



## Complete Summary

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### GUIDELINE TITLE

The role of taxanes in neoadjuvant chemotherapy for women with non-metastatic breast cancer.

### BIBLIOGRAPHIC SOURCE(S)

Breast Cancer Disease Site Group. Trudeau M, Sinclair S, Clemons M, Shelley W. The role of taxanes in neoadjuvant chemotherapy for women with non-metastatic breast cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Dec 10. 32 p. (Practice guideline report; no. 1-20). [53 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)

Non-metastatic breast cancer

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Management  
Treatment

## **CLINICAL SPECIALTY**

Oncology

## **INTENDED USERS**

Physicians

## **GUIDELINE OBJECTIVE(S)**

- To evaluate the effect of neoadjuvant taxane-containing regimens on clinically meaningful outcomes (clinical response, pathologic response, breast conservation, disease-free survival, or overall survival) relative to other neoadjuvant regimens
- To evaluate the effect of neoadjuvant taxane-containing regimens on clinically meaningful outcomes relative to adjuvant taxane-containing regimens
- To evaluate the preferred dose and schedule for neoadjuvant taxane administration
- To evaluate the harms associated with neoadjuvant taxane-containing regimens

## **TARGET POPULATION**

Women with non-metastatic breast cancer who are candidates for neoadjuvant chemotherapy

## **INTERVENTIONS AND PRACTICES CONSIDERED**

1. Neoadjuvant paclitaxel-containing regimens versus other neoadjuvant regimens
2. Neoadjuvant paclitaxel-containing regimens versus paclitaxel-containing adjuvant regimen
3. Neoadjuvant paclitaxel dose and/or schedule
4. Neoadjuvant docetaxel-containing regimens versus other neoadjuvant regimens
5. Neoadjuvant docetaxel dose and/or schedule
6. Neoadjuvant anthracycline-based chemotherapy

## **MAJOR OUTCOMES CONSIDERED**

- Clinical response
- Pathologic response
- Node response
- Breast conservation
- Disease-free survival
- Overall survival
- Toxicity

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

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

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

MEDLINE was searched to September 2004 using a disease-specific medical subject heading (MeSH) term ("breast neoplasms"), treatment-specific title or abstract terms ("induction chemotherapy" or "primary chemotherapy" or "neoadjuvant chemotherapy" or "preoperative chemotherapy"), and an agent-specific MeSH term ("taxoids"). The Excerpta Medica database (EMBASE) was also searched up to September 2004 using a disease-specific Excerpta Medica Tree (EMTREE) term ("breast cancer"), treatment specific keywords ("induction chemotherapy" or "primary chemotherapy" or "neoadjuvant chemotherapy" or "preoperative chemotherapy"), and agent-specific EMTREE terms ("paclitaxel" or "docetaxel"). These terms were then combined with the search terms for the following publication types: practice guideline, randomized controlled trial, systematic review, and meta-analysis. Issue 3 (2004) of the Cochrane Library and online conference proceedings from the American Society of Clinical Oncology (<http://www.asco.org/ac/1,1003,12-002095,00.asp>; 1999-2004) and the San Antonio Breast Cancer Symposium (<http://www.sabcs.org/SymposiumOnline/index.asp#abstracts>; 2001-2003) were also searched. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guideline Clearinghouse (<http://www.guideline.gov/>) were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by three reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

### Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- A neoadjuvant taxane-containing regimen was evaluated using any of the publication types listed in the search strategy (practice guideline, randomized controlled trial, systematic review, or meta-analysis).
- Reported outcomes included rates of clinical response, pathologic response, breast conservation, disease-free survival (DFS), or overall survival.
- Clinical trial results were reported in either full papers or abstracts. Although data presented in meeting abstracts may not be as reliable and complete as that from papers published in peer-reviewed journals, abstracts can be a source of important evidence from randomized trials and add to the evidence available from fully published studies. These data often appear first in meeting abstracts and may not be published for several years.

**Exclusion Criterion**

Trials published in a language other than English were excluded.

**NUMBER OF SOURCE DOCUMENTS**

Eighteen randomized trials and one practice guideline 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**

Systematic Review with Evidence Tables

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

The trials of neoadjuvant taxane therapy were too clinically heterogeneous to pool.

**METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

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

In the context of current clinical practice, the Breast Cancer Disease Site Group (DSG) discussed the evidence for neoadjuvant taxanes in the treatment of women with non-metastatic breast cancer. The DSG agreed that the primary goal for treatment in this population is to achieve the longest survival with the best quality of life, using a treatment with acceptable toxicity. Refer to the original guideline document for a summary of the Breast Cancer DSG's interpretation of the evidence and consensus.

**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**

Practitioner feedback was obtained through a mailed survey of 113 practitioners in Ontario (57 medical oncologists, 20 surgical oncologists, 35 surgeons, and one medical resident). 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. The practitioner feedback survey was mailed out on June 30, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer Disease Site Group (DSG) reviewed the results of the survey.

Sixty-three responses were received out of the 113 surveys sent (56% response rate).

Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee and the Breast Cancer Disease Site Group.

## **RECOMMENDATIONS**

### **MAJOR RECOMMENDATIONS**

- When neoadjuvant 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) or doxorubicin and cyclophosphamide (AC) chemotherapy regimen is planned for a woman with non-metastatic breast cancer, a neoadjuvant taxane (paclitaxel or docetaxel) should also be offered. Based on evidence from clinical trials, the following regimens are recommended:
  - Paclitaxel (80 mg/m<sup>2</sup>), administered weekly for 12 weeks prior to the anthracycline-based regimen
  - Docetaxel (100 mg/m<sup>2</sup>), administered every three weeks for four cycles following the anthracycline-based regimen
- There is no evidence at this time to suggest that one taxane is superior to the other in the neoadjuvant setting.

### **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

Appropriate use of taxanes in neoadjuvant chemotherapy for women with non-metastatic breast cancer

### POTENTIAL HARMS

- The following are toxicities associated with taxanes:
  - Paclitaxel: hematologic toxicity (neutropenia/febrile neutropenia, anemia), cardiotoxicity, neurotoxicity, gastrointestinal toxicity, and other toxicities (infection)
  - Docetaxel: hematologic toxicity (neutropenia/febrile neutropenia, leukopenia), neurotoxicity, cardiotoxicity, gastrointestinal toxicity, and other toxicities (hand-foot syndrome, death)

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

- Since disease-free and overall survival data are limited, the recommendations for neoadjuvant taxane chemotherapy are often based on pathologic and clinical complete-response data.
- Neoadjuvant therapy is not the standard of care for operable breast cancer but is usually given to improve the likelihood of breast conservation for large operable breast cancer or to increase the possibility of operability for locally advanced or inflammatory breast cancer.
- There is no evidence in the neoadjuvant setting for the use of taxanes after optimally dosed anthracycline-based regimens, such as 5-fluorouracil, epirubicin, and cyclophosphamide (FEC-100 or CEF).
- The recommended schedule for paclitaxel therapy (i.e., weekly) is based on two trials of weekly versus three-weekly regimens. There were no direct comparisons available for docetaxel; therefore, the recommended schedule (i.e., three-weekly) is based on that which showed improved efficacy in trials comparing a docetaxel-containing regimen with a non-docetaxel regimen. The suggested doses for paclitaxel and docetaxel are those associated with the recommended schedule.
- While neoadjuvant paclitaxel and docetaxel are recommended in sequence with a standard anthracycline-based regimen, it may be appropriate to switch to an anthracycline-based regimen from paclitaxel or to docetaxel from an anthracycline-based regimen earlier if the patient's disease progresses while on the initial regimen.
- Tumours that fail to respond to two cycles of neoadjuvant therapy are likely resistant (in terms of subsequent pathologic complete response rates) to chemotherapy, including taxane-anthracycline combinations, vinorelbine, and capecitabine. For these patients, a novel therapy may be considered.
- The data supporting neoadjuvant taxane therapy are maturing. While results to date do not support an increase in adverse events relative to other settings, physicians should monitor patients carefully for toxicity, especially

- hematologic toxicity, neurologic toxicity (with paclitaxel), and hand-foot syndrome (with docetaxel).
- There is at present no literature to support the use of adjuvant taxane-based therapy for residual tumour found after neoadjuvant anthracycline-based therapy.
  - This practice guideline report is based upon the reported neoadjuvant literature and cannot be extrapolated to endorse the use of adjuvant docetaxel after adjuvant anthracyclines. Studies exploring that sequence of treatments are underway.
  - Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline 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

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

2004 Dec 10

**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**

Provincial Breast Cancer 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 (DSG) 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:

- The role of taxanes in neoadjuvant chemotherapy for women with non-metastatic breast cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO). Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- 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.

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This summary was completed by ECRI on January 18, 2005. The information was verified by the guideline developer on February 10, 2005.

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