



## Complete Summary

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### GUIDELINE TITLE

Epirubicin, as a single agent or in combination, for metastatic breast cancer.

### BIBLIOGRAPHIC SOURCE(S)

Breast Cancer Disease Site Group, Systemic Treatment Disease Site Group. Findlay BP, Walker-Dilks C, Pritchard K. Epirubicin, as a single agent or in combination, for metastatic breast cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Apr 30 [online update]. 15 p. (Practice guideline report; no. 1-6). [21 references]

### GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

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## SCOPE

### DISEASE/CONDITION(S)

Metastatic breast cancer

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Treatment

### **CLINICAL SPECIALTY**

Oncology

### **INTENDED USERS**

Physicians

### **GUIDELINE OBJECTIVE(S)**

To make recommendations about the use of epirubicin, particularly compared with doxorubicin, in patients with metastatic breast cancer

### **TARGET POPULATION**

Women with metastatic breast cancer

### **INTERVENTIONS AND PRACTICES CONSIDERED**

1. Epirubicin (Pharmorubicin®) at doses equal to and higher than those of doxorubicin, and at escalating doses
2. Doxorubicin (Adriamycin®)

### **MAJOR OUTCOMES CONSIDERED**

- Survival
- Response rate
- Toxicity

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

### **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

#### **Original: October 1997**

MEDLINE and CANCERLIT were searched (1985 to 1996) using the terms "epirubicin", "doxorubicin", and "breast neoplasms". The Physician Data Query (PDQ) (U.S. National Cancer Institute) database was searched for ongoing trials using the terms "breast cancer" and "epirubicin."

#### **Update: April 2003**

The literature search was revised to combine disease-specific text words 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]). The literature search has been updated with the revised search terms using MEDLINE (through April 2003), the Cochrane Library (Issue 1, 2003), the Physician Data Query (PDQ) database, and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997-2002) and the San Antonio Breast Cancer Symposium (2001-2002).

### **Inclusion Criteria**

1. Articles were selected for inclusion in this systematic review of the evidence if they were randomized controlled trials comparing epirubicin with doxorubicin in metastatic breast cancer, either as single agents or in combination, and as either first- or second-line chemotherapy.
2. Trials were also selected if they compared different dosages of epirubicin.

### **NUMBER OF SOURCE DOCUMENTS**

Eighteen randomized controlled trials were reviewed.

### **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Expert Consensus (Committee)

### **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

### **METHODS USED TO ANALYZE THE EVIDENCE**

Meta-Analysis of Randomized Controlled Trials  
Systematic Review with Evidence Tables

### **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

#### **Original: October 1997**

In order to obtain a more precise assessment of the relative effects (on response rate, survival, and toxicity) of epirubicin compared with doxorubicin, the results of the randomized trials of equal doses of these two agents were pooled using the software Metaanalyst<sup>0.988</sup> (Dr. Joseph Lau, Tufts New England Medical Centre, Boston). Results are expressed as the risk ratio (RR) and its 95% confidence interval (CI). An RR of more than 1.0 favours doxorubicin, and an RR of less than 1.0 favours epirubicin for all variables. Data were analyzed using fixed effects models when no significant heterogeneity was found among the studies.

#### **Update: April 2003**

The information above remains current.

### **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

### **Original: October 1997**

The draft evidence-based recommendation, which was written by a member of the provincial Systemic Treatment Program Committee, was reviewed and discussed by the provincial Breast Cancer Disease Site Group (DSG). Evidence from randomized trials suggests that epirubicin and doxorubicin, when delivered at equivalent doses, are equally efficacious. However, epirubicin is slightly less toxic than doxorubicin. There is no evidence that, at equal doses, epirubicin is superior to doxorubicin in improving either response rates or overall survival. Given that doxorubicin has been a mainstay of chemotherapy treatment for metastatic breast cancer for many years, the Breast Cancer DSG felt that the evidence of efficacy was not strong enough to recommend a definitive switch from the use of doxorubicin to the use of epirubicin. However, given that the two agents appear to be equally efficacious and given that epirubicin has a lower incidence of cardiac toxicity and is generally less toxic than doxorubicin, the Breast Cancer DSG does support the use of epirubicin as a reasonable alternative to doxorubicin.

### **Update: April 2003**

The information above remains current.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

## **COST ANALYSIS**

A formal cost analysis was not performed and published cost analyses were not reviewed.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review  
Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

### **Original: October 1997**

Practitioner feedback was obtained through a mailed survey of 91 practitioners in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations 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 Breast Cancer Disease Site Group.

This practice guideline has been reviewed and approved by the Breast Cancer Disease Site Group, which is comprised of surgeons, medical oncologists, epidemiologists, a pathologist, a medical sociologist, and a patient representative.

**Update: April 2003**

No further external review.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Epirubicin, at doses equivalent to doxorubicin, has been shown to be equally efficacious and less toxic than doxorubicin. Doxorubicin, however, is an acceptable alternative.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

**Original: October 1997**

No significant differences were observed in response rate or median survival in the seven trials comparing equal doses of epirubicin and doxorubicin or in the three trials comparing epirubicin at a higher dose than that of doxorubicin. An increased response rate was observed with higher doses of epirubicin in the three trials that compared escalating doses; no difference in survival was observed.

**Update: April 2003**

- Seven randomized trials comparing epirubicin and doxorubicin at equal doses (as single agents in three trials and as part of multi-agent chemotherapy in four trials) found no significant differences in tumour response rate or survival between these two agents. Survival data from published reports of five trials and response data for six trials were available for meta-analysis by the guideline developers. The meta-analysis did not detect differences in pooled one-year survival rates (risk ratio for mortality, 1.01; 95% confidence interval, 0.85 to 1.2;  $p=0.87$ ) or response rate (risk ratio, 1.04; 95% confidence interval, 0.92 to 1.18;  $p=0.51$ ).
- Five randomized trials comparing epirubicin at a higher dose to doxorubicin (as single agents in four trials and as part of multi-agent chemotherapy in

one trial) detected no significant differences between these two agents in response rate or survival.

- Significantly higher response rates were observed with higher doses of epirubicin in the five of six randomized trials that compared escalating doses of epirubicin (as a single agent in two trials and as part of multi-agent chemotherapy in four trials); no differences in survival were observed between doses.

## **POTENTIAL HARMS**

Less nausea and vomiting (risk ratio, 0.76; 95% confidence interval [CI], 0.63 to 0.92;  $p=0.0048$ ), neutropenia (risk ratio, 0.52; 95% CI, 0.35 to 0.78;  $p=0.0017$ ), and cardiac toxicity (risk ratio, 0.43; 95% CI, 0.24 to 0.77;  $p=0.0044$ ), including a trend towards fewer episodes of congestive heart failure (risk ratio, 0.38; 95% CI, 0.14 to 1.04;  $p=0.059$ ), were observed with epirubicin compared to doxorubicin.

## **QUALIFYING STATEMENTS**

### **QUALIFYING STATEMENTS**

#### **Original: October 1997**

- No studies (comparing doxorubicin and epirubicin) have reported data on quality of life.
- Some evidence exists that higher doses of epirubicin improve response rate compared with lower doses but higher doses of epirubicin have not been shown to be better than standard doses of doxorubicin.

#### **Update: April 2003**

- In the comparison of doxorubicin and epirubicin at equal doses, the Fossati meta-analysis is of interest in that it reported a hazard ratio for mortality suggesting an almost significant benefit in favour of doxorubicin. However, the guideline developers' direct contact with Fossati regarding his exclusion of the Lawton study, which tends to influence the guideline's meta-analysis to a more neutral position, indicated that Fossati would have included this study if he had known of its existence.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

## **IMPLEMENTATION OF THE GUIDELINE**

### **DESCRIPTION OF IMPLEMENTATION STRATEGY**

An implementation strategy was not provided.

## **INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES**

### **IOM CARE NEED**

End of Life Care  
Living with Illness

### **IOM DOMAIN**

Effectiveness

## **IDENTIFYING INFORMATION AND AVAILABILITY**

### **BIBLIOGRAPHIC SOURCE(S)**

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### **ADAPTATION**

Not applicable: The guideline was not adapted from another source.

### **DATE RELEASED**

1997 Mar 11 (updated online 2003 Apr 30)

### **GUIDELINE DEVELOPER(S)**

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

### **GUIDELINE DEVELOPER COMMENT**

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

### **SOURCE(S) OF FUNDING**

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

### **GUIDELINE COMMITTEE**

Breast Cancer Disease Site Group  
Systemic Treatment Disease Site Group

## **COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE**

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

Members of the Breast Cancer Disease Site Group disclosed potential conflict of interest information.

## **GUIDELINE STATUS**

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## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following are available:

- Epirubicin, as a single agent or in combination, for metastatic breast cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2003 Apr. Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RS, 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.

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This summary was completed by ECRI on January 5, 1999. The information was verified by the guideline developer as of February 22, 1999. This NGC summary was updated by ECRI on December 3, 2001. The updated information was

reviewed by the guideline developer as of January 10, 2002. This summary was updated again by ECRI on July 5, 2002. The updated information was verified by the guideline developer on August 19, 2002. This summary was most recently updated by ECRI on April 19, 2004. The updated information was verified by the guideline developer on April 29, 2004.

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