The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation


Authors' objectives
To review the clinical effectiveness and cost-effectiveness of vinorelbine in the management of breast cancer (BC).

Searching
A range of electronic databases were searched as documented in the report. Manufacturer and sponsor submissions were reviewed, as were the bibliographies of retrieved articles and conference proceedings. Internet searches for ongoing trials were also performed. Full details of the search strategy were provided in the report. No language restrictions were applied to the searches.

Study selection
Study designs of evaluations included in the review
 Initially, only randomised controlled trials (RCTs) were included in the review of clinical effectiveness. Subsequently non-comparative phase II studies were included in an update of the review. Studies that included fewer than 14 participants were excluded from the review.

Specific interventions included in the review
To be eligible for inclusion in the review, trials had to compare vinorelbine (used alone or in combination with other agents) with systemic therapy without vinorelbine. When updating the review, vinorelbine was only considered when used as a first-line treatment for advanced breast cancer.

Participants included in the review
Initially, trials needed to include participants with breast cancer at all stages of the disease. When updating the review, only patients with advanced breast cancer (locally advanced or metastatic disease) were included.

Outcomes assessed in the review
The primary outcomes were tumour response (complete and partial), progression-free survival, overall survival, relief of symptoms, quality of life, adverse events as documented in the report and cost.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for possible relevance to the review. Any disagreements were resolved by consensus or, when necessary, by recourse to a third reviewer.

Assessment of study quality
The methodological quality of each included study was assessed using predefined checklists for each study type, as documented in the report. Two reviewers independently conducted the quality assessment. Any disagreements were resolved by consensus or, when necessary, by recourse to a third reviewer.

Data extraction
One reviewer extracted the data using predefined data extraction forms, while a second reviewer checked the extraction. Any disagreements were resolved by consensus or, when necessary, by recourse to a third reviewer. Studies in English, German, Dutch and French were included in the analyses, whereas bibliographic details of other non-English language studies were presented in the report. Where sufficient data were presented, the treatment effect and 95% confidence interval were estimated for each individual study. Where possible, intention-to-treat data were used.
Relative risks were calculated for dichotomous outcome measures. Median survival rates, along with measures of
variance, were also obtained.

Methods of synthesis
How were the studies combined?
The studies were grouped according to the type of therapy (first- or second-line) and intervention (monotherapy or combination therapy). The studies were combined narratively and, where no significant diversity or statistical heterogeneity was detected, were pooled using meta-analysis. Publication bias was assessed in relation to the observational studies.

How were differences between studies investigated?
Both clinical diversity and statistical heterogeneity were investigated.

Results of the review
Seven RCTs and 65 uncontrolled studies were included in the review.

Vinorelbine monotherapy (2 RCTs of poor quality).

There were no significant differences between groups for partial, complete or overall response, stable disease and disease progression. Time to treatment failure and progression-free survival were significantly longer in participants treated with vinorelbine than those treated with melphalan (12 versus 8 weeks for both outcomes). The median overall survival was also significantly longer (35 weeks versus 31 weeks, P=0.034). Compared with 5-fluorouracil plus leucovorin, with or without mitoxantrone, the median survival, duration of response and time to treatment failure appeared similar in all the groups. There were no significant differences between the groups in either trial for any of the reported grade 3 or grade 4 adverse events.

Vinorelbine combination therapy (5 RCTs of moderate to poor quality).

Vinorelbine as combination therapy with doxorubicin, 5-fluorouracil or mitoxantrone did not appear more effective than alternative combinations of chemotherapy in the treatment of metastatic breast cancer. One trial suggested that vinorelbine plus mitoxantrone might be associated with less nausea or vomiting (8% versus 16%, P=0.03) and less alopecia (7% versus 30%, P=0.0001) than 5-fluorouracil plus adriamycin (doxorubicin) plus cyclophosphamide/5-fluorouracil plus epirubicin plus cyclophosphamide (FAC/FEC), while another trial suggested that vinorelbine plus mitoxantrone might result in more febrile neutropenia (15% versus 2%, P=0.001).

Evidence from uncontrolled phase II studies appeared to complement the RCT findings but did not compensate for the lack of RCTs. These studies were compromised by potential biases, clinical diversity, statistical heterogeneity and a lack of precision.

Cost information
Four economic evaluations were included in the review. When comparing the cost-effectiveness of vinorelbine, paclitaxel and docetaxel, one study found vinorelbine to be the most cost-effective intervention, one found vinorelbine to be the least expensive but also the least effective, and another found docetaxel to be the most cost-effective. In the final study, capecitabine was found to be the most cost-effective therapy in comparison with vinorelbine, 5-fluorouracil and gemcitabine.

Authors’ conclusions
Based on current evidence, vinorelbine had a similar efficacy and toxicity profile to standard first-line chemotherapy with anthracyclines and other non-taxane-containing regimens.

CRD commentary
This was a well-conducted review with a clear question, stated inclusion criteria and a thorough search of the literature.
Validity was assessed and its potential impact on the results was carefully outlined. The authors used procedures to minimise bias at all stages of the review process. The conclusions of the review are, therefore, likely to be reliable. The authors' advice to conduct further research appears appropriate given the limitations of the primary research evidence presented.

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

**Practice:** The authors stated that vinorelbine might present a possible option when an alternative chemotherapy agent is required.

**Research:** The authors stated that further large, well-conducted RCTs using appropriate comparators are required to investigate the use of vinorelbine alone or in combination with other chemotherapy agents. Further cost-effectiveness studies of vinorelbine should use the same combinations as were examined in the included trials.

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