Complete Summary

GUIDELINE TITLE

The role of trastuzumab in adjuvant and neoadjuvant therapy in women with HER2/*neu*-overexpressing breast cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Trudeau M, Madarnas Y, McCready D, Pritchard KI, Messersmith H, Breast Cancer Disease Site Group. The role of trastuzumab in adjuvant and neoadjuvant therapy in women with HER2/neu-overexpressing breast cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 May 12. 28 p. (Evidence-based series; no. 1-24). [58 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, 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.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

On August 31, 2005, Genentech and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of updated cardiotoxicity information related to the use of Herceptin (trastuzumab), obtained from the National Surgical Adjuvant Breast and Bowel Project (NSABP) study (B-31), a randomized, Phase III trial that was conducted in 2043 women with operable, HER2 overexpressing breast cancer (IHC 3+ or FISH+). This study demonstrated a significant increase in cardiotoxicity in patients who were randomized to the Herceptin-containing arm as compared to patients who received chemotherapy alone. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **
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)

HER2/*neu*-overexpressing breast cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

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

- To evaluate whether trastuzumab in combination with chemotherapy, compared with adjuvant or neoadjuvant chemotherapy alone, improves clinically meaningful outcomes (overall response rate, time-to-disease-progression, overall survival, toxicity, or quality of life)
- To evaluate whether single-agent trastuzumab adjuvant or neoadjuvant therapy compared with placebo or observation, improves clinically meaningful outcomes
- To determine the best way to identify women who will benefit from adjuvant or neoadjuvant trastuzumab therapy
- To evaluate the adverse events associated with adjuvant or neoadjuvant trastuzumab therapy
- To determine the optimal dose, schedule, and duration for adjuvant trastuzumab therapy

TARGET POPULATION

Women with HER2/*neu*-overexpressing breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

Trastuzumab following neoadjuvant or adjuvant chemotherapy

MAJOR OUTCOMES CONSIDERED

- Overall response rate
- Time-to-disease-progression
- Overall survival
- Toxicity
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE and EMBASE were searched up to the first week of May 2006 using the search criteria outlined in Table 1 in the original guideline document. The online abstract databases of the American Society of Clinical Oncology (ASCO) annual meetings (http://www.asco.org), San Antonio Breast Cancer Symposia (http://www.sabcs.org), and the European Society of Medical Oncology biennial congress (http://www.esmo.org), were all searched for appropriate data as shown in Table 2 in the original guideline document. The Cochrane Library was also searched for all entries that contained the keywords "trastuzumab" or "herceptin", with relevant items reviewed and included.

Inclusion Criteria

Trials were included if they met the following criteria:

- Trastuzumab, in combination or alone, was evaluated using a randomized controlled trial (RCT), meta-analysis, or evidence-based clinical practice guidelines.
- Reported outcomes included at least one of overall response rate, time-to-progression, overall survival, toxicity, or quality of life.
- Clinical trial results were published in full papers or publicly available abstracts and presentations.

Exclusion Criteria

Trials were excluded if they were published in a language other than English, as translation capabilities were not available.

NUMBER OF SOURCE DOCUMENTS

Six randomized trials were identified.

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

Synthesizing the Evidence

Because the number of trials with appropriate efficacy measures (disease-free survival [DFS], overall survival [OS], etc.) was small, and two of those trials have already been analysed in a combined analysis, no pooling of the evidence of the trials was performed.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by one member of the PEBC Breast Cancer Disease Site Group (BCDSG) and one methodologist.

The series is a convenient and up-to-date source of the best available evidence on the role of trastuzumab in (neo)adjuvant systemic therapy in women with HER2/*neu* overexpressing breast cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

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

Report Approval Panel

Prior to the submission of this Evidence-based Series report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel, and the response to them, are described in the original guideline document.

External Review

Following the review and approval of the report by the PEBC Report Approval Panel, the Breast Cancer Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Feedback was obtained through a mailed survey of 108 practitioners in Ontario (72 medical oncologists and 36 radiation oncologists or surgeons). 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. The survey was mailed out on April 10, 2008. Follow-up reminders were sent at two weeks (complete package mailed again). The Breast Cancer DSG reviewed the results of the survey.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

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.

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

- In the Herceptin Adjuvant (HERA) trial, 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, the addition of one-year trastuzumab concurrent with adjuvant paclitaxel following adjuvant doxorubicin and cyclophosphamide was superior to no trastuzumab in terms of disease-free survival (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).

POTENTIAL HARMS

Based on experience in the metastatic setting, the concurrent use of trastuzumab and anthracyclines has prohibitive cardiac toxicity. Based on the current reports, the cardiac toxicity with adjuvant trastuzumab appears to be acceptable, although the reported rate of cardiac events was higher in the concurrent versus sequential trastuzumab arm (in National Surgical Adjuvant Breast and Bowel Project [NSABP] B31 4.1% vs 0.7%, HR of 7.2; in North Central Cancer Treatment Group [NCCTG] 9831 3.3% vs 2.2%). The non-cardiac toxicity reported appears acceptable.

QUALIFYING STATEMENTS

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 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 paclitaxel 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.
- The Herceptin Adjuvant (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% 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 Breast Cancer International Research Group (BCIRG) 006 trial 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 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 DSG 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 in the original guideline document. Before the end of 2006, the Breast Cancer DSG plans to create a summary practice guideline covering all areas of adjuvant systemic therapy.
- 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 guarantees of any kind whatsoever regarding their content or use or application and disclaims any 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)

Trudeau M, Madarnas Y, McCready D, Pritchard KI, Messersmith H, Breast Cancer Disease Site Group. The role of trastuzumab in adjuvant and neoadjuvant therapy in women with HER2/neu-overexpressing breast cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 May 12. 28 p. (Evidence-based series; no. 1-24). [58 references]

ADAPTATION

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

DATE RELEASED

2006 May 12

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is 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

Three lead authors of this document (YM, DM, HM) reported no potential conflict of interest. KP reported receiving consultant or advisory fees from several pharmaceutical companies that produce agents evaluated by this document. MT reported receiving support through the National Cancer Institute of Canada for a clinical trial of trastuzumab from an involved pharmaceutical company.

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, 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.

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 Trastuzumab in adjuvant and neoadjuvant therapy in women with HER2/neu-overexpressing breast cancer: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 May 12. Various p. (Practice guideline; no. 1-24). 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 NGC summary was completed by ECRI on June 21, 2006. The information was verified by the guideline developer on July 6, 2006.

COPYRIGHT STATEMENT

This NGC summary is based on the original guideline, which is subject to the guideline developer's copyright restrictions. Please refer to the Copyright and Disclaimer Statements posted at the Program in Evidence-Based Care section of the Cancer Care Ontario Web site.

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

© 1998-2008 National Guideline Clearinghouse

Date Modified: 9/22/2008