Complete Summary

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.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

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$^{0.988}$ (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

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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.

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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

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