CRD summary
This review assessed the evidence for vinorelbine as second-line chemotherapy for women with stage IV breast cancer. The available evidence suggested that vinorelbine was an acceptable treatment option for women considering second-line chemotherapeutic options. It is difficult to assess the reliability of this conclusion as details on the review methods and on the quality of the included studies are lacking.

Authors’ objectives
To assess the evidence for vinorelbine as second-line chemotherapy for women with stage IV (metastatic) breast cancer.

Searching
MEDLINE (January 1992 to November 2003), Cancerlit (January 1992 to November 1998), the Cochrane Library (Issue 1, 2003), PDQ (to April 2003), and the proceedings of meetings of the American Society of Clinical Oncology (to 2002) and the San Antonio Breast Cancer Symposium (to 1998) were searched. Unpublished information was provided by GlaxoWellcome in 1996.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of vinorelbine alone or combined with other agents were eligible for inclusion, as were prospective case series of single-agent vinorelbine. The authors sought meta-analyses as part of the search strategy to identify relevant studies, but these were not explicitly listed in the inclusion criteria.

Specific interventions included in the review
Studies were eligible for inclusion if they assessed vinorelbine alone or combined with other agents as second-line chemotherapy. The authors did not pre-specify the duration of treatment or the comparators. The majority of the studies used an intravenous dose of 30 mg/m² per week. The regimens compared with single-agent vinorelbine included melphalan; 5-fluorouracil (5-FU) plus leucovorin; and mitoxantrone, 5-FU and leucovorin. The regimens used in combined chemotherapy included combinations of doxorubicin, cyclophosphamide, epirubicin and mitoxantrone.

Participants included in the review
Studies were eligible for inclusion if they included women with stage IV breast cancer undergoing second-line chemotherapy. The authors did not provide details of the participants’ ages or ethnic groups.

Outcomes assessed in the review
The authors did not specify any outcome criteria for selecting studies for the review. Data on survival, toxicity, quality of life, functional status, response rate and response duration were included in the review.

How were decisions on the relevance of primary studies made?
Evidence was selected and reviewed by one member of the Breast Cancer Disease Site group and methodologists. Apart from this, the authors did not state how the papers were selected for the review. The number of methodologists involved was not reported.

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

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The extracted data included: the numbers of women who achieved tumour response; median duration of response; median survival time; the number and type of adverse events; and quality of life or functional status outcomes, as reported.

Methods of synthesis
How were the studies combined?
The authors classified the study results according to the type of first-line chemotherapy the women received. For each first-line therapy group, the authors pooled response rates by dividing the total number of treatment responses by the total number of women in each group of studies. They calculated 95% confidence intervals (CIs) for the pooled response rates. All other data were synthesised narratively.

This review was originally performed in 1996 and has been updated regularly. Data from updated searches were reported narratively, but were not included in the pooled analysis of treatment response.

How were differences between studies investigated?
The authors classified study results according to the type of first-line chemotherapy the women received: prior anthracycline or mitoxantrone; no prior anthracyclines for metastases; or prior chemotherapy for metastases with variable use of anthracyclines. They did not state a statistical method for assessing any differences between the studies (heterogeneity) in the pooled analysis of treatment response.

Results of the review
The authors included 16 studies: 3 phase III RCTs, one phase II RCT and 12 case series. One summary review was also included. The authors did not report the total number of participants. Data on treatment response were available from at least 436 women.

Single-agent vinorelbine.

One RCT with 179 women found that single-agent vinorelbine increased survival compared with melphalan: median survival was 35 weeks with vinorelbine versus 31 weeks with melphalan (P=0.03), while 1-year survival rates were 35.7% and 21.7%, respectively (P-value not reported). Another trial (n=98) found no survival benefit over 5-FU plus leucovorin, with or without mitoxantrone.

Data pooled from one phase III RCT and 8 phase II case series found that 24% of women responded to treatment using single-agent vinorelbine (95% CI: 20, 28). In anthracycline-resistant disease, the pooled response rate was 19% (95% CI: 14, 24).

Combined therapy.

One RCT in women treated with doxorubicin, with or without vinorelbine (n=303; 289 assessable), found no significant difference in median survival, response rate, or duration of response. Another RCT (n not reported) compared vinorelbine plus doxorubicin plus cyclophosphamide (FAC). Treatment response was 76% for the vinorelbine group versus 85% for the FAC group (P-value not reported). The duration of follow-up was too short for survival analysis.

Toxicity.

The authors found that vinorelbine had an acceptable toxicity profile. Most adverse events were haematological (neutropenia, febrile neutropenia and anaemia). Other adverse events included nausea, vomiting, diarrhoea, constipation, alopecia and peripheral neuropathy.

Cost information
A cost-utility analysis conducted in Toronto, Canada, evaluated total resource consumption among 88 women with anthracycline-resistant metastatic breast cancer treated with paclitaxel, docetaxel, or vinorelbine. There was a trend
towards vinorelbine being the least costly (Can$3,259 per person versus Can$6,039 for paclitaxel and Can$10,090 with docetaxel; P-value not reported), although the authors reported that there was no overall difference in cost.

**Authors’ conclusions**
Vinorelbine is an acceptable treatment for women considering second-line or greater chemotherapy for metastatic breast cancer. Survival and objective response appear similar to other chemotherapeutic options, and toxicity is reasonable.

**CRD commentary**
Although this review focused on a defined research question, it was limited by a lack of information about the studies included and by the pooling of events across uncontrolled trials to obtain simple averages. The authors searched two major databases plus other sources, but the review strategy might have been limited. The authors suggested that unpublished data were provided by GlaxoWellcome, but they did not clarify how these unpublished industry data were used in the review, nor did they describe whether other industry sources or experts were approached for unpublished data.

The authors did not provide full details of their inclusion and exclusion criteria, or the methods used to assess the relevance or validity of the studies included in the review. They did not describe how data were extracted for the review or what quality checks were in place, nor did they describe potential publication bias or English language bias (one Chinese study was excluded from the review due to translation difficulties). The report omitted essential details such as the total number of participants included. The structure was such that it is difficult to extract this information.

The authors pooled data on response rates, but no other outcomes. Most of the data were drawn from case series. It is questionable whether it was appropriate to pool this data across disparate study designs and with participants who might have been exposed to different first-line regimens (although the studies were stratified broadly according to previous chemotherapy regimens).

The authors noted that there is not enough evidence upon which to base a practice guideline, yet they concluded that vinorelbine is an acceptable treatment option for women undergoing second-line therapy or greater. Overall, it is difficult to assess whether this conclusion is supported by the data, given the limited details provided on the study designs, treatment regimens, sample sizes and participants’ characteristics.

**Implications of the review for practice and research**
Practice: The authors suggested that vinorelbine is an acceptable treatment option for women considering second-line chemotherapy or greater for metastatic disease.

Research: The authors suggested that randomised trials comparing vinorelbine with standard regimens for metastatic breast cancer are needed. Cost-benefit assessments may also be useful.

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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.