The clinical effectiveness of trastuzumab for breast cancer: a systematic review


Authors' objectives
The authors stated that their objective was to assess the clinical effectiveness of trastuzumab for managing advanced breast cancer. However, people with breast cancer of any stage were eligible for inclusion.

Searching
MEDLINE, EMBASE, Cancerlit, BIOSIS Previews, the Index to Scientific and Technical Proceedings, the Cochrane Controlled Trials Register, DARE, NHS EED and the National Research Register were searched to August 2001; the search terms and strategies were reported in depth. The authors identified additional references through reviewing submissions (to the National Institute of Clinical Excellence) by manufacturers, by checking the bibliographies of retrieved articles, and by searching conference proceedings and the Internet. Studies reported in English, German, Dutch and French were eligible for inclusion in the report, but the search strategy had no language restrictions.

Study selection
Study designs of evaluations included in the review
Initially, only randomised controlled trials (RCTs) were eligible for inclusion. However, the authors did not identify any RCTs of trastuzumab as monotherapy for people with breast cancer. Therefore, the inclusion criteria were broadened to include non-comparative phase II studies (cohort studies, case-control studies, and case series) of trastuzumab monotherapy.

Specific interventions included in the review
To be eligible for inclusion, studies had to evaluate trastuzumab alone or combined with other agents in comparison with systemic therapy without trastuzumab. When no suitable studies of trastuzumab monotherapy were identified, the authors broadened their criteria to include studies comparing trastuzumab monotherapy versus no other systemic therapy, or versus a different dose of trastuzumab. Non-comparative studies of trastuzumab monotherapy were also included. The interventions included in the review were: trastuzumab monotherapy of varying doses; intravenous chemotherapy with 175 mg/m2 paclitaxel over 3 hours every 3 weeks; or intravenous chemotherapy with 60 mg/m2 doxorubicin or 75 mg/m2 epirubicin and 600 mg/m2 cyclophosphamide. The exact trastuzumab regimens varied between the included studies and were tabulated in the review.

Participants included in the review
Studies of people with breast cancer of any stage were eligible for inclusion. Only those with breast cancer overexpressing human epidermal growth factor receptor 2 (HER2) at level 3+ who had been pre-treated with an anthracycline and/or taxane, or for whom these treatments were unsuitable, were eligible for inclusion from non-comparative phase II studies of trastuzumab monotherapy. All included studies were conducted in women with metastatic or advanced breast cancer.

Outcomes assessed in the review
The authors did not explicitly state the outcomes that studies had to include in order to be eligible for the review. The primary outcomes of interest were complete and partial tumour response, progression-free survival, overall survival, symptom relief, quality of life and adverse effects.

How were decisions on the relevance of primary studies made?
Two authors independently assessed titles and, where possible, abstracts of potential studies for relevance. If either author considered the paper potentially relevant, they obtained a copy of the full manuscript and assessed it against the inclusion criteria. Any disagreements were resolved by consensus, with the involvement of a third author if necessary.

Assessment of study quality
The authors assessed the methodological quality of each included study using predefined checklists developed by the NHS Centre for Reviews and Dissemination (see Other Publications of Related Interest). The assessment criteria for RCTs included allocation concealment, method of randomisation, baseline comparability, specified eligibility criteria, blinding, intention-to-treat analysis and description of withdrawals. The assessment criteria for case series included sample representativeness, inclusion criteria, blinding, outcome measurement and follow-up duration. Further details were provided in the report. Two authors assessed study quality independently. Any disagreements were resolved by consensus, with the help of a third author if necessary.

Data extraction
One author abstracted the data into an electronic database using predefined data extraction forms. A second author checked the extraction. Any disagreements were resolved by consensus, with the help of a third author if necessary. Studies reported in multiple publications were collated and reported only once.

Where possible, treatment effects and 95% confidence intervals were calculated for each study on an intention-to-treat basis. Relative risks were calculated for dichotomous outcomes, and for time-to-event outcomes hazard ratios were reported if given, as well as median survival and measures of variance.

Methods of synthesis
How were the studies combined?
The authors provided a narrative synthesis of their findings and tabulated the extracted data. The results were not pooled because of differences between studies in the types of intervention, stage of therapy, dose and study design, and the limited number of trials identified.

How were differences between studies investigated?
The authors grouped studies according to whether the intervention involved monotherapy or combined therapy. A formal statistical analysis of heterogeneity was not presented, owing to the small number of studies included. Differences between the studies in terms of participants, dose regimen and aspects of study quality were discussed in the text.

Results of the review
Four studies with 850 participants were included. There was one RCT of combination therapy (n=469), one RCT of trastuzumab monotherapy at different doses (n=113), and two case series of monotherapy (n=268).

Trastuzumab monotherapy. Based on two case series and one randomised trial of different doses of trastuzumab (n=381), the authors found that trastuzumab monotherapy had some effect on overall tumour response (range 12 to 24% in three studies). Two non-comparative phase II studies reported average tumour responses of about 9 months (9 and 9.1 months). One phase II study found that overall tumour response was 31% for people with tumours overexpressing HER2 at level 3+, while another study reported tumour response as 18% in this group.

Two phase II studies reported survival outcomes from trastuzumab therapy: the range was 0.5 to 30 months in one study (median 13 months) and 1.2 to 35.3 months in the other (67% were alive at 11 months). Trastuzumab monotherapy was associated with relatively low toxicity.

Combination therapy.
The authors found one randomised trial (n=469) of trastuzumab with or without chemotherapy (cyclophosphamide plus anthracycline or paclitaxel). This study included women with treatment-naive HER2 overexpressing metastatic breast cancer at level 2+ or 3+. Compared with chemotherapy alone, trastuzumab combination therapy was associated with less disease progression and treatment failure, longer progression-free survival, and greater complete and overall tumour response. However, women receiving combined therapy had a statistically significantly greater incidence of congestive heart failure than women receiving chemotherapy alone. The incidence appeared greatest with anthracycline-based chemotherapy.
The report provided further details about toxicity and quality of life.

**Cost information**
The authors noted that cost-effectiveness analyses were submitted by industrial sources, but they did not report the findings in detail.

**Authors' conclusions**
Trastuzumab combined with chemotherapy is more effective than chemotherapy alone for metastatic breast cancer overexpressing HER2 at level 3+. However, trastuzumab combination therapy may be associated with congestive heart failure, especially in people receiving anthracycline-based chemotherapy. There was weak evidence of the effectiveness of trastuzumab monotherapy for people with metastatic breast cancer overexpressing HER2 at level 3+, based on non-comparative studies of moderate quality.

**CRD commentary**
This review included a well-defined research question with clear pre-specified inclusion and exclusion criteria. The search strategy and methods used to assess relevance and validity and to synthesise data were described in detail. The search strategy appears to have been appropriate and extensive, while the methods used to assess relevance and validity seem appropriate and robust.

Owing to the limited number of studies identified, the authors did not pool the data, or present formal heterogeneity or sensitivity analyses, or analyses of publication bias. This seems appropriate, as does the narrative synthesis of the findings.

The authors drew their conclusions about the effectiveness of trastuzumab monotherapy and combination therapy based on a small number of studies of limited quality. While the data presented support the authors' conclusions, it may be premature to conclude that trastuzumab combination therapy is effective based, for instance, on just one trial. The duration of follow-up in the included studies was short. The authors noted the methodological weaknesses of the studies included in the review, but could have advised more caution when generalising the results given the paucity of evidence synthesised.

**Implications of the review for practice and research**
Practice: The authors did not explicitly state any implications for practice. They suggested that trastuzumab plus chemotherapy appears more effective than chemotherapy alone as second-line therapy for HER2 overexpressing metastatic breast cancer at level 3+. However, trastuzumab may be associated with congestive heart failure when combined with anthracycline-based chemotherapy. Evidence of the effectiveness of both monotherapy and combined therapy came from a small number of studies.

Research: The authors stated that well-conducted RCTs are needed to provide more evidence of the effectiveness of trastuzumab for licensed and unlicensed indications.

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