Adjuvant/neoadjuvant trastuzumab therapy in women with HER-2/neu-overexpressing breast cancer: a systematic review
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CRD summary
This review evaluated the safety and effectiveness of trastuzumab as (neo)adjuvant therapy for women with HER-2/neu-positive breast cancer and concluded that evidence supported use of trastuzumab for one year in certain populations. Uncertainty surrounding study quality and limited review methods means the authors' conclusions should be interpreted with caution.

Authors' objectives
To evaluate the safety and effectiveness of trastuzumab as (neo)adjuvant therapy for women with HER-2/neu-positive breast cancer.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from inception to May 2007 for studies written in English; search terms were reported. Online abstract databases of American Society of Clinical Oncology Annual Meetings and Annual San Antonio Breast Cancer Symposia were searched up to 2006.

Study selection
Randomised controlled trials (RCTs) of trastuzumab (in combination with existing (neo)adjuvant chemotherapy or as a single agent) in women with HER-2/neu-positive breast cancer were eligible for inclusion. Trials had to report at least one of the following outcomes: overall response rate; disease-free survival; overall survival; toxicity; and quality of life. Trial results had to be published peer-reviewed articles or publicly available abstracts or presentations.

Six studies were of adjuvant (postoperative) trastuzumab and two of (neo)adjuvant (preoperative) trastuzumab. Most studies used trastuzumab for one year in doses of either 6mg/kg every 21 days or 2mg/kg weekly. Studies used a varied range of concomitant chemotherapy treatments that included drugs such as doxorubicin, cyclophosphamide, docetaxel and 5-fluorouracil. These were also the comparator treatments (either individually or in combination). Non-chemotherapy agents such as tamoxifen were also used. One trial used radiation therapy. Studies used different inclusion criteria, but all patients had either high risk or positive lymph nodes.

The authors stated that three reviewers were involved in the process of selecting studies, but no further details were provided.

Assessment of study quality
Study quality was assessed using the following criteria: method of randomisation; patient stratification; use of intention-to-treat (ITT) analysis; and assessment of power/sample size calculation. The authors did not state how many reviewers performed the assessment.

Data extraction
Hazard ratios with 95% confidence intervals and associated p values were extracted.

The authors stated neither how data were extracted for the review nor how many reviewers performed the data extraction.

Methods of synthesis
A narrative synthesis was presented, supplemented by tables of study details.

Results of the review
Eight RCTs were included in the review (n=14,134, range 22 to 5,102 participants). Only the six adjuvant trials were quality assessed; five studies reported both use of a power calculation and ITT analyses, but methods of randomisation were generally poorly reported.

All six trials of adjuvant trastuzumab found disease-free survival to be significantly improved with trastuzumab treatment. Four trials found significant improvement in overall survival with trastuzumab. The two small trials of neoadjuvant trastuzumab found a significantly better pathological complete response in patients who received trastuzumab. The incidence of immediate cardiac events was substantially higher (in three large adjuvant trials) in the groups that received trastuzumab. Further results were reported.

Authors’ conclusions
Although the optimal duration, schedule and timing of adjuvant trastuzumab remained undefined, the bulk of available evidence supported that adjuvant trastuzumab be offered for one year to all patients with HER-2-positive and node-positive or high-risk node-negative primary breast cancer who were receiving or had received (neo)adjuvant chemotherapy.

CRD commentary
The review addressed a clear question supported by appropriate inclusion criteria. Several databases were searched. But, the restriction to studies written in English and the absence of searches for unpublished studies meant that some relevant studies may have been missed and the review may have been subject to language and publication biases. The methods used to select studies, extract data and assess study quality were either poorly reported or not reported at all, so it was possible that these processes may have been subject to reviewer error and bias. The tables of study details did not include demographic details (such as ages of participants), which made it more difficult to compare study results. A quality assessment was undertaken, but it did appear that it was used in interpreting the results and it did not appear that a quality assessment was made for the neoadjuvant trials. In view of the observed clinical heterogeneity, a narrative synthesis appeared appropriate. The narrative largely focused on a description of individual studies, or on synthesising dosage, scheduling and toxicity data, rather than effectiveness data. Considering the doubts surrounding the randomisation/allocation concealment processes used, along with the possibility of missed studies and reviewer errors and bias, the authors’ conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: See Authors’ Conclusions. Also, stronger deliberation regarding receipt of trastuzumab should be given to those patients thought to be at risk for cardiac toxicity, elderly patients and patients with tumours less than 1cm in size.

Research: The authors outlined and listed the ongoing RCTs of trastuzumab and stated the need for further trials with direct comparisons of sequential versus concurrent trastuzumab.

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