



Complete Summary

GUIDELINE TITLE

The role of HER2/neu in systemic and radiation therapy for women with breast cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Dhesy-Third B, Pritchard KI, Messersmith H, O'Malley F, Elavathil L, Trudeau M, Breast Cancer Disease Site Group. The role of HER2/neu in systemic and radiation therapy for women with breast cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Nov 10. 50 p. (Evidence-based series; no. 1-17). [120 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.

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SCOPE

DISEASE/CONDITION(S)

Breast cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Obstetrics and Gynecology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate, in the absence of trastuzumab systemic therapy:

- if the efficacy of tamoxifen (compared with no tamoxifen) depends on HER2/*neu* status
- if the relative efficacies of different tamoxifen durations depend on HER2/*neu* status
- if the relative efficacies of aromatase inhibitors (compared with tamoxifen) depend on HER2/*neu* status
- if the efficacy of ovarian ablation (compared with no ovarian ablation) depends on HER2/*neu* status
- if the efficacy of anthracycline-based regimens (compared with non-anthracycline-based regimens) depend on HER2/*neu* status
- if the relative efficacies of different anthracycline-based regimens depend on HER2/*neu* status
- if the efficacy of taxane-containing regimens (compared with non-taxane-containing regimens) depend on HER2/*neu* status
- if the relative efficacies of different taxane-containing regimens depend on HER2/*neu* status
- if the effect of tamoxifen and chemotherapy (compared with tamoxifen alone) depend on HER2/*neu* status
- if the efficacy of radiation therapy (compared with no radiation therapy) depend on HER2/*neu* status

TARGET POPULATION

Women with breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Tamoxifen versus no tamoxifen by HER2/*neu* status
2. Different tamoxifen durations by HER2/*neu* status
3. Aromatase inhibitors versus tamoxifen by HER2/*neu* status
4. Ovarian ablation versus no ovarian ablation by HER2/*neu* status
5. Anthracycline-based regimens versus non-anthracycline-based regimens by HER2/*neu* status
6. Different anthracycline-based regimens by HER2/*neu* status

7. Taxane-containing regimens versus non-taxane-containing regimens by HER2/*neu* status
8. Different taxane-containing regimens by HER2/*neu* status
9. Tamoxifen and chemotherapy versus tamoxifen by HER2/*neu* status
10. Radiation therapy versus no radiation therapy by HER2/*neu* status

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Disease-free survival
- Time-to-progression
- Objective response rate
- Progression-free survival

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 December 2005 using a disease-specific medical subject heading (MeSH) term ("breast neoplasms"), marker-specific MeSH terms ("receptor, erbB-2" OR "genes, erbB-2" OR "oncogene proteins v-erbB"). The Excerpta Medica database (EMBASE) was similarly searched up to September 2005 using a disease-specific Excerpta Medica Tree (EMTREE) term ("breast cancer") and a marker-specific EMTREE term ("oncogene c erb"). The same, and design-specific EMTREE terms ("clinical study" OR "clinical trial").

Articles containing the trastuzumab EMTREE term ("trastuzumab") were excluded. Search terms for the following publication types and study designs were also included in each strategy: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and controlled clinical trials. Due to the large volume of studies on trastuzumab, articles containing this term in the title or abstract were excluded from both strategies.

Issue 1 (2005) of the Cochrane Library and online conference proceedings from the American Society of Clinical Oncology (ASCO) (<http://www.asco.org>; 1999-2005) and the San Antonio Breast Cancer Symposium (SABCS) (<http://www.sabcs.org/SymposiumOnline/index.asp#abstracts>; 2001-2004) 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 one reviewer, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

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

- The effects of systemic and/or radiation therapy was analyzed according to HER2/*neu* status in a phase III randomized controlled trial.
- Reported outcomes included disease-free survival, regression-free survival, time-to-progression, objective response rate, or overall survival.
- Clinical trial results were reported in 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. In addition, clinical practice guidelines were included if they addressed relevant topics.

Exclusion Criterion

Trials published in a language other than English were excluded due to the lack of translation resources.

NUMBER OF SOURCE DOCUMENTS

Thirty-one trials and one practice guideline were eligible for inclusion in this systematic review of the evidence.

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

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Where possible, meta-analyses were conducted to create summary estimates of the treatment effects by HER2/*neu* status for disease-free and overall survival. The methods described by Parmar et al. were used to derive the log-hazard ratio and its standard error. When these values were derived from survival curves, two independent analysts conducted the derivation from the curve, and their results were averaged. Analysis was conducted using the Review Manager software, version 4.2.7. Because the analyzed trials deal with different treatment regimens and patient groups, the assumption, necessary for fixed effects modelling, of a

common treatment effect to be measured was not supportable. Therefore, a random effects model was used for all summary estimates. With time-to-event outcomes, analysis was conducted using the generic inverse variance method with random effects. In one case (aromatase inhibitors versus tamoxifen in the neoadjuvant setting), overall response rate was combined via meta-analysis, also using a random-effects model.

In order to formally test the interaction of treatment and HER2/*neu* status for time-to-event outcomes where meta-analysis was performed, the difference between the HER2/*neu*-positive and HER2/*neu*-negative log hazard ratios was taken for each study and analyzed using the generic inverse variance method with random effects. The standard error of this difference was calculated using the following formula:

$$SE_{diff} = \text{sqrt} [(SE_{HER2+})^2 + (SE_{HER2-})^2]$$

where SE_{diff} is the standard error of the difference in log-hazard ratios, SE_{HER2+} is the standard error of the log-hazard ratio in the HER2/*neu*-positive subgroup, and SE_{HER2-} is the standard error of the log-hazard ratio in the HER2/*neu* negative subgroup. If the estimate of the difference was found to be significantly different from zero, this was interpreted as evidence of an interaction between treatment and HER2/*neu* status.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Endocrine Therapy - Tamoxifen

Three trials were identified that evaluated the efficacy of tamoxifen by HER2/*neu* status; two compared tamoxifen to observation, one compared tamoxifen plus goserelin to cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), and one compared five years versus two years of tamoxifen. In addition, two trials of aromatase inhibitors and tamoxifen reported results of interest to the question of tamoxifen interaction with HER2/*neu* status. The weight of the identified evidence, especially the Gruppo Universitario Napoletano (GUN) trial, suggests that the efficacy of tamoxifen is greater in HER2/*neu*-negative patients than in positive patients. However, while there is evidence to suggest tamoxifen is more effective in HER2/*neu*-negative patients, there is insufficient evidence to suggest tamoxifen is ineffective in HER2/*neu*-positive patients. Therefore, no definitive recommendations can be made at this time.

Endocrine Therapy - Aromatase Inhibitors

Two trials were identified that evaluated the efficacy of letrozole compared with tamoxifen according to HER2/*neu* status and one that evaluated anastrozole. Trials that evaluated exemestane were not identified. None of these trials reported significance testing of the interaction between HER2/*neu* status and treatment,

although the Pennsylvania State University Hershey Medical Center (PSUHMC) trial suggests that, in the metastatic setting, letrozole benefit to objective response rate (ORR) may be more pronounced in patients with HER2/*neu*-negative breast cancer.

Full results regarding HER2/*neu*-status subgroup analysis have not yet been published from the following large trials of aromatase inhibitors: aromatase, tamoxifen, alone or in combination (ATAC), Intergroup Exemestane Study (IES), and Breast International Group (BIG) 1-98. An abstract from the 2003 San Antonio Breast Cancer Symposium (SABCS) by Dowsett et al reported on a subgroup analysis of the ATAC trial comparing time-to-recurrence by estrogen-receptor (ER) and progesterone-receptor (PR) status. The abstract reported a marginally significant difference ($p=0.05$) between the ER+/PR+ (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.65-1.03) and ER+/PR- (HR 0.48, 95% CI 0.33 to 0.71) subgroups. As HER2/*neu* status and anastrozole therapy. However, an abstract from the 2005 SABCS by Viale et al, detailing the results by ER and PR status from the BIG 1-98 trial, reported no obvious difference between ER+/PR+ (HR 0.84, 95% CI 0.69 to 1.03) and the ER+/PR- (HR 0.83, 95% CI 0.62 to 1.10) subgroups comparing letrozole versus tamoxifen, and so this relationship may not hold across all aromatase inhibitors. If and when HER2/*neu* subgroup analyses are published from these trials, it may then be possible to make a definitive statement regarding the interaction of aromatase inhibitor therapy and HER2/*neu* status.

Endocrine Therapy - Ovarian Ablation

Two trials evaluated some form of ovarian ablation by HER2/*neu* status. Neither of these trials reported significant interaction between HER2/*neu* status and efficacy.

Chemotherapy - Anthracyclines

Ten trials, all conducted in the adjuvant setting, analysed the efficacy of anthracycline-based regimens versus non-anthracycline-based regimens according to HER2/*neu* status. While only two of these trials reported statistically significant interaction between HER2/*neu* status and treatment arm (anthracycline-containing regimen versus non-anthracycline-containing regimen) for an efficacy outcome, all of these trials were consistent in showing a trend for HER2/*neu*-positive patients experiencing greater benefit from anthracycline-based therapy than HER2/*neu*-negative patients. Additionally, the evidence suggests that HER2/*neu*-negative patients gain no benefit from anthracycline-based chemotherapy compared to CMF. This is borne out by the meta-analysis of the trials, where a significant benefit from anthracycline-based therapy in terms of disease-free and overall survival was found in HER2/*neu*-positive patients only.

Four trials evaluated more intensive (either higher dose or dose-dense) anthracycline-based regimens versus less intensive ones. The trials included in the meta-analysis varied in terms of the anthracycline used (doxorubicin or epirubicin), and the type of intensification (increased dosage versus shorter time frame at same dosage). The evidence from these trials and a meta-analysis of three of them support the conclusion that more intense anthracycline regimens may provide more benefit in HER2/*neu*-positive patients. These results are not conclusive; a significant interaction could not be established definitively in the

meta-analysis, as the choice of testing method used in the Belgian trial made a considerable difference in the results. It should be noted that the testing method most similar to that used in the other two included trials, immunohistochemistry (IHC) by CB-11 antibody, yielded the least statistical heterogeneity of the three results that could have been included, and also was the only result that implied a statistically significant interaction. However, as there were fewer than 30 patients per arm in the HER2/*neu*-positive subgroup, this association with testing may well be simply an artefact of low numbers.

One trial examined the efficacy of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) versus FEC combined with high-dose chemotherapy. This trial found a significant interaction in terms of disease-free survival, with HER2/*neu*-negative patients being the only patients who received any significant benefit from the addition of high-dose chemotherapy. It is important to note that the FEC regimen received in both arms differed only by a single cycle (four cycles in the high-dose chemotherapy arm versus five cycles in the other arm), and so this interaction is likely solely due to the high-dose chemotherapy.

Chemotherapy - Taxanes

Four trials conducted in the metastatic setting and one trial in the neoadjuvant setting evaluated the efficacy of taxane-containing regimens versus non-taxane regimens according to HER2/*neu* status. One other trial evaluated the efficacy of three different dose levels of paclitaxel. Overall, these trials provide no evidence that taxane-based therapy, compared to non-taxane based therapy, is either more or less efficacious based on HER2/*neu* status.

Chemoendocrine Therapy

One trial evaluated the efficacy of tamoxifen and chemotherapy compared with tamoxifen alone according to HER2/*neu* status. This trial found no significant interaction between therapy and HER2/*neu* status, but its results were consistent with the tamoxifen trials identified above.

Radiation Therapy

There were no studies identified that evaluated the efficacy of radiation therapy compared to no radiation therapy by HER2/*neu* status that met the inclusion and exclusion criteria.

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

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.

Feedback was obtained through a mailed survey of 105 practitioners in Ontario, including 68 medical oncologists and 37 surgeons or radiation oncologists. 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 July 10, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The authors reviewed the results of the survey.

This report reflects the integration of feedback obtained through the external review process with final approval given by the Breast Cancer Disease Site Group (DSG) and the Report Approval Panel of the Program in Evidence-based Care.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Patients with HER2/*neu*-positive breast cancer should be considered for chemotherapy containing an anthracycline instead of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or melphalan and 5-fluorouracil (PF) chemotherapy.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendation is supported by randomized trials, meta-analyses, and one practice guideline.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Although the current evidence does not support a definitive recommendation regarding tamoxifen therapy and HER2/*neu* status, the weight of the

- evidence, especially the Gruppo Universitario Napoletano (GUN) trial, suggests that the efficacy of tamoxifen may be greater in HER2/*neu*-negative patients than in HER2/*neu*-positive patients. However, the evidence does not support a recommendation against tamoxifen therapy in HER2/*neu*-positive patients. While it is possible that tamoxifen is more effective in HER2/*neu*-negative patients, there is still sufficient evidence that it is effective in HER2/*neu*-positive patients as well.
- Ten studies of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or melphalan and 5-fluorouracil (PF) versus an anthracycline-containing chemotherapy were identified that also performed a substudy analysis by HER2/*neu* status. Two of these studies reported a significant interaction between HER2/*neu* status and treatment. A meta-analysis of these studies by HER2/*neu* status found a significant benefit in terms of both overall survival (OS) (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.63 to 0.87) and disease-free survival (DFS) (HR 0.73, 95% CI 0.63 to 0.85) for the use of anthracycline-based chemotherapy compared to CMF or PF in patients with HER2/*neu*-positive breast cancer, but found no evidence of a benefit in HER2/*neu*-negative patients (HR 1.04 for overall survival, 1.00 for disease-free survival). The interaction between treatment and HER2/*neu* status was found to be significant in the meta-analysis (difference in log overall survival HRs -0.32 [95% CI -0.51 to -0.12], difference in log disease-free survival HRs -0.29 [95% CI -0.47 to -0.10]).

POTENTIAL HARMS

There are possible cardiac toxicities associated with the use of trastuzumab and anthracycline combination therapy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Patients with HER2/*neu*-positive breast cancer may derive more benefit from a more intense anthracycline regimen, in terms of dose or schedule, over a less intense one. Four of the identified studies comparing more intense anthracycline-based regimens to less intense ones were identified that also performed a substudy analysis of HER2/*neu* status. Three of these studies found a significant overall survival benefit for more intense anthracycline regimens versus less intense. A meta-analysis of these studies by HER2/*neu* status found a significant benefit in terms of disease-free survival (DFS) (hazard ratio [HR] 0.53, 95% confidence interval [CI] 0.37 to 0.77) for patients with HER2/*neu*-positive breast cancer receiving more intense anthracycline-based chemotherapy. This meta-analysis found no benefit in HER2/*neu*-negative patients (hazard ratio 1.09). However, this analysis was found to be sensitive as to which of three different possible sets of hazard ratios were selected in one study. In that study, the analysis of time-to-progression was conducted using three different methods of HER2/*neu* testing, and the significance of the meta-analysis of the differences in log hazard ratio between the HER2/*neu* subgroups was significant or not significant depending on the choice of testing. Therefore, a firm recommendation was not possible, as absence of interaction could not be definitively rejected.

- The Breast Cancer Disease Site Group (DSG) has produced two separate guidelines on trastuzumab systemic therapy, Practice Guideline (PG) #1-15 (metastatic) and Evidence Based Series (EBS) #1-24 (adjuvant), described in the original guideline document. These guidelines provide important information regarding the use of trastuzumab and anthracyclines sequentially or in combination with regards to concerns about cardiac toxicity. Physicians are encouraged to review the recommendation and qualifying statements in light of the information provided in those guidelines if combination or sequential trastuzumab/anthracycline therapy is being considered. Physicians are discouraged from using trastuzumab concurrently with anthracyclines.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series 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)

Dhesy-Thind B, Pritchard KI, Messersmith H, O'Malley F, Elavathil L, Trudeau M, Breast Cancer Disease Site Group. The role of HER2/neu in systemic and radiation therapy for women with breast cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Nov 10. 50 p. (Evidence-based series; no. 1-17). [120 references]

ADAPTATION

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

DATE RELEASED

2006 Nov 10

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

The lead authors of this document were asked to report any conflicts of interest. BD, LE, FO, KP, HM, declared that they had no potential conflicts; MT reported receiving per-patient funding for clinical trials.

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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 HER2/neu in systemic and radiation therapy for women with breast cancer: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Nov 10. Various p. (Evidence-based series #1-17). 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 29, 2007. The information was verified by the guideline developer on February 6, 2007.

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