Evidence-based Series 1-24 Version 2 was reviewed in January 2014 and the Breast Disease Site Group (DSG) made the decision that EBS 1-24 Version 2 will not be updated as it will be replaced by a comprehensive practice guideline on Optimal Systematic Therapy for Early Female Breast Cancer that include the more recent literature.

Evidence-based Series (EBS) 1-24 Version 2, the resulting review report, consists of the following 5 parts:

1. Guideline Report Overview
2. Section 1: Clinical Practice Guideline
3. Section 2: Systematic Review
4. Section 3: Guideline Development and External Review
5. Document Assessment and Review Tool

and is available on the CCO Web site (http://www.cancercare.on.ca) PEBC Breast Cancer DSG page at: http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/

Release Date: September 15, 2011

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822  Fax: 905-526-6775  E-mail: ccopgi@mcmaster.ca


Guideline Citation (Vancouver Style): Members of the Breast Cancer Disease Site Group. The role of trastuzumab in adjuvant and neoadjuvant therapy in women with HER2/neu-overexpressing breast cancer. Madarnas Y, Tey R, reviewers. Toronto (ON): Cancer Care Ontario; 2011 Sep 15 [IN REVIEW 2014 Feb]. Program in Evidence-based Care Evidence-Based Series No.: 1-24 Version 2 IN REVIEW
# TABLE OF CONTENTS

**Overview**
Guideline Report History .................................................................................. iii
Guideline Review Summary ................................................................................. iv

**SECTION 1: Clinical Practice Guideline**
Questions ........................................................................................................ 1
Recommendations and Key Evidence ................................................................. 2
Qualifying Statement .......................................................................................... 2
Related Guideline .............................................................................................. 3
Funding, Copyright, Disclaimer & Contact Information .................................. 3
References ........................................................................................................ 5

**SECTION 2: Systematic Review**
Questions ........................................................................................................ 1
Introduction ...................................................................................................... 1
Methods ........................................................................................................... 2
Results ............................................................................................................ 3
Discussion ........................................................................................................ 9
Ongoing Trials ................................................................................................ 11
Conclusions ..................................................................................................... 11
Conflict of Interest ......................................................................................... 11
Journal Reference .......................................................................................... 12
Acknowledgements ........................................................................................ 12
Funding, Copyright, Disclaimer, & Contact Information ............................... 12
References ........................................................................................................ 13

**SECTION 3: Guideline Development and External Review**
The Program in Evidence-Based Care ............................................................... 1
The Evidence-Based Series ............................................................................ 2
Development of This EBS ............................................................................. 2
Policy Review .................................................................................................. 6
Related print and electronic publications ...................................................... 6
Funding, Copyright, Disclaimer, & Contact Information ............................... 6
Reference .......................................................................................................... 7
EBS 1-24 Document Assessment and Review Tool ...................................... 8
The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/neu-overexpressing Breast Cancer

Guideline Report History

<table>
<thead>
<tr>
<th>GUIDELINE VERSION</th>
<th>SYSTEMATIC REVIEW</th>
<th>PUBLICATIONS</th>
<th>NOTES AND KEY CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original version</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Version 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/neu-overexpressing Breast Cancer

Guideline Review Summary

Review Date: June 2010

The 2006 guideline recommendations are ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW
Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care, Cancer Care Ontario, in 2006. In June 2009, the PEBC guideline update strategy was applied and the new updated document released in September 2011. The Clinical Practice Guideline and Systemic Review in this version are the same as in the May 2006 version.

Update Strategy

Using the Document Assessment and Review Tool (at the end of this report), the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Questions Considered

In women with HER2/neu-overexpressing breast cancer:

1. Does trastuzumab, alone or in combination with other adjuvant or neoadjuvant systemic therapy improve clinically meaningful outcomes (overall response rate, time-
to-disease-progression, overall survival, toxicity, or quality of life) compared with adjuvant or neoadjuvant systemic therapy without trastuzumab?

2. What are the adverse events associated with adjuvant or neoadjuvant trastuzumab therapy?

3. What are the optimal dose, schedule, and duration for adjuvant trastuzumab therapy?

**Literature Search and New Evidence**

The new search (May 2006 to Sept 2009) yielded 32 relevant new publications from 13 RCTs. Initial publications of five randomized controlled trials (RCTs) were already included in the original document. Brief results of these publications are shown in the Document Assessment and Review Tool.

**Impact on Guidelines and Its Recommendations**

New evidence still compares trastuzumab with chemotherapy and still supports existing recommendation. Hence, the Breast Cancer DSG ENDORSED the 2006 recommendations.

With regard to tumour size <1cm, no changes to the recommendations are necessary since studies did not present results separately for this subgroups of patients. However, it was also mentioned that it is now time to re-examine this situation and determine whether people at high enough risk should be able to qualify for Herceptin, since there will never likely be any trials of Herceptin versus nothing in patients with tumours <1 cm. Although there are no individual trials for subgroups of patients with tumour sizes <1 cm or separate results for subgroups that would be statistically significant in and of themselves, a number of trials now have Forrest Plots that show that patients with tumours <1 cm have an equal relative benefit from the addition of Herceptin. Furthermore, there are a number of studies of patients with HER2-positive tumours <1 cm that suggest that they do poorly related to their HER2 positivity.
Evidence-based Series #1-24: Section 1

The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/neu-overexpressing Breast Cancer: A Clinical Practice Guideline


A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)


Report Date: May 12, 2006

Questions
In women with HER2/neu-overexpressing breast cancer:

1. Compared with adjuvant or neoadjuvant chemotherapy alone, does trastuzumab in combination with chemotherapy improve clinically meaningful outcomes (overall response rate, time-to-disease-progression, overall survival, toxicity, or quality of life)?

2. Compared with placebo or observation, does single-agent trastuzumab adjuvant or neoadjuvant therapy improve clinically meaningful outcomes?

3. What is the best way to identify women who will benefit from adjuvant or neoadjuvant trastuzumab therapy?

4. What are the adverse events associated with adjuvant or neoadjuvant trastuzumab therapy?

5. What are the optimal dose, schedule, and duration for adjuvant trastuzumab therapy?
Recommendations and Key Evidence

**Trastuzumab should be offered for one year to all patients with HER2-positive node-positive or node-negative, tumour greater than 1 cm in size, and primary breast cancer and who are receiving or have received (neo)adjuvant chemotherapy. Trastuzumab should be offered after chemotherapy.**

- In the Herceptin Adjuvant (HERA) trial (1), the addition of one-year trastuzumab following (neo)adjuvant chemotherapy was superior to observation after chemotherapy in terms of disease-free survival (DFS) (hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.43 to 0.67), recurrence-free survival (HR 0.50, 95% CI 0.40 to 0.63), and distant-disease-free survival (HR 0.40, 95% CI 0.40 to 0.66).
- In a combined analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trial and the North Central Cancer Treatment Group (NCCTG) N9831 trial (2), the addition of one-year trastuzumab concurrent with adjuvant paclitaxel following adjuvant doxorubicin and cyclophosphamide was superior to no trastuzumab in terms of DFS (HR 0.48, p-value 3x10^{-12}), time-to-first-distant-recurrence (TTR) (HR 0.47, p-value 8x10^{-10}), and overall survival (OS) (HR 0.67, p-value 0.015).

**Qualifying Statements**

- HER2 positive means the patient’s breast cancer overexpresses HER2/neu (>10% cells positive with strong intensity staining) as determined by immunohistochemistry (IHC) or the HER2/neu gene is amplified as determined by fluorescent in situ hybridization (FISH).
- There is evidence in favour of both concurrent and sequential administration of trastuzumab with adjuvant paclitaxel or docetaxel (2,3) after three-weekly doxorubicin and cyclophosphamide. Therefore, it is the expert opinion of the Breast Cancer Disease Site Group (DSG) that, for patients receiving three-weekly doxorubicin and cyclophosphamide followed by paclitaxel or docetaxel, it may be reasonable to give trastuzumab either with the taxane or after it. However, in the B-31 trial, there was a rate of 4.1% congestive heart failure for concurrent paclitaxel and trastuzumab following doxorubicin and cyclophosphamide (4).
- The HERA trial allowed any “approved” adjuvant chemotherapy regimen, with over 90% of patients receiving anthracycline- or anthracycline/taxane-based regimens. The trastuzumab was started after all other therapy except hormonal therapy.
- The HERA trial dose schedule of trastuzumab was three-weekly 6 mg/kg for one year, with an 8 mg/kg loading dose in the first cycle.
- There were significantly more grade 3/4 adverse events (7.9% versus [vs.] 4.4%) and serious events (7.0% vs. 4.7%) in the HERA trial in those receiving trastuzumab compared to those under observation. However, that toxicity is considered acceptable, given the increase in survival.
- The dose and schedule of doxorubicin and cyclophosphamide was the same for the B-31 and N9831 trials, four three-weekly cycles of 60 mg/m^2 doxorubicin and 600 mg/m^2 cyclophosphamide. The dose and schedule of trastuzumab was also the same, 4 mg/kg trastuzumab as a loading dose followed by 51 weekly cycles of 2 mg/kg trastuzumab.
- The B-31 and N9831 dose and schedule of paclitaxel following doxorubicin and cyclophosphamide differed between the two trials; B-31 patients received four three-weekly cycles of 175 mg/m^2 paclitaxel, while N9831 patients received 12 weekly cycles of 80 mg/m^2 paclitaxel.
- The HERA trial discontinued its control (observation) arm but continues with a one-year trastuzumab and a two-year trastuzumab arm. Until the results of that trial are available, the relative merits of one versus two years of trastuzumab are unknown.
There is evidence from the BCIRG 006 trial (3) that suggests that the combination of docetaxel, carboplatin, and trastuzumab may be similarly effective to doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab, with reduced cardiac toxicity. However, to date the full details of this trial, particularly the direct comparison of these two regimens, have not been published. Until such time as these results are available, the Breast Cancer DSG cannot make any recommendation regarding the docetaxel, carboplatin, and trastuzumab regimen.

There is evidence from the FinHer trial (5) that indicates that nine weeks of trastuzumab, given concurrently with either vinorelbine or docetaxel prior to cyclophosphamide, epirubicin and 5-fluorouracil is superior to the same regimen without trastuzumab. However, neither of the base regimens compared in this trial are commonly used; until such time as randomized trials comparing these regimens to standard trastuzumab containing regimens are reported, the Breast Cancer Disease Site Group cannot make any recommendation regarding their use.

So far, the only data available are for trastuzumab in patients who have (neo)adjuvant chemotherapy. There are no data available as yet for trastuzumab in patients who have received other forms of (neo)adjuvant therapy.

For related recommendations, clinicians are encouraged to review the clinical practice guidelines listed under Related Guidelines. Before the end of 2006, the Breast Cancer Disease Site Group plans to create a summary practice guideline covering all areas of adjuvant systemic therapy.

NOTE: An earlier version of this clinical practice guideline was released to Ontario hospitals in July 2005 as part of the Drug Quality Therapeutics Committee-Special Oncology Subcommittee (DQTC-SOS) funding process in Ontario. This version, along with the systematic review and methods and results document that make up this evidence-based series, replaces that document.

Related Guidelines
- PG 1-7: Adjuvant Taxane Therapy for Early-stage Invasive Breast Cancer - January 2006
- EBS 1-17: The Role of HER2/neu Expression in Systemic Therapy for Women with Breast Cancer - In development.

Funding
The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Copyright
This report is copyrighted by Cancer Care Ontario; the report 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 report. Nonetheless, any person seeking to apply or consult the report 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 guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Contact Information

For further information about this report, please contact:

Dr. Andrea Eisen, Co-chair, Breast Cancer Disease Site Group
Odette Cancer Centre, 2075 Bayview Ave, Toronto ON, M4N 3M5
Phone: 416-480-5000 ext. 4617  Fax: 416-217-1338  E-mail: andrea.eisen@sunnybrook.ca

or

Dr. Maureen Trudeau, Co-chair, Breast Cancer Disease Site Group
Odette Cancer Centre, 2075 Bayview Ave, Toronto ON, M4N 3M5
Phone: 416-480-5145  Fax: 416-217-1338  E-mail: maureen.trudeau@sunnybrook.ca

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822  Fax: 905-526-6775  E-mail: ccopgi@mcmaster.ca
REFERENCES


