The clinical efficacy of cytotoxic agents in locally advanced or metastatic breast cancer patients pretreated with an anthracycline and a taxane: a systematic review

Jassem J, Carroll C, Ward SE, Simpson E, Hind D

CRD summary
The review found that evidence was extremely limited on the efficacy of chemotherapy regimens currently available in Europe for women with locally advanced or metastatic breast cancer previously treated with a taxane and an anthracycline. Although there was some possibility that foreign language studies were missed, the review was well conducted in most respects and the authors’ cautious conclusions appear reliable.

Authors’ objectives
To determine the efficacy of the principal cytotoxic agents used in Europe for treating locally advanced or metastatic breast cancer after previous treatment with an anthracycline and a taxane.

Searching
The Cochrane Central Register of Controlled Trials (CENTRAL) and the American Society of Clinical Oncology (ASCO) conference proceedings were searched from inception for randomised controlled trials (RCTs) published in English. MEDLINE, EMBASE, CINAHL, the Science Citation Index and ASCO proceedings were searched from inception for non-RCTs in any language. Search terms were reported. Reference lists of retrieved studies and relevant reviews were checked and industry experts were consulted for additional studies.

Study selection
Controlled trials of chemotherapy for locally advanced or metastatic breast cancer in women, aged at least 18 years, previously treated with an anthracycline and a taxane were eligible for inclusion. Trials of the following chemotherapy agents were eligible: capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel, and paclitaxel protein-bound particles; these could be administered as monotherapy or in combination (with each other or other chemotherapy agents). Control groups could receive any drug or placebo. The authors excluded trials restricted to human epidermal growth factor receptor 2 (HER2) positive patients, trials of high-dose chemotherapy, trials where under half the participants received both an anthracycline and a taxane, and phase 1 trials.

The primary outcomes were overall survival and progression-free survival. Secondary outcomes included duration of response, overall response, toxicity, and quality of life.

Participants in the included studies were women with a median age of 51 to 58 years. The number of previous chemotherapy regimens they had received for metastatic breast cancer ranged from nil to five; most women had received one or two such regimens (where reported). The number of women with three or more metastatic sites ranged across study groups from 26 to 58% (where reported). Interventions included vinorelbine, either alone or in combination with gemcitabine or 5-fluorouracil, and capecitabine, as monotherapy or in combination with bevacizumab. It appeared that one trial compared vinorelbine or mitomycin plus vinblastine versus doxorubicin. Comparators differed across studies, and included capecitabine or vinorelbine alone, oxaliplatin and 5-fluorouracil, and pegylated liposomal doxorubicin.

A single reviewer selected studies for inclusion, checking with a second reviewer when in doubt. A second reviewer also checked 10% of the citations. Disagreements were resolved by consensus.

Assessment of study quality
The following components of study quality were assessed: randomisation and recruitment, comparability of groups, blinding, and analysis. Studies were described using quality ratings (e.g. high, good, low), but rating criteria were not clearly defined. The Downs and Black checklist was used for non-RCTs.
Validity assessment was conducted by a single reviewer and checked by a second.

Data extraction
For primary outcomes, the hazard ratio and associated variances were extracted, or calculated using published methods (Parmar 1998). Secondary outcomes were extracted separately for each study group as percentages experiencing the event for dichotomous data, and as medians with range for continuous data. For adverse events, only grade three or four events experienced by more than 5% of participants were included in analysis.

Data were extracted by a single reviewer and checked by a second.

Methods of synthesis
Studies were combined in a narrative synthesis, organised by outcome.

Results of the review
Five studies were included in the review (n=1,291 women, range 137 to 462): four RCTs (n=1,151 women) and one retrospective chart review (non-RCT, n=140 women). Three RCTs were good quality and one poor quality (published only as an abstract). The non-RCT was poor quality. All the RCTs reported inclusion criteria and baseline characteristics and used intention-to-treat analysis. Three RCTs accounted for withdrawals, but only one reported allocation concealment and only one blinded outcomes assessment. The non-RCT had no allocation concealment or blinding and had a high rate of unexplained withdrawals.

Overall survival and progression-free survival (four RCTs and one non-RCT): Gemcitabine and vinorelbine achieved significantly higher rates of progression-free survival than vinorelbine alone (median 6 months versus 4 months; p=0.0028; one RCT; n=251 women). Vinorelbine achieved significantly lower rates of overall survival than capecitabine or vinorelbine plus capecitabine (both p=0.001; one non-RCT; n=140 women). There was no statistically significant difference between the groups for any other analyses.

Overall response (four RCTs) and duration of response (three RCTs): Capecitabine and bevacizumab achieved significantly higher rates of overall response than capecitabine alone (19.8% versus 9.1%, p=0.001, one RCT n=462). There was no statistically significant difference between the intervention and control groups for duration of response.

Quality of life (two RCTs and one non-RCT): Pegylated liposomal doxorubicin appeared to be associated with superior global quality of life compared with control interventions in one RCT (n=301 women). A second RCT (n=462 women) comparing capecitabine plus bevacizumab versus capecitabine alone found no statistically significant difference between the groups. The non-RCT used an invalidated measure for this outcome.

Descriptive data on safety outcomes were also reported in the review.

Authors' conclusions
Evidence was extremely limited on the efficacy of chemotherapy regimens currently available in Europe for treating women with locally advanced or metastatic breast cancer previously treated with a taxane and anthracycline.

CRD commentary
The objectives and inclusion criteria of the review were clear in most respects. However, it was unclear whether one of the included studies was strictly eligible for inclusion, as it appeared that some women in the intervention group were treated with mitomycin and vinblastine. Relevant sources were searched for published and unpublished studies. It was unclear why the search for RCTs was limited to studies in English, as this led to the possibility that studies were missed. Initial study selection was undertaken by a single reviewer, which increased the risk of reviewer bias and error. However, some steps were taken to minimise this risk (i.e. appraisal of a proportion of citations in duplicate). The processes of validity assessment and data extraction were double-checked. In view of heterogeneity between the studies, the decision to combine them by narrative synthesis was appropriate.
Although there was some possibility that foreign language studies were missed, the review was well conducted in most respects and the authors' cautious conclusions appear reliable.

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

**Practice:** The authors stated that a great deal of caution is needed in drawing conclusions about the efficacy of currently used chemotherapy for women with locally advanced or metastatic breast cancer. None of the therapies appear more effective than others.

**Research:** The authors stated that high quality multicentre blinded RCTs are needed, comparing optimal doses of drugs for second or third line treatment of advanced breast cancer.

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