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PRACTICE GUIDELINE

Systemic targeted therapy for HER2-positive early female breast cancer: a systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline

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ABSTRACT

Background

This systematic review addresses the question "What is the optimal targeted therapy for female patients with early-stage human epidermal growth factor receptor 2 (HER2)–positive breast cancer?"

Methods

The MEDLINE and EMBASE databases were searched for the period January 2008 to May 2014. The Standards and Guidelines Evidence directory of cancer guidelines and the Web sites of major guideline organizations were also searched.

Results

Sixty publications relevant to the targeted therapy portion of the systematic review were identified.

In four major trials (HERA, National Surgical Adjuvant Breast and Bowel Project B-31, North Central Cancer Treatment Group N9831, and Breast Cancer International Research Group 006), adjuvant trastuzumab for 1 year was superior in disease-free survival (DFS) and overall survival (OS) to no trastuzumab; trastuzumab showed no benefit in one trial (PACS 04). A shorter duration of trastuzumab (less than 1 year compared with 1 year) was evaluated, with mixed results for DFS: one trial showed superiority (FINHER), one trial could not demonstrate noninferiority (PHARE), another trial showed equivalent results (E 2198), and one trial is still ongoing (PERSEPHONE). Longer trastuzumab duration (HERA: 2 years vs. 1 year) showed no improvement in DFS or OS and a higher rate of cardiac events.

Newer HER2-targeted agents (lapatinib, pertuzumab, T-DM1, neratinib) have been or are still being evaluated in both adjuvant and neoadjuvant trials, either by direct comparison with trastuzumab alone or combined with trastuzumab. In the neoadjuvant setting (NEOALTTO, GeparQuinto, Neosphere), trastuzumab alone or in combination with another anti-HER2 agent (lapatinib, pertuzumab) was compared with either lapatinib or pertuzumab alone and showed superior or equivalent rates of pathologic complete response. In the adjuvant setting, lapatinib alone or in combination with trastuzumab, compared with trastuzumab alone (ALTTO) or with placebo (TEACH), was not superior in DFS. The results of the completed APHINITY trial, evaluating the role of dual HER2 blockade with trastuzumab and pertuzumab, are highly anticipated. Ongoing trials are evaluating trastuzumab as a single agent without adjuvant chemotherapy (RESPECT) and in patients with low HER2 expression (National Surgical Adjuvant Breast and Bowel Project B-47).

Conclusions

Taking into consideration disease characteristics and patient preference, 1 year of trastuzumab should be offered to all patients with HER2-positive breast cancer who are receiving adjuvant chemotherapy. Cardiac function should be regularly assessed in this patient population.

KEY WORDS

Early breast cancer, HER2, targeted therapy, trastuzumab, lapatinib, pertuzumab

1. INTRODUCTION

The outcomes of patients with early breast cancer have been improved with the use of adjuvant systemic treatments[1], which include chemotherapy, endocrine

The complete version of this guideline is posted on the Cancer Care Ontario Web site at https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/.

Supplemental material available at http://www.current-oncology.com.

therapy, and targeted agents (trastuzumab) for eligible subgroups of patients. Several clinical practice guidelines have made recommendations for the selection of adjuvant systemic therapy based on primary evidence or consensus, or both. Despite the existence of those guidelines, practice is variable in the Ontario health care setting[2]. The Program in Evidence-Based Care (PEBC), together with the Breast Cancer Disease Site Group of Cancer Care Ontario (CCO), is charged with developing evidence-based practice guidelines pertaining to breast cancer care. Over many years, the PEBC has created clinical practice guidelines addressing various aspects of adjuvant systemic therapy for early breast cancer. The creation of an updated, comprehensive guideline pertaining to all aspects of early breast cancer systemic therapy was recently identified as a priority. The resulting guideline is most applicable to the Canadian—and particularly Ontario—setting, but any high-resource health care context could find this guideline applicable.

A systematic review of the evidence was conducted to inform the guideline recommendations. Thereafter, expert consensus was used to validate the compiled recommendations, leading to creation of the final guideline. The guideline recommendations and a summary of the consensus process are published in this supplement and on the CCO Web site[3]. This article presents the evidence base used to develop the recommendations for targeted therapy in female patients with early-stage HER2 (human epidermal growth factor receptor 2)–positive breast cancer; it can be used as a standalone reference reviewing the extensive data in this important area. The evidence reviews for endocrine therapy in hormone receptor–positive cancer and for chemotherapy are published elsewhere in this supplement.

For the purposes of this guideline, early breast cancer was defined primarily as invasive cancers stage I–IIA (T1N0–1, T2N0). Studies in breast cancer described as operable or stage I–IIIA were also included (see the Methods section). Although several of the systemic therapies discussed here can be considered for use in the neoadjuvant setting, the review focuses on trials with endpoints of disease-free survival (DFS) or overall survival (OS), and thus excludes several neoadjuvant trials that used only pathologic complete response (PCR) as the primary endpoint.

2. METHODS

One systematic review was conducted for all systemic therapies, and therefore the search strategy and subsequent overall results apply to chemotherapy, hormonal therapy, and targeted therapy combined.

2.1 Literature Search Strategy

The MEDLINE and EMBASE databases were searched for the period January 2008 to March 5, 2012; the search was later updated to May 12, 2014. Publications had to include terms related to both breast cancer and systemic therapy (chemotherapy; endocrine therapy, including ovarian suppression; and targeted agents). The search was limited to randomized controlled trials (RCTS), guidelines, systematic reviews, and meta-analyses. In most cases, systemic agents were indexed using terms such as "adjuvant therapy," but individual chemotherapy agents or regimens were also included. The full database search strategy is set out in Supplementary Appendix 1. Guidelines were also located using the Standards and Guidelines Evidence directory of cancer guidelines and the Web sites of organizations known to produce oncology-related guidelines [National Institute for Health and Clinical Excellence (United Kingdom), Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Comprehensive Cancer Network (United States), National Health and Medical Research Council (Australia), New Zealand Guidelines Group]. Evidence was selected and reviewed by one member (GGF) of the PEBC Early Breast Cancer Systemic Therapy Working Group; all authors provided input about the included publication once the initial screening was complete.

2.2 Study Selection Criteria: RCTs

Clinical trials were included if they evaluated at least 100 female patients with early-stage breast cancer randomized to at least 1 systemic agent and used survival (generally OS or DFS) as one of the primary or secondary outcomes. Studies had to describe the patients as having early or operable breast cancer, or allow the population characteristics to be ascertained from the methods or results. Trials evaluating patients with stages IIB and IIIA cancers were included only if stage IIA cases also formed part of the patient population and if at least half the patients had stages I–IIB cancer. When only tumour size and nodal status were reported, stage was estimated according to the *AJCC Cancer Staging Manual,* 6th edition[4,5] to decide whether the study met the inclusion criteria. Studies with mostly stage III or locally advanced tumours were excluded, as were studies that focused on stage IV (metastatic) breast cancer, noninvasive cancers (ductal carcinoma *in situ* or lobular carcinoma *in situ*), or treatment of cancer relapse. Trials primarily evaluating antiemetic drugs, erythropoiesis-stimulating agents, or autologous hematopoietic stem-cell transplantation were excluded. Studies of bisphosphonates to prevent metastasis or cancer recurrence were included; studies evaluating any bone-targeted agents to treat bone metastasis were excluded. Studies were eliminated if they were not relevant to the current practice setting in Ontario (for example, they evaluated older drugs no longer used), reported only exploratory analyses or correlations, or did not report survival endpoints.

2.3 Selection of Other Publications

Clinical practice guidelines were considered relevant if their recommendations were based on a systematic review of the literature or were described as evidence-based consensus. Systematic reviews and meta-analyses were also evaluated. The quality of the systematic reviews and meta-analyses was assessed using the AMSTAR tool[6]. For the RCTs, study or trial design and quality characteristics were assessed; however, RCTs included in high-quality systematic reviews and meta-analyses were not separately appraised. Relevant RCTs cited in systematic reviews, guidelines, or meta-analyses were compared with those found during the MEDLINE and EMBASE database searches. Studies that were not captured in the database review were retrieved if deemed important for further evaluation. Studies whose long-term follow-up data were pending and studies referenced in abstract form only were targeted for retrieval of potentially updated publications. Referenced trials from before 2008 were also retrieved when deemed appropriate. Abstracts presented at major conferences were initially searched as part of the grey literature; however, most relevant studies were found to be included in the updated EMBASE database results, and therefore conference proceedings were not explicitly included.

3. RESULTS

After removal of duplicate citations, the searches of MEDLINE and EMBASE located 14,444 publications (11,435 RCTs and 3009 systematic reviews, guidelines, or meta-analyses). Of the guidelines, systematic reviews, and meta-analyses, 287 were of some relevance, and portions were either cited in the current literature review or used to locate RCTs that might not have appeared in the database searches. After screening based on the inclusion and exclusion criteria and the addition of publications from other sources (reference lists, targeted searches for publications of studies initially found only as abstracts), 516 publications of trials were located, of which 60 were relevant to the targeted therapy (HER2-positive) portion of the systematic review.

3.1 Guidelines

Clinical practice guidelines located in the literature search are summarized in Supplementary Table 1[7–10].

3.2 Meta-analyses

3.2.1 The Cochrane Collaboration

For the Cochrane Collaboration, Moja *et al.*[11] concluded that trastuzumab-containing regimens improve rates of OS (hazard ratio: 0.66; $p < 0.00001$) and DFS (hazard ratio: 0.60; $p < 0.00001$). Risk of congestive heart failure [relative risk (RR): 5.11; $p < 0.00001$] and decline in left ventricular ejection fraction (RR: 1.83; $p = 0.0008$) were increased with trastuzumab. Cardiotoxicity is often reversible if trastuzumab is stopped immediately on toxicity occurrence. No difference in hematologic adverse effects was observed.

In patients at high risk of recurrence and without heart problems, the trastuzumab benefit is much greater than the risk. The risk–benefit balance in patients at low risk of recurrence is less clear. Two small trials of trastuzumab administered for 6 months or less compared with no trastuzumab at all (FINHER[12] and Buzdar *et al.*[13], 273 patients in total) found efficacy similar to that in longer studies, but with less cardiotoxicity. The shorter regimens were associated with a hazard ratio of 0.31 for the DFS rate ($p = 0.04$) and a RR of 0.89 (no difference) for decline in left ventricular ejection fraction. Risk of congestive heart failure was lower (RR: 0.5), but that statistic was based on only 3 events. The Cochrane meta-analysis excluded the docetaxel–carboplatin–trastuzumab (TCH) arm of Breast Cancer International Research Group (BCIRG) 006[14] (in which cardiotoxicity was found to be less than that found with anthracyclines) and did not include the sequential arm of North Central Cancer Treatment Group N9831[15] because it had not yet been published.

3.2.2 Yin et al.*, 2011*

The analysis Yin *et al.*[16] also found better rates of DFS, OS, locoregional recurrence, and distant recurrence (all $p < 0.001$) when trastuzumab was added to adjuvant chemotherapy. The authors did not comment on cardiotoxicity, but found a higher incidence of central nervous system recurrence ($p = 0.01$), which was suggested to possibly be related to the prolonged survival of patients receiving trastuzumab.

3.3 Neoadjuvant Trials, Including Systematic Reviews and Meta-analyses

Several systematic reviews of neoadjuvant trastuzumab have recently been published[17–21]. Most RCTs (and thus reviews) reported PCR as the primary endpoint. All the reviews concluded that, compared with chemotherapy alone, trastuzumab plus chemotherapy significantly increased PCR in patients with HER2-positive cancer (RR for probability of PCR: 1.85 and 2.07, $p < 0.001$, in favour of trastuzumab in two of the meta-analyses). Only a study by Buzdar *et al.*[13] focused on early breast cancer; it did not meet our inclusion criteria because of its small number of patients, and therefore it does not appear in the data table. The study compared paclitaxel plus trastuzumab (every 3 weeks for 4 cycles) → FEC (5-fluorouracil–epirubicin–cyclophosphamide) plus trastuzumab (every 3 weeks for 4 cycles) with the same regimen without trastuzumab and found PCR

rates of 65% and 26% and 3-year DFS rates of 100% and 85% ($p = 0.041$) respectively.

3.4 Meta-analyses or Reviews of Cardiotoxic Effects

3.4.1 Chen et al.*, 2011*

The meta-analysis by Chen *et al.*[22] of 11,882 patients in ten RCTs found rates of left ventricular ejection fraction decline and congestive heart failure to be 7.5% and 1.9% respectively among patients receiving trastuzumab. Those rates were significantly higher than the rates in patients receiving no trastuzumab (RR: 2.13; $p = 0.003$; and RR: 4.19; $p < 0.00001$). A congestive heart failure effect was found in both early and metastatic disease. The effect was highly significant in patients receiving anthracycline-based chemotherapy (RR: 4.27; $p < 0.00001$; almost all with early breast cancer), but more uncertain in patients receiving non-anthracycline chemotherapy [three small studies that included 495 patients with metastatic breast cancer (RR: 2.42; 95% confidence interval: 0.36 to 16.19; $p = 0.36$)]. The meta-analysis did not consider the non-anthracycline arm of BCIRG 006[14].

3.4.2 Costa et al.*, 2010*

A review by Costa *et al.*[23] considered six major studies, focusing on efficacy and cardiac safety. Cardiac events occurred at rates of 1.9%–3.8% in the anthracycline plus trastuzumab arms; rates were lowest with the TCH regimen (0.4%). Compared with control subjects, patients receiving TCH experienced less cardiotoxicity and better survival rates, but whether TCH is as effective as AC (doxorubicin–cyclophosphamide) → docetaxel plus trastuzumab → trastuzumab is uncertain. Most of the studies excluded patients who had pre-existing heart problems or who experienced cardiotoxicity during chemotherapy. In FINHER[12], trastuzumab was administered for a shorter time before anthracycline (9 weeks), and negligible cardiotoxicity was found (although the study was small and requires confirmation). Several trials to compare 9 weeks with 1 year of trastuzumab are ongoing. For patients having risk factors for cardiac dysfunction or patients with a low risk of recurrence, the review suggested that AC → taxane plus trastuzumab is difficult to justify; use of TCH or trastuzumab after completion of chemotherapy (as in the HERA trial[24,25]) might be preferable.

3.5 Individual RCTs with Trastuzumab

The literature search located updated data for six of the seven studies in the PEBC guideline, and identified nine new studies and seven ongoing studies. Two studies on locally advanced or metastatic breast cancer and one study with fewer than 100 patients did not meet the inclusion criteria for the present guideline. Because earlier guidelines were based on limited studies, most of which now have updated results, Supplementary Table 2 summarizes all the studies and the most recent results[12,14,15,24–65].

4. DISCUSSION

The subsections that follow discuss issues related to patient selection and optimal administration of trastuzumab (timing, duration), including whether the benefit of trastuzumab in preventing recurrence outweighs the risk of cardiotoxicity or other adverse effects.

4.1 Is Trastuzumab Beneficial in Patients with Small Node-Negative Tumours?

Most RCTs exclude patients with small node-negative cancers (T <1 cm; T <2 cm and N0), and so evidence to evaluate the question of whether trastuzumab is beneficial in patients with such tumours is limited. The HERA[24,42,43,66] study included patients with small N0 tumours (<1 cm, $n = 60$; 1 cm, $n = 33$; >1 cm and <2 cm, $n = 510$), finding that the efficacy of trastuzumab was not different for N+ and N0 tumours. At 2 years, trastuzumab was effective in both 0–2 cm and 2–5 cm tumours; at 3 years, the trastuzumab effect was similar for N0 tumours overall and for N0 tumour subgroups classified as 1.1–2 cm and as 2 cm or larger in size. The BCIRG 006[14,58] study found benefit for trastuzumab in patients with N0 and N+ cancers; results were not further divided by tumour size for patients with N0 cancer. Trastuzumab was beneficial in patients having tumours less than 1 cm, less than 2 cm, and 2 cm or larger in size, but not in those whose tumours were 1–2 cm in size. That inconsistency could be a result of the small number of patients in each category. In the N9831 study[15,51–56], 39% of tumours were smaller than 2 cm, with some being 1–2 cm and N0, but data were not reported separately for the latter group.

Petrelli and Barni[67] summarized the studies of very-early-stage pT1a/bN0M0 HER2-positive breast cancers, including both RCTs and retrospective case series. They concluded that patients with such cancers experience a higher rate of relapse and poorer survival rates than do those with HER2-negative cancers of the same size and stage, and that, for small N0 tumours, biology or prognostic factors (proliferative index, hormone receptor status, etc.) should have greater influence than tumour size in guiding choice of treatment.

Exploratory analyses in the FINHER trial[12,36] found that a subgroup of patients with very high HER2-positive content did not benefit from trastuzumab.

4.2 What Is the Optimal Duration of Trastuzumab Therapy?

Results from HERA[24,42,43,66] indicated that 1 year of trastuzumab is as good as 2 years and is associated

with fewer adverse effects. The small FINHER trial[12,36] found that 9 weeks of trastuzumab is more effective than none at all (control), with no difference in cardiotoxicity or brain metastasis. The E2198 trial[40] found no difference between 12 weeks and 1 year of trastuzumab; however, its results have been published only as an abstract. The PHARE[37–39,68] trial was inconclusive with respect to whether 6 months of trastuzumab is noninferior to 12 months, although a nonsignificant trend favouring 12 months was observed. The optimal duration of trastuzumab is therefore still unknown. One year is suggested to be standard, but lower cardiotoxicity might justify a shorter duration for some patients, and 6 months of trastuzumab is better than no trastuzumab at all.

4.3 Should Trastuzumab Be Administered Concurrently With or Sequentially After Chemotherapy?

No adjuvant studies gave trastuzumab concurrently with anthracyclines. Most gave either anthracycline → taxane → trastuzumab or anthracycline → taxane plus trastuzumab. In the N9831 study[15,51–56], trastuzumab was administered either concurrently or sequentially with taxanes, and a trend toward an increase in the DFS rate was observed for concurrent compared with sequential administration, but the difference was not statistically significant. Ongoing studies are giving trastuzumab and anthracyclines concurrently in the neoadjuvant setting.

4.4 What Is the Most Appropriate Chemotherapy for Use in Conjunction with Trastuzumab?

Available data are limited because only BCIRG 006[14,58] compared a non-anthracycline regimen with an anthracycline regimen. In that study, adverse effects were fewer with TCH (docetaxel–carboplatin every 3 weeks × 6 plus trastuzumab for 52 weeks) than with AC→T plus trastuzumab (AC→TH), and with respect to DFS and OS, both regimens were superior to AC→T alone. A direct comparison was not made between the two trastuzumab regimens; however, both were compared with the same control (AC→T). Rates of DFS were 84% for AC→TH, 81% for TCH, and 75% for AC→T. Rates of congestive heart failure and cardiac dysfunction were higher in the AC→TH group than in the TCH group ($p < 0.001$). Acute leukemia occurred in 7 patients receiving AC-based therapy and in 1 receiving TCH (the latter patient had received anthracycline outside the study). Whether TCH is as effective as AC→TH is uncertain; however, because of lower rates of cardiotoxicity and leukemia, TCH might be preferred for some patients. As suggested in the review by Costa *et al.*[23], TCH might be preferred for patients with risk factors for cardiac dysfunction.

4.5 HER2 Status and Taxane Efficacy

Meta-analysis of 11,631 patients in six studies found taxanes to be superior to non-taxane-based regimens for DFS in both HER2-positive and HER2-negative disease. No evidence of interaction between HER2 status and taxane efficacy was observed[69].

5. CONCLUSIONS

Adjuvant trastuzumab should be offered to all patients with HER2-positive breast cancer (node-positive and node-negative with a tumour size exceeding 1 cm) who are receiving adjuvant chemotherapy. Adjuvant trastuzumab can be considered in small (≤1 cm) tumours as part of clinical studies or evidence-building programs (such as the Evidence-Building Program currently available in Ontario). Trastuzumab can be combined with any appropriate adjuvant chemotherapy (for example, FEC→T or AC→T). The TCH regimen has been found to be associated with lower rates of cardiotoxicity and might be preferred for some patients. Administration of trastuzumab concurrently with the anthracycline component of a chemotherapy regimen is generally not recommended because of the potential for increased cardiotoxicity, although concurrent anthracycline and trastuzumab has been safely administered in the neoadjuvant setting. Adjuvant trastuzumab can be initiated either concurrently or sequentially with the taxane portion of a chemotherapy regimen. Patients should be offered 1 year of adjuvant trastuzumab, with regular assessments of cardiac function (every 3–4 months).

The recommendations and justification in the accompanying clinical practice guideline in the present supplement are based on the evidence presented here and can be considered to be more detailed conclusions from the evidence summary. Table I summarizes the recommendations.

6. REVIEW AND UPDATE

Practice guidelines and literature reviews developed by the PEBC are regularly reviewed and updated. For the full 1-21 evidence-based series and subsequent updates, please visit the CCO Web site at: https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/.

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TABLE I Recommendations for trastuzumab use in patients with cancer positive for the human epidermal growth factor receptor 2 (HER2)

Only patients with HER2-positive breast cancer (3+ by immunohistochemistry, an *in situ* hybridization ratio ≥2, or 6 or more HER2 gene copies per cell nucleus) should be offered adjuvant trastuzumab.
Trastuzumab plus chemotherapy is recommended for all patients with HER2-positive node-positive breast cancer and for patients with HER2-positive node-negative breast cancer greater than 1 cm in size.
Trastuzumab therapy can be considered in small tumours (≤1 cm) as part of clinical studies or of evidence-building programs (such as the Evidence-Building Program currently available in Ontario).
Trastuzumab can be administered with any acceptable adjuvant chemotherapy regimen.
Administration of trastuzumab concurrently with the anthracycline component of a chemotherapy regimen is generally not recommended because of the potential for increased cardiotoxicity.
Adjuvant trastuzumab can be initiated either concurrently or sequentially with the taxane portion of a chemotherapy regimen.
Docetaxel–carboplatin–trastuzumab (TCH) is less cardiotoxic than doxorubicin–cyclophosphamide followed by docetaxel–trastuzumab; TCH is recommended for patients at higher risk for cardiotoxicity.
No phase III evidence exists for the addition of trastuzumab to some chemotherapy regimens such as docetaxel–cyclophosphamide. However, such regimens might be in use and are reasonable options, particularly to mitigate cardiotoxicity in certain patients.
Patients should be offered 1 year total of adjuvant trastuzumab, with regular cardiac function assessments during that period.

8. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SG has received speaking honoraria from Novartis. AE has received a grant from Genomic Health for a pending research study and was a NCIC principal investigator for the olympiA trial. SFD was a principal investigator for the APHINITY trial and has received speaking honoraria from Hoffman–La Roche, Amgen, and Novartis; travel support from Celgene and Roche; and unrestricted education grants from Roche, Pfizer, GlaxoSmithKline, and Amgen. MET has overseen funds from Roche and Amgen for the Sunnybrook Odette Cancer Centre chemotherapy suite renovation, from Amgen for a drug reimbursement specialist, and from Eisai, Roche, Novartis, and Amgen for fellowship funding. MET has also received grants or research support from Astellas, Medivation, and Novartis. The other working group members declared they had no conflicts.

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