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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

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The full Evidence-based Series #1-24 is comprised of 3 sections
and is available on the CCO website (<http://www.cancercare.on.ca>)

PEBC Breast Cancer DSG page at:

<http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/>

Section 1: Clinical Practice Guideline

Section 2: Systematic Review

Section 3: Guideline Development and External Review - Methods and Results

Question

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 3×10^{-12}), time-to-first-distant-recurrence (TTR) (HR 0.47, p-value 8×10^{-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/m² doxorubicin and 600 mg/m² 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/m² paclitaxel, while N9831 patients received 12 weekly cycles of 80 mg/m² 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
- PG 1-8: *Adjuvant Systemic Therapy for Node-Negative Breast Cancer* - May 2003.
- PG 1-15: *The Role of Trastuzumab (Herceptin) in the Treatment of Women with HER2/neu-overexpressing Metastatic Breast Cancer* - November 2005.
- EBS 1-17: *The Role of HER2/neu Expression in Systemic Therapy for Women with Breast Cancer* - In development.
- PG 1-20: *The Role of Taxanes in Neoadjuvant Chemotherapy for Women with Non-metastatic Breast Cancer* - December 2004.

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3. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Pawlicki M, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC>T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC>TH) with docetaxel, carboplatin, and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study [abstract]. *Breast Cancer Res Treat* 12-8-2005;94 Suppl 1:A1
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