Epirubicin, alone or in combination chemotherapy, for metastatic breast cancer

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Authors' objectives
To make recommendations about the use of epirubicin, particularly in comparison with doxorubicin, in women with metastatic breast cancer.

Searching
For the original review, MEDLINE and Cancerlit were searched from 1985 to 1996 using the terms 'epirubicin', 'doxorubicin' and 'breast neoplasms'. The PDQ database was searched for ongoing trials using the terms 'breast cancer' and 'epirubicin'. For the update review, the search was revised to combine disease-specific textwords and subject headings (‘breast’, ‘mammary’, ‘cancer’, ‘carcinoma’, ‘neoplasm/s’), treatment-specific terms (‘epirubicin’, ‘doxorubicin’ and ‘adriamycin’) and design-specific terms (‘meta-analysis’, ‘randomized controlled trial/s’). MEDLINE (through January 2002), the Cochrane Library (Issue 2, 2000), PDQ, and the proceedings of the annual meetings of the American Society for Clinical Oncology (1997 to 2001) and the San Antonio Breast Cancer Symposium (2001) were searched using these revised terms.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Epirubicin compared with doxorubicin. Studies were eligible for inclusion if they compared epirubicin and doxorubicin, either as single agents or as part of combination chemotherapy, and as either first- or second-line chemotherapy. The included studies compared the following:

- equal doses of epirubicin and doxorubicin (20, 40, 50 or 70 mg/m2);
- epirubicin at a higher dose than doxorubicin (90 versus 75, 90 versus 60, 85 versus 60, 65 versus 50, 50 versus 20 mg/m2); or
- escalating doses of epirubicin (120 versus 60, 100 versus 50, 135 versus 90 versus 60 versus 40 mg/m2).

The treatment regimens used in each trial were given in an appendix in the report.

Participants included in the review
Women with metastatic breast cancer. Most of the included trials included only women who had not received prior chemotherapy for metastatic disease, although some trials included some women who had undergone prior chemotherapy.

Outcomes assessed in the review
The outcomes of interest were response rate (complete response, and partial plus complete response), survival and toxicity.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.
**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following data were extracted from each trial: the trial name; the number of evaluable patients; the drug and dose in each treatment group; and the outcomes.

**Methods of synthesis**

How were the studies combined?
The results from the RCTs that compared equal doses of epirubicin and doxorubicin were pooled in a meta-analysis and expressed as the risk ratio (RR) with the 95% confidence interval (CI). The meta-analysis was conducted using a fixed-effect model when no significant heterogeneity was found among the studies. The results from other trials were synthesised in a narrative summary.

How were differences between studies investigated?
The studies were grouped according to the drug dosage: epirubicin and doxorubicin at equal doses; epirubicin dose higher than doxorubicin; and escalating doses of epirubicin. A statistical test of heterogeneity was used in the meta-analysis. In the narrative summary, differences between the treatment regimens used in the different trials were discussed.

**Results of the review**

In the original review, 11 published trials and 2 trial reports available only as abstracts were included. Another 5 trials were added in the update.

Epirubicin and doxorubicin at equal doses: 7 trials (1,083 evaluable patients) included in the original review.

Epirubicin at a higher dose than doxorubicin: 3 trials (792 evaluable patients) included in the original review; a further 2 trials (381 evaluable patients) were included in the update.

Epirubicin at escalating doses: 3 trials (613 evaluable patients) included in the original review; a further 3 trials (724 evaluable patients) were included in the update.

Epirubicin and doxorubicin at equal doses.

The meta-analysis showed no significant difference in the response rate (6 trials) or in survival at 1 year (5 trials). Based on 4 trials that reported WHO grade 3 and 4 nausea and vomiting, epirubicin was better than doxorubicin (RR 0.76, 95% CI: 0.63, 0.92, p=0.0048). Fewer patients who received epirubicin had congestive heart failure (RR 0.38, 95% CI: 0.14, 1.04, p=0.059) or other cardiotoxic effects (6 trials) (RR 0.43, 95% CI: 0.24, 0.77, p=0.0044).

Epirubicin at a higher dose than doxorubicin.

The 3 trials included in the original review showed no difference in response rate or survival. Patients receiving epirubicin had slightly fewer occurrences of congestive heart failure and other cardiotoxic effects. One trial reported less nausea and vomiting associated with epirubicin, and 2 reported no difference in other side-effects. Neither of the 2 additional trials included in the update showed a statistically-significant difference in response rates or survival. In one trial, patients who received epirubicin had significantly higher rates of nausea, vomiting and alopecia; the other trial showed no difference in grade 3 and 4 nausea and vomiting. In the latter trial, three doxorubicin patients, but no epirubicin patients, died with infectious complications.

Epirubicin at escalating doses.

The 3 trials included in the original review showed an increased response rate with higher doses of epirubicin, but no difference in survival. Two studies reported more nausea and vomiting associated with higher doses. The other toxic
effects recorded in these studies included more alopecia, myelosupression, mucositis, anaemia and granulocytopenia, stomatitis, and decreased white blood cell and platelet counts. In the 3 additional trials included in the update, higher doses of epirubicin were more likely to cause greater grade 3 and 4 neutropenia with no difference in overall survival. Two trials reported significantly higher response rates with a higher dose, whilst one trial showed no difference. In one trial, the time to progression was significantly longer with higher dose treatment, whereas another trial comparing the same doses found no difference. There were no significant differences between the higher and lower doses in terms of cardiac events.

Cost information
The list price (1997) of epirubicin and doxorubicin was quoted in the original review as approximately $520 for the treatment of one woman.

Authors’ conclusions
Epirubicin, at doses equivalent to or somewhat higher than doxorubicin, was equally efficacious and less toxic than doxorubicin for the treatment of metastatic breast cancer. Epirubicin taken to much higher doses may be more efficacious, but is also more toxic.

CRD commentary
This review is regularly updated (see Other Publications of Related Interest). The review addressed a clear question in terms of the participants, intervention, outcomes and study design. The search strategy was adequate. Details of how the review was conducted were not reported. Although the review included only RCTs, there was no description of a validity assessment and, consequently, no indication of how well these trials were designed and conducted in terms of minimising bias. The characteristics of the included studies were presented adequately in tabular format, although it would have been helpful if the inclusion criteria for the participants in each trial had also been presented. These features are important to assess differences between the individual trials and the generalisability of the results. The meta-analysis and narrative summary used to combine the studies were appropriate.

The authors’ conclusion that epirubicin has been shown to be equally efficacious to doxorubicin is questionable. Unless the included trials were designed to test equivalence, a more balanced conclusion is that these trials found no difference in efficacy between the two drugs when used at the same dose.

Implications of the review for practice and research
Practice: The authors state that for the treatment of metastatic breast cancer in which the goal of treatment is palliation, epirubicin (at doses equivalent to doxorubicin) has been shown to be equally efficacious and less toxic than doxorubicin. Doxorubicin is, however, an acceptable alternative.

Research: The original review states that a comparison of the full cost of the two treatments, including the treatment of side-effects, would be informative.

Funding
Cancer Care Ontario, Ontario Ministry of Health.

Bibliographic details

PubMedID
10093625
Other publications of related interest
This paper is based on a practice guideline 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/ This abstract is based on the journal article and the web version accessed 06/03/2002.


Indexing Status
Subject indexing assigned by NLM

MeSH
Antibiotics, Antineoplastic /therapeutic use; Antineoplastic Combined Chemotherapy Protocols /therapeutic use; Breast Neoplasms /drug therapy; Canada; Doxorubicin /therapeutic use; Epirubicin /therapeutic use; Female; Humans; Randomized Controlled Trials as Topic

AccessionNumber
11999003609

Date bibliographic record published
31/08/2002

Date abstract record published
31/08/2002

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.