $0.50/mg, or $250 per 500 mg vial. Based on a dosage ratio of 10:1 (dexrazoxane: doxorubicin) and assuming it is given once per cycle, the cost of dexrazoxane would be $250 per cycle.

X. PRACTICE GUIDELINE

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

Target Population

These recommendations apply to 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/m² 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/m² (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/m², as the recommended maximum cumulative dose in Canada is 1000mg/m².
- 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.

XI. JOURNAL REFERENCE

Seymour L, Bramwell V, Moran LA and the Provincial Systemic Treatment Disease Site Group. Use of dexrazoxane as a cardioprotectant in patients receiving doxorubicin or epirubicin chemotherapy for the treatment of cancer. *Cancer Prev Control* 1999;3(2):145-159.

XII. ACKNOWLEDGEMENTS

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For a complete list of the Systemic Treatment Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the PEBC section of the Cancer Care Ontario Web site at: http://www.cancercare.on.ca/access_PEBC.htm.

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Update

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

1u. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The Practice Guidelines Development Cycle: A conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13:502-12.
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Appendix 1. Dose, route and schedule for RCTs with dexrazoxane (breast cancer).

Trial	Rx	Ratio of Dexrazoxane: Anthracycline	Drug and Dose	Schedule
Breast Cancer: Doxorubicin				
Speyer et al, 1992 (14)	Rx1 Rx2	20:1	FAC: 5-fluorouracil 500 mg/m^2 Doxorubicin 50 mg/m^2 cyclophosphamide 500 mg/m^2 dexrazoxane 1000 mg/m^2 FAC	every 3 weeks
Swain et al, 1997 (17)	Rx1 Rx2	20:1 then 10:1	FAC: 5-fluorouracil 500 mg/m^2 doxorubicin 50 mg/m^2 cyclophosphamide 500 mg/m^2 dexrazoxane 1000 mg/m^2 (then 500 mg/m^2) FAC Placebo	IV, first day of each course IV, 15-30 minutes prior to doxorubicin IV, first day of each course
Swain et al, 1997 (18)	Rx1 Rx2	10:1	FAC: 5-fluorouracil 500 mg/m^2 doxorubicin 50 mg/m^2 cyclophosphamide 500 mg/m^2 dexrazoxane 500 mg/m^2 FAC Placebo	IV, first day of each course IV, 15-30 minutes prior to doxorubicin IV, first day of each course IV, 15-30 minutes prior to doxorubicin
Breast Cancer: Epirubicin				
Venturini et al, 1996 (15)	 Rx1 Rx2	 10:1	All patients pretreated: Patients with prior chemo: (CEF) cyclophosphamide 600 mg/m^2 Epirubicin 60 mg/m^2 fluorouracil 600 mg/m^2 Anthracycline naive patients: (HD-Epi) epirubicin 120 mg/m^2 Dexrazoxane 1200 mg (HD-Epi) or dexrazoxane 600 mg (CEF) chemotherapy alone	 day 1, every 3 weeks
Lopez et al, 1998 (19)	Rx1 Rx2	6:1	Epirubicin 160 mg/m^2 dexrazoxane 1000 mg/m^2 epirubicin 160 mg/m^2	 IV, every 3 weeks 30 minutes prior to epirubicin

Appendix 2. Dose, route and schedule for RCTs with dexrazoxane (other tumour sites).

Trial	Rx	Ratio of Dexrazoxane: Anthracycline	Drug and Dose	Schedule
Other tumour sites: Doxorubicin				
Feldman et al, 1992 (20)	Rx1	20:1	doxorubicin 50 mg/m^2 vincristine 2.0 mg/m^2 cyclophosphamide + 50 mg/m^2 dexrazoxane 1000 mg/m^2	every 3 weeks IV bolus, 30 minutes prior to doxorubicin
	Rx2		doxorubicin 50 mg/m^2 vincristine 2.0 mg/m^2 cyclophosphamide + 50 mg/m^2 placebo	every 3 weeks IV bolus, 30 minutes prior to doxorubicin
Lopez et al, 1998 (19)	Rx1	6:1	epirubicin 160 mg/m^2 dexrazoxane 1000 mg/m^2	IV, every 3 weeks 30 minutes prior to epirubicin
	Rx2		epirubicin 160 mg/m^2	
Wexler et al, 1996 (16)	Rx1	20:1	VAdriaC: doxorubicin 70 mg/m^2 vincristine 2.0 mg/m^2 cyclophosphamide 1800 mg/m^2 with mesna AND doxorubicin 50 mg/m^2 vincristine 2.0 mg/m^2 cyclophosphamide 1200 mg/m^2 with mesna AND ifosfamide 1800 mg/m^2/d mesna & etoposide 100 mg/m^2/d AND dexrazoxane 500 mg/m^2 (or 20:1)	over 2 days/ cycle in cycles 1,3,5 over 2 days/ cycle in cycles 9,11,13,15 over 5 days/cycle in cycles 2,4,6,8,10, 12,13, 16-18 IV, 15 minutes prior to doxorubicin
	Rx2		as above without dexrazoxane	