Integrating trastuzumab in the neoadjuvant treatment of primary breast cancer: accumulating evidence of efficacy, synergy and safety
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CRD summary
This review concluded that a number of neoadjuvant trastuzumab-containing therapies for the treatment of primary breast cancer were both safe and effective despite the lack of long-term data. However, the conclusions may not be reliable given concerns about the review methods and the quality of the included data and synthesis.

Authors’ objectives
To assess the efficacy, synergy and safety of neoadjuvant trastuzumab for the treatment of primary breast cancer.

Searching
PubMed was searched. Search terms, but not search dates were reported. Abstracts and full text articles from the following meetings (2000- 2006) were searched manually: American Society of Clinical Oncology (ASCO); San Antonio Breast Cancer Symposium (SABCS); and the European Society of Medical Oncology (ESMO).

Study selection
Clinical phase II or III trials of trastuzumab-containing primary systemic therapy in women with histologically verified primary breast adenocarcinoma (resectable or irresectable locally advanced), were eligible for inclusion in the review. Eligible trials had to report data on the efficacy or toxicity of the neoadjuvant trastuzumab.

Included studies were of various drug regimens (taxane-based, non-anthracycline, non-platinum containing; platinum-based; and other chemotherapeutic regimens) where neoadjuvant trastuzumab was used alone or in combination with cytotoxic chemotherapies. The main therapy used was docetaxel. Other therapies included epidoxorubicin/docetaxel, paclitaxel, vinorelbine, platinum-taxane and capecitabine-docetaxel. Details of the included regimens and comparators (where appropriate) were reported in the review. The majority of included women had stage II/III disease and all were human epidermal growth factor receptor-2 (HER2) positive, as determined usually by either immunohistochemistry or fluorescent in-situ hybridisation (FISH).

Studies assessed complete response rates (pathological and clinical) and survival (overall and disease-free). The incidence of breast-conserving surgery (BCS) and toxicity (in particular cardiac toxicity) were also reported.

The authors stated neither how papers were selected for review nor how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors stated neither how data were extracted for the review nor how many reviewers performed the data extraction. Percentage values were reported where available.

Methods of synthesis
A narrative synthesis accompanied by data tables was used. Studies were grouped according to the type of treatment regimen used.

Results of the review
Twenty-three studies (n=585) were included in the review, Sample sizes ranged from nine to 119 (most studies included less than 40 participants). Only two studies were randomised controlled trials (RCTs).

Six studies (n=214), one of which was an RCT (n=42), assessed the effectiveness of trastuzumab anthracycline-based
regimens. Complete response rates (pathologic) were reported in all of the studies and ranged from seven per cent to 71 per cent. In the RCT, pathological complete response rates significantly (p=0.02) favoured the chemotherapy and trastuzumab regimen (65 per cent reported in the results table and 66.7 per cent reported in the text) in preference to the non-trastuzumab chemotherapy regimen (23 per cent reported in the results table and 25 per cent reported in the text). A subsequent follow-up trial where all participants were treated with the trastuzumab regimen reported a response rate of 54.5 per cent (reported as 60 per cent in the text).

Ten studies (n=248) assessed trastuzumab taxane-based, non-anthracycline, non-platinum containing regimens. Overall clinical complete response rates (seven studies) ranged from 60 per cent to 84 per cent and pathological complete response rates (nine studies) from 12 per cent to 54 per cent.

Three studies (n=70), one of which was a small RCT (n=22), assessed platinum-based regimens containing trastuzumab. Pathological complete response rates varied from nine per cent to 78 per cent. In the RCT the trastuzumab-containing regimen had a 36.4 per cent pathological complete response rate in comparison to nine per cent in the control group. Cardiotoxicity was reduced by over 10 per cent (in 18.6 per cent of participants).

Three studies (n=69) assessed other trastuzumab-containing regimens and reported pathological complete response rates of between nine per cent and 29 per cent and clinical complete response rates of between 73 per cent and 93 per cent.

Across all of the different regimens cardiotoxicity, where reported was low and usually limited to one or two patients per study or to lower grades of toxicity. Fifteen studies assessed other adverse events, six assessed breast conserving surgery rates and four reported disease-free or overall survival. Further data were reported in the review.

**Authors’ conclusions**

Trastuzumab in combination with various chemotherapy regimens was both effective and safe, although further data was required on the long-term effects and safety of the drug.

**CRD commentary**

This review answers a clear research question, using broad criteria for intervention, study design, outcomes and population. Only one electronic database was searched in addition to various meeting abstracts and it is unclear whether the review was at risk from language and publication bias. The review may also have been at risk from reviewer error and bias as the authors did not report their methods when selecting studies and extracting data. No assessment of study validity was carried out, so it was difficult to determine whether the data were reliable. However, that most studies were small, uncontrolled phase II studies suggests that the review was not based on the most rigorous of data. Important information about the HER2 receptor status and disease stage were reported, but a number of other important baseline characteristics of the participants were not reported, including whether the participants have previously received any other therapy (drugs, radiation or surgery) and their menopausal status, age and estrogen receptor (ER) status. All these factors can influence the effectiveness of different cancer drug therapies. From the details that were presented it would appear that the studies varied considerably in terms of their interventions and populations, suggesting that the authors’ narrative approach was justifiable. It would have been preferable for survival to be reported using hazard ratios so that the censoring of data over time could have been accounted for. It would also have been helpful to know if any treatment withdrawals occurred due to adverse effects, given the nature of the side effects experienced. There were also some discrepancies between the outcome data quoted in the tables and those quoted in the text. Overall, given the concerns about the review methods and the quality of the included data and synthesis, the authors’ conclusions may not be reliable and should be interpreted with caution.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that a number of factors needed to be addressed in further research, including: long term effects of trastuzumab; the optimal schedule and duration of drug administration; the most active drug combination; and the identification of surrogate biomarkers for sensitivity and resistance to antineoplastic therapy.
Funding
Not stated.

Bibliographic details

PubMedID
17766143

DOI
10.1016/j.critrevonc.2007.07.002

Indexing Status
Subject indexing assigned by NLM

MeSH
Antibodies, Monoclonal /therapeutic use; Antibodies, Monoclonal, Humanized; Antineoplastic Agents /therapeutic use; Antineoplastic Combined Chemotherapy Protocols /therapeutic use; Breast Neoplasms /chemistry /drug therapy; Clinical Trials as Topic; Drug Synergism; Female; Humans; Neoadjuvant Therapy; Receptor, ErbB-2 /analysis; Trastuzumab

AccessionNumber
12008103769

Date bibliographic record published
23/12/2008

Date abstract record published
03/06/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.