



program in
evidence-based care
a cancer care ontario program

programme de soins
fondé sur des preuves
un programme de action cancer ontario

The Role of the Taxanes in the Management of Metastatic Breast Cancer Practice Guideline Report # 1-3

*S Verma, M Trudeau, K Pritchard, T Oliver,
and members of the Breast Cancer Disease Site Group*

Report Date: April 24, 2003

SUMMARY

Guideline Question

What is the role of the taxanes in the management of metastatic breast cancer?

Target Population

These recommendations apply to women with metastatic breast cancer for whom first- or greater-line chemotherapy is being considered outside the context of a clinical trial.

Recommendations

- In ***anthracycline-naïve 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/m² over one hour every three weeks.
 - Docetaxel or paclitaxel in combination with doxorubicin.
- In ***anthracycline-naïve patients for whom anthracyclines are contraindicated:***
 - Treatment with single-agent docetaxel 100 mg/m² 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/m² over one hour every three weeks) or paclitaxel (175 mg/m² 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.

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/m² 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.

Methods

The literature was searched using MEDLINE (through July 2002), the Cochrane Library (Issue 2, 2002), the Physician Data Query (PDQ) database, clinical trial and practice guideline Internet sites, and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the European Society for Medical Oncology.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative's Breast Cancer Disease Site Group and methodologists. This practice guideline has been reviewed and approved by the Breast Cancer Disease Site Group, which is comprised of surgeons, medical oncologists, radiation oncologists, epidemiologists, a pathologist, a medical sociologist, and a patient representative.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature and where appropriate, integration of this literature with the original guideline information.

Key Evidence

There is evidence from 17 randomized trials (9 published reports and 8 reports in abstract form) that compared paclitaxel or docetaxel, as single agents or in combination with other chemotherapeutic agents, as first- or second-line chemotherapy for the treatment of metastatic breast cancer.

Anthracycline-naïve patients

- Seven randomized trials assessed the use of paclitaxel in anthracycline-naïve patients and four randomized trials investigated the use of docetaxel in this setting.
- 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. Such therapy, however, was associated with

higher rates of grade 3/4 neutropenia and neuropathy compared to standard anthracycline regimens.

Anthracycline-resistant patients

- Four randomized trials evaluated the use of docetaxel for anthracycline-resistant metastatic breast cancer and two small randomized trials investigated the use of paclitaxel in this setting.
- 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.
- The taxanes were associated with higher rates of grade 3/4 neutropenia and neuropathy than mitomycin plus vinblastine.
- 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.

Treatment Alternatives

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.

Related Practice Guidelines Initiative Guidelines and Evidence Summaries (available at <http://www.cancercare.on.ca/ccopgi/>):

- #1-6: *Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer*
- #1-4: *Use of Vinorelbine in Stage IV Breast Cancer*
- #1-15: *Use of Trastuzumab (Herceptin) in Metastatic Breast Cancer*
- #1-16: *Use of Capecitabine in Stage IV Breast Cancer*

For further information about this practice guideline, please contact:

Dr. Maureen Trudeau; Co-chair, Breast Cancer Disease Site Group; Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Ave, Toronto ON, M4N 3M5; Telephone 416-480-5145; FAX 416-217-1338; E-mail: maureen.trudeau@tsrcc.on.ca

or

Dr. Wendy Shelley; Co-chair, Breast Cancer Disease Site Group; Kingston Regional Cancer Centre, 25 King St W, Kingston ON, K7L 5P9; Telephone: 613-544-2631 x4502; Fax: 613-546-8209; E-mail: wendy.shelley@krcc.on.ca.

*The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.*

Visit www.ccopebc.ca for all additional Practice Guidelines Initiative reports.

PREAMBLE: About our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives and CCO executives. Formal approval of a practice guideline by the PGCC does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network in consultation with relevant stakeholders, including CCO.

Reference:

¹ 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.

**For the most current versions of the guideline reports and information about the PGI and the Program, please visit our Internet site at:
<http://www.cancercare.on.ca/ccopgi/>
For more information, contact our office at:
Phone: 905-525-9140, ext. 22055
Fax: 905-522-7681**

Copyright

This guideline is copyrighted by Cancer Care Ontario; the guideline and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

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.