Use of dexrazoxane as a cardioprotectant in patients receiving doxorubicin or epirubicin chemotherapy for the treatment of cancer
Seymour L, Bramwell V, Systemic Treatment Disease Site Group

CRD summary
This meta-analysis assessed dexrazoxane for preventing cardiotoxicity in people with advanced or metastatic non-haematological malignancies receiving doxorubicin or epirubicin. Dexrazoxane reduced the relative risk of cardiotoxicity by 77% (6 studies) and had no statistically significant effect on objective response (5 studies). The review appears to have been conducted appropriately, but details of the validity assessment and participants' characteristics were not reported.

Authors' objectives
The objective was to assess the efficacy of dexrazoxane for preventing cardiotoxicity in people with non-haematological malignancies receiving chemotherapy regimens containing an anthracycline (doxorubicin or epirubicin). More specifically, the authors examined whether dexrazoxane should be used routinely in people with advanced or metastatic cancer who are at risk of cardiotoxicity from chemotherapy containing doxorubicin or epirubicin, and whether dexrazoxane should be used alongside anthracyclines for this population.

Searching
MEDLINE (1987 to January 2004), Cancerlit (1987 to 1997), EMBASE (1998 to January 2004), the Cochrane Library (Issue 4, 2003), proceedings of annual meetings of the American Society of Clinical Oncology (1995 to 2003), PDQ, and the reference lists of identified papers were searched; the search terms were reported. Full papers and abstracts were included. Papers published in languages other than English were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), or reviews containing RCTs, were eligible for inclusion. Phase I and II studies, letters and editorials were excluded.

Specific interventions included in the review
Studies that compared the addition of dexrazoxane or a placebo or no treatment to anthracycline-containing chemotherapy (doxorubicin or epirubicin) were eligible for inclusion in the review. The doses and regimens varied between the studies; details of them were tabulated in the review.

Participants included in the review
To be eligible, the studies had to include people with non-haematological malignancies. Most of the studies included in the review focused on people with breast cancer (4 out of 7 studies), but some included people with tumours at other sites (soft tissue sarcoma, small cell lung cancer, sarcoma). The authors did not report other characteristics of the participants.

Outcomes assessed in the review
To be eligible for inclusion, the studies had to report on clinical or sub-clinical cardiotoxicity, noncardiac toxicity, response rates, or overall survival. The outcome measures used to report clinical and sub-clinical cardiotoxicity were consistent between trials (congestive heart failure, a decrease of 20% or more from baseline in left ventricular ejection fraction, and a fall in resting left ventricular ejection fraction to less than or equal to 45%).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were assessed for relevance. However, they reported that the papers were selected and reviewed by two investigators plus methodologists.
Assessment of study quality
The authors did not state that they assessed validity. However, they reported that the papers were ‘assessed’ by two investigators plus methodologists, but it was unclear whether this was a validity assessment.

Data extraction
The authors did not state how the data were extracted for the review. However, they reported that the papers were selected and reviewed by two investigators plus methodologists.

Methods of synthesis
How were the studies combined?
Data on clinical cardiotoxicity and on objective response were pooled quantitatively using a software package. Due to suspected statistical heterogeneity, the authors used a random-effects model when pooling the data. The findings of the individual trials were reported in narrative and tabular formats.

How were differences between studies investigated?
The authors conducted tests of statistical heterogeneity to assess whether differences in chemotherapy regimen (doxorubicin or epirubicin), dose ratio of dexrazoxane to chemotherapy agent, or tumour type had any effect on the findings. They reported their findings grouped by the type of cancer (breast cancer or other tumour sites) and type of anthracycline used (doxorubicin or epirubicin).

Results of the review
The authors included 7 RCTs (1,108 evaluable participants), two with placebo controls.

Data pooled from 6 randomised trials (n=1,070) suggested that dexrazoxane reduced the relative risk of cardiotoxicity by 77% (odds ratio, OR=0.21, 95% confidence interval, CI: 0.08, 0.51, P=0.0006; chi-squared test for heterogeneity 6.82, P=0.23).

A meta-analysis of 5 trials of people with breast cancer (n=818) found no statistically significant difference in objective tumour response to chemotherapy between dexrazoxane and controls (OR 0.80, 95% CI: 0.61, 1.06, P=0.12; chi-squared test for heterogeneity 3.62, P=0.46).

There were trends toward increased mild haematologic toxicity in people receiving chemotherapy plus dexrazoxane compared with chemotherapy alone, including the incidence of thrombocytopenia, myelosuppression and other noncardiac toxicities.

The findings of the individual trials were reported in more depth in the review.

Cost information
The authors reported one analysis of costs based on modelled data. They suggested that the approximate cost of dexrazoxane would be Can$250 per chemotherapy cycle, but that the findings of the cost analysis should be interpreted with caution.

Authors' conclusions
There is evidence to support the use of dexrazoxane to protect against the cardiotoxicity associated with conventional-dose epirubicin and doxorubicin in people with advanced but anthracycline-sensitive cancer in whom the continued use of anthracycline-containing chemotherapy is indicated. It was recommended that dexrazoxane be used after the cumulative dose of doxorubicin reaches 300 mg/m2 (55% of the recommended maximum). No data on doses were available for epirubicin, but the authors suggested that a similar formula could be used: using dexrazoxane when the cumulative dose of epirubicin reaches 550 mg/m2 (55% of the recommended maximum).
CRD commentary
This review focused on defined research questions with pre-specified inclusion criteria. The search strategy appears adequate although, as studies in languages other than English were not eligible, some relevant studies might have been omitted. The authors did not report in detail the methods used to select and assess the studies for the review, although it appears that more than one reviewer independently assessed each study. They did not report the characteristics of the participants in the included studies in any detail, which makes it difficult to generalise the findings. Although the authors stated that two investigators plus methodologists ‘assessed’ each paper, it was unclear whether this included a validity assessment. It seems that the authors might not have assessed the internal and external validity of the studies, thus making it difficult to assess the generalisability of the findings and the quality of the review itself.

The narrative and quantitative methods used to synthesise the data appear appropriate. The authors justified their use of a random-effects model, and conducted statistical tests to assess the impact of differences between the studies on the findings. However, they did not pool the data on adverse effects, nor provide a reason for not doing so. As some adverse effects were identified, it might have been helpful had they had been able to quantify these in the same way as the benefits were reported.

The authors provided specific recommendations about the use of dexrazoxane in chemotherapy regimens containing three main types of drugs. These conclusions appear appropriate, based on the data presented.

Implications of the review for practice and research
Practice: The authors stated that dexrazoxane can be used to protect against cardiotoxicity from conventional-dose doxorubicin in people with advanced anthracycline-sensitive cancer who have received 300mg/m2 or more of doxorubicin; that dexrazoxane can be used to protect against the cardiotoxicity associated with conventional-dose epirubicin in people with advanced anthracycline-sensitive cancer, but there is insufficient evidence about the optimal cumulative dose of epirubicin at which dexrazoxane should be implemented; and dexrazoxane is not recommended for use with mitoxantrone (although this was not based on the results of the review).

Research: The authors did not identify any implications for future research. They reported one ongoing randomised trial (as of January 2004) of doxorubicin and cyclophosphamide with or without dexrazoxane, followed by paclitaxel with or without trastuzumab, followed by surgery and radiotherapy with or without trastuzumab in women with HER-2+ stage IIIA or IIIB or regional stage IV breast cancer.

Funding
Cancer Care Ontario; Ontario Ministry of Health and Long-term Care.

Bibliographic details

This paper is produced by Cancer Care Ontario Practice Guidelines Initiative. The series is published on the Internet and regularly updated. To ensure that you are viewing the most up to date version, go to the Cancer Care Ontario website at: http://www.cancercare.on.ca/english/toolbox/qualityguidelines/pebc/

Original Paper URL
https://www.cancercare.on.ca/toolbox/qualityguidelines/clin-program/systemic-ebs/

Other publications of related interest

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Antibiotics, Antineoplastic /administration & dosage /therapeutic use; Antineoplastic Agents /administration & dosage /adverse effects /therapeutic use; Breast Neoplasms /drug therapy; Cardiovascular Agents /administration & dosage /adverse effects /therapeutic use; Clinical Trials as Topic; Doxorubicin /administration & dosage /adverse effects /therapeutic use; Drug Administration Schedule; Epirubicin /administration & dosage /adverse effects /therapeutic use; Evidence-Based Medicine; Heart /drug effects; Heart Failure /chemically induced; Neoplasms /drug therapy; Odds Ratio; Randomized Controlled Trials as Topic; Razoxane /administration & dosage /adverse effects /therapeutic use; Time Factors

**AccessionNumber**
12005008168

**Date bibliographic record published**
31/07/2005

**Date abstract record published**
31/07/2005

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.