Complete Summary

GUIDELINE TITLE

The role of the taxanes in the management of metastatic breast cancer.

BIBLIOGRAPHIC SOURCE(S)

Breast Cancer Disease Site Group. Verma S, Trudeau M, Pritchard K, Oliver T. The role of the taxanes in the management of metastatic breast cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Apr 24. 31 p. (Practice guideline; no. 1-3). [116 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
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of taxanes in the management of metastatic breast cancer

TARGET POPULATION

Women with metastatic breast cancer for whom first- or greater-line chemotherapy is being considered outside the context of a clinical trial

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

Anthracycline-naive patients

1. Single-agent docetaxel
2. Docetaxel or paclitaxel in combination with doxorubicin

Anthracycline-naive patients for whom anthracyclines are contraindicated

1. Single-agent docetaxel

Anthracycline-resistant patients or patients who have previously received an anthracycline as adjuvant therapy

1. Single-agent docetaxel
2. Single-agent paclitaxel
3. Docetaxal and capecitabine

Treatment alternatives considered but not recommended in the guideline:

1. Common treatment alternatives include single-agent doxorubicin, single-agent epirubicin, combinations of 5-fluorouracil and cyclophosphamide with doxorubicin (FAC) or with epirubicin (FEC) or with methotrexate (CMF), capecitabine, trastuzumab (Herceptin), mitomycin, vinblastine, and vinorelbine.

MAJOR OUTCOMES CONSIDERED

- Complete response rates
- Overall response rates
- Median time to progression
- Median survival
- Quality of life
- Toxicities

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

A MEDLINE search was conducted for the period from 1966 to June 2001 using disease-specific terms [(breast neoplasms/ or breast cancer.tw. or mammary neoplasms/) and (neoplasm metastasis/ or metast:.tw. or advanced.tw.)] with treatment-specific terms (taxane:.tw. or paclitaxel/ or paclitaxel.tw. or taxol.tw. or docetaxel.tw. or taxotere.tw.) and design-specific terms (meta-analysis.pt,sh,tw. or randomized controlled trial:.sh,pt,tw. or random:.tw.). The search was updated in July 2002. Issue 2 (2002) of the Cochrane Library, the Physician Data Query database (http://cnetdb.nci.nih.gov/trialsrch.shtml), clinical trial and practice guideline Internet sites, conference proceedings from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology, article bibliographies, and personal files were also searched up to July 2002.

Inclusion Criteria

Published reports or abstracts were selected for inclusion if they met the following criteria:

- Randomized controlled trials on the use of paclitaxel or docetaxel as single agents or in combination with other chemotherapeutic agents, as first- or second-line chemotherapy, for metastatic breast cancer.
- Reported results for at least one of the outcomes of interest: quality of life, survival, time to disease progression, tumour response, and adverse effects.

Evidence-based clinical practice guidelines from guideline-development groups were also reviewed.

Exclusion Criteria

Letters and editorials were not eligible.

NUMBER OF SOURCE DOCUMENTS

14 randomized phase III trials, three randomized phase II trials, and one evidence-based 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

Because of the heterogeneity in dose, schedule, and drug combinations used in the experimental (i.e., taxane) and control arms of the trials reviewed, the guideline authors decided not to pool the results of the randomized trials.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Disease Site Group Consensus Process

In the context of current clinical practice, the Breast Cancer Disease Site Group (DSG) discussed the evidence surrounding the role of the taxanes in the treatment of women with 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. There is very little reported difference in overall survival among the standard chemotherapeutic drugs available for patients with metastatic breast cancer. While there is some variability, it is now conventional practice to commence therapy with an anthracycline-containing regimen, followed by a taxane as a single agent as second-line treatment. Third-line treatment usually consists of capecitabine or vinorelbine. As they have in the past, members of the DSG acknowledge that there is a role for innovative treatments and investigational agents at each point in this treatment algorithm, including the introduction of investigational new drugs in patients who are chemotherapy-naive.

The DSG considered the evidence regarding the use of a taxane (either alone or in combination with other agents) in the first-line setting, where anthracycline-based chemotherapy would ordinarily be considered. Members of the DSG acknowledged

that a survival advantage for a taxane-based regimen over a standard anthracycline-based regimen has not yet been demonstrated. However, it was also pointed out that significant increases in response rates and time to progression have been demonstrated in this setting, when a taxane is used alone or in combination with an anthracycline. In particular patients, those with aggressive, symptomatic disease, a taxane-based combination in the first-line setting might offer a *higher probability* of response, and by inference, a relief of symptoms. In patients with particularly aggressive, rapidly progressing disease, a taxane-based treatment in the first-line setting might be the preferred choice to provoke a more rapid response. However, this argument could not be resolved with the currently available data, because time to response is rarely reported in trial results. After considering these issues, the DSG members agreed that in the first-line setting, either paclitaxel or docetaxel could be considered as reasonable treatment options for patients with metastatic breast cancer who receive multi-agent chemotherapy. The DSG members recommended that the choice should be offered to patients who are fully informed about the harms and benefits associated with each drug or drug combination, especially as cardiotoxicity and febrile neutropenia remain of concern.

The DSG also considered the evidence regarding the effectiveness of docetaxel over paclitaxel. Docetaxel appears to be more effective than paclitaxel, based on indirect comparisons, but published results of an ongoing trial directly comparing the two drugs are not yet available.

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 83 medical oncologists in Ontario. The survey consisted of 21 questions about the quality of the practice-guideline-in-progress (PGIP) report and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The guideline report and questionnaire were mailed on April 18th, 2002. Follow-up reminders were sent two weeks (post card) and four weeks (complete package mailed again) later. The Breast Cancer Disease Site Group (DSG) reviewed the results of the survey.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to ten members of the Practice Guidelines Coordinating Committee (PGCC). Seven members of the PGCC returned ballots. Four PGCC members approved the practice guideline as written, with one member providing suggestions for consideration by the Breast Cancer DSG. Two members approved the guideline conditional on the DSG addressing specific concerns.

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Breast Cancer DSG and the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

In ***anthracycline-naive patients***, who would ordinarily be offered treatment with a single-agent anthracycline (doxorubicin or epirubicin) or an anthracycline in a standard combination, the following options are also reasonable:

- Treatment with single-agent docetaxel 100 mg/m^2 over one hour every three weeks
- Docetaxel or paclitaxel in combination with doxorubicin

In ***anthracycline-naive patients for whom anthracyclines are contraindicated***:

- Treatment with single-agent docetaxel 100 mg/m^2 over one hour every three weeks is recommended.

In ***anthracycline-resistant patients or patients who have previously received an anthracycline as adjuvant therapy***:

- Either docetaxel (100 mg/m^2 over one hour every three weeks) or paclitaxel (175 mg/m^2 over three hours every three weeks) may be considered as a treatment option after failure of prior anthracycline treatment or in women whose disease is resistant to anthracyclines. The evidence supporting the use of single-agent docetaxel is more consistent and is based on a larger number of trials and patients than the evidence for paclitaxel.
- In selected patients, the combination of docetaxel and capecitabine is a therapeutic option. Due to the toxicity of the combination, patient selection for good performance status or younger age is recommended. It is recommended that capecitabine in the docetaxel/capecitabine combination be given at 75% of full dose.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The evidence supporting the recommendations is from randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Anthracycline-naive patients

- One randomized trial evaluated the use of single agent docetaxel versus doxorubicin. The trial reported a higher response rate and less febrile neutropenia, stomatitis, and nausea/vomiting with docetaxel than with doxorubicin monotherapy.
- Evidence from the three randomized trials of single-agent paclitaxel versus doxorubicin-based chemotherapy was conflicting.
- Paclitaxel or docetaxel, in combination with doxorubicin, was associated with higher response rates compared to standard anthracycline combinations in three randomized trials and longer time to disease progression and survival in one trial.

Anthracycline-resistant patients

- One of two small randomized trials detected improved time to progression with paclitaxel compared to non-taxane-containing chemotherapy. The other trial reported no significant difference in time to progression.
- Two of three randomized trials that compared docetaxel with non-taxane-containing chemotherapy detected improved response rates and time to progression with docetaxel, while the third reported no significant difference for these outcome measures. One trial also detected a significant survival advantage with docetaxel compared to mitomycin/vinblastine. The other trial that reported survival data did not detect a significant survival difference.
- One randomized trial that compared docetaxel plus capecitabine to docetaxel alone demonstrated a superior response rate, time to progression, and survival rate for the combination, with high rates of toxicity in both treatment arms.

POTENTIAL HARMS

- Paclitaxel or docetaxel, in combination with doxorubicin, was associated with higher rates of grade 3/4 neutropenia and neuropathy compared to standard anthracycline regimens.
- The taxanes were associated with higher rates of grade 3/4 neutropenia and neuropathy than mitomycin plus vinblastine.
- Clinical studies of epirubicin with either docetaxel or paclitaxel have not detected any significant incidence of congestive heart failure. In pharmacokinetic studies of epirubicin and the taxanes, no significant negative

interactions between epirubicin and either taxane were detected but increased area under the concentration curves of epirubicinol and 7-deoxydoxorubicin were noted. However, these metabolites are either less active or inactive when compared to the parent compound, and cardiotoxicity was not observed.

- An early study had detected reduced clearance of doxorubicin, when given in combination with paclitaxel, which resulted in high rates of clinical congestive heart failure. Strategies used to decrease the risk of congestive heart failure seen with the doxorubicin-paclitaxel combination have included: add dexrazoxane, substitute epirubicin or liposomal doxorubicin for doxorubicin, use docetaxel rather than paclitaxel if a doxorubicin combination is considered, limit the total dose of doxorubicin administered ($\leq$360 mg/m^2), change the schedule of infusion of doxorubicin, or separate doxorubicin and paclitaxel administration by 16 to 24 hours.
- Data on serious hematologic, gastrointestinal, and neurological adverse effects from randomized trials appear in Table 6 in the original guideline document. Data on congestive heart failure and toxic death are presented in Table 7 in the original guideline document.
- O'Shaughnessy et al noted a decreased tolerance to the combination of docetaxel and capecitabine in women $\geq$60 years of age. They suggested that a 25% reduction in the starting dose of capecitabine should be considered for these patients, as well as for patients with compromised performance status or comorbidity.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Patients should be fully informed of all the treatment options and should be aware of the risks and benefits associated with each of them.
- There is generally little difference in overall survival between chemotherapeutic agents in the treatment of metastatic breast cancer. Treatment in this setting should be based on clinical considerations and patient preferences, with a focus on palliation and quality of life.
- There is no evidence that initial combination therapy with anthracyclines and taxanes in the metastatic setting provides a survival advantage over the usual sequence of treatments conventionally employed in patients with metastatic breast cancer (e.g., an anthracycline followed by a taxane followed by capecitabine).
- The combination of paclitaxel (infused over three hours) and doxorubicin in rapid sequence should not exceed doses of doxorubicin >360 mg/m^2 due to the high incidence of congestive heart failure.
- Although few trials have compared weekly to three-weekly taxane therapy, the toxicities observed with weekly taxane therapy appear to be lower than those observed with the conventional three-weekly regimen. Weekly therapy could be considered for selected patients (elderly, low performance status, or women who wish to avoid some of the toxicities associated with the three-weekly taxane therapy).
- Women should be encouraged to enter clinical trials assessing novel treatments in the setting of metastatic breast cancer.
- 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

Living with Illness

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

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

DATE RELEASED

2003 Apr 24

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 disclosed information on potential conflict of interest before discussing this practice guideline.

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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 the taxanes in the management of metastatic breast cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2003 Apr. Various p. (Practice guideline; no. 1-3). 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 23, 2004. The information was verified by the guideline developer as of February 25, 2004.

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