Vinorelbine for breast cancer

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

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Executive summary

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Executive summary

Background

Breast cancer is the leading cause of cancer deaths amongst women in the UK. Figures suggest that about 14% of women initially presenting with breast cancer have advanced disease (stage III or IV) and about 50% presenting with early or localised breast cancer will eventually develop advanced disease.

The prognosis of metastatic breast cancer (MBC) depends on age, extent of disease, oestrogen receptor status and previous chemotherapy treatment. MBC is considered to be incurable and treatment is usually focused on relieving symptoms and improving quality of life (QoL) with as little treatment-related toxicity as possible. The choice between endocrine therapy or chemotherapy and the selection of a specific drug regimen for first-line treatment of MBC is based on a variety of clinical factors, such as what drugs have already been given as adjuvant treatment, the likelihood of benefit balanced against the adverse event profile of the given drug and the given drug's tolerability. Vinorelbine (Navelbine®, Pierre Fabre Ltd, Winchester, UK), an anti-cancer agent used in patients with advanced disease, including MBC, relapsing after anthracycline treatment, may be a useful addition to the drugs available for the treatment of MBC. It can be used in a range of combination chemotherapy regimens in first- or second-line treatment, and may be used as monotherapy for vulnerable groups, such as the elderly.

Objectives

The objectives of the review were to evaluate the clinical effectiveness and cost-effectiveness of vinorelbine in the management of breast cancer.

Methods

Only randomised controlled trials (RCTs) and full economic evaluations were initially considered for inclusion. Included trials had to evaluate vinorelbine alone or in combination with other agents versus systemic therapy without vinorelbine. Only trials that included individuals with breast cancer were included. The National Institute for Clinical Excellence (NICE) subsequently requested that non-comparative Phase II studies of vinorelbine (alone or in combination with other agents) as first-line therapy for advanced breast cancer (ABC) be evaluated for inclusion in the review. These data were added as part of an update of this review.

Several databases were searched using strategies designed specifically for each database. Additional references were identified through reviewing manufacturer and sponsor submissions made to NICE, the bibliographies of retrieved articles, conference proceedings and by searching the Internet.

Data were extracted by one reviewer and checked by a second. Quality assessment was conducted independently by two reviewers. Disagreements were resolved by consensus and, when necessary, by recourse to a third reviewer. The primary outcomes of interest were response, QoL, time to disease progression, overall survival, relief of symptoms and cost. Results of data extraction and quality assessment were presented in structured tables and as a narrative summary. Studies were grouped according to the type of therapy (first- or second-line) and intervention (monotherapy or combination therapy).

Results

Clinical effectiveness data

RCTs

Vinorelbine monotherapy

Two included RCTs investigated the use of vinorelbine monotherapy. One evaluated its use as second-line or salvage therapy for MBC, whilst the other used vinorelbine for either first- (9% of patients) or second-line or subsequent treatment for ABC, compared with melphalan and 5-fluorouracil plus leucovorin with or without mitoxantrone. The overall quality of these two trials was poor.

There were no significant differences between the intervention groups for partial, complete or ▶

overall response, stable disease and disease progression. Time to treatment failure, progression-free survival and median overall survival were significantly longer in participants treated with vinorelbine compared with those treated with melphalan. However, melphalan is not considered to be an appropriate comparator because it is not representative of conventional treatment for MBC, which limits the generalisability of the findings to the clinical setting. When compared to 5-fluorouracil plus leucovorin with or without mitoxantrone, the median survival, duration of response and time to treatment failure appeared to be similar in all three groups. There were no significant differences between the groups in either trial for any of the reported grade 3 or 4 adverse events. One trial assessed QoL and differences between groups were not significant for all dimensions, except physical function.

Vinorelbine combination therapy

Five included RCTs investigated the use of vinorelbine in combination with other chemotherapy agents for MBC. The overall quality of these was moderate to poor.

When vinorelbine plus doxorubicin was compared with doxorubicin alone as mainly first-line therapy, there were no statistically significant differences in any of the parameters of tumour response or survival, adverse events or QoL measures. These data would suggest that the addition of vinorelbine conferred little, if any, treatment benefit above that of doxorubicin alone. However, it is unclear whether the non-significant results are due to a small sample size or the fact that the interventions are similar. In addition, 80% of the participants were treated with a dose (20 mg/m^2) that is lower than that recommended for vinorelbine when used in combination schedules, due to the occurrence of febrile neutropenia.

No statistically significant differences in effectiveness or adverse events were identified when vinorelbine plus doxorubicin was compared with 5-fluorouracil plus doxorubicin plus cyclophosphamide (FAC) for first-line therapy. Similarly, there were no statistically significant differences between vinorelbine plus mitoxantrone and 5-fluorouracil plus doxorubicin or epirubicin plus cyclophosphamide (FAC/FEC) in tumour response or progression-free or overall survival. However, serious febrile neutropenia was more frequent in the vinorelbine/mitoxantrone group, whilst severe nausea and vomiting and alopecia occurred more frequently in the FAC/FEC group.

The comparison of vinorelbine plus docetaxel with docetaxel plus gemcitabine as second-line therapy found no statistically significant differences between the treatments for tumour response. No survival data were reported.

Little data were available for the final trial, which compared vinorelbine plus 5-fluorouracil with docetaxel as first- or second-line therapy (available as an abstract only). Median progression-free survival appeared similar, but there were no statistical comparisons. No tumour response data were reported. The report suggested that toxic deaths in the vinorelbine groups were more frequent, however, the reliability of the reporting is debatable.

The findings of the individual combination therapy RCTs may not be reliable: none of the findings detailed above can be considered definitive. Unfortunately, the use of different combinations and different comparators means that the results of individual trials could not be directly combined in an attempt to derive a more precise estimate of the effectiveness of vinorelbine used as combination therapy. It is also not possible to discern the true effect of vinorelbine itself from that of any interaction that occurs between vinorelbine and other agents when used in the different combinations included in this review.

Uncontrolled Phase II studies

Fourteen uncontrolled studies of vinorelbine monotherapy and 51 of combination therapy were included in the review. These studies were clinically diverse, investigating various vinorelbine-based regimens in a range of populations. Many of the studies were small with limited follow-up times. Only a few subsets of studies, where the diversity appeared to be minimal, were investigated by statistical pooling and even these results must be interpreted with caution.

Overall, for intravenous vinorelbine monotherapy, the complete tumour response rate ranged from 0 to 20% and the overall tumour response rate ranged from 0 to 60%. Median duration of overall tumour response ranged from 1.8 to 9 months, median overall survival ranged from 9.9 to 16.8 months, median time to disease progression ranged from 3 to 6 months and median time to treatment failure ranged from 4.6 to 6 months.

For vinorelbine combination therapy, complete tumour response ranged from 5 to 32% and overall tumour response ranged from 22 to

79%. Studies of vinorelbine plus doxorubicin reported complete and overall tumour response rates ranging from 6 to 32% and 29 to 74%, respectively. For vinorelbine used in combination with epirubicin, reported complete and overall tumour response rates were 6–19% and 50–77%, respectively. Studies of vinorelbine plus paclitaxel reported overall tumour response as 47–67%. Other combinations were investigated in small numbers of clinically diverse studies. For all combination studies, the median duration of overall tumour response ranged from 6 to 16 months, and the median overall survival ranged from 12.3 to 31 months. The median time to disease progression ranged from 3.9 to 15 months, and median time to treatment failure ranged from 7 to 12 months.

Vinorelbine monotherapy may be particularly associated with leukopenia, granulocytopenia, nausea/vomiting and constipation. Vinorelbine combination therapy appeared to be associated with neutropenia, alopecia and nausea/vomiting, although different combinations had differing profiles, the exact nature of which were difficult to discern from the limited data available.

Comparison of effectiveness data from RCTs and uncontrolled Phase II studies

The evidence from uncontrolled Phase II studies appeared to complement the RCT findings. However, Galbraith and funnel plots showed that the findings of the uncontrolled studies did not compensate for the lack of available RCTs. In other words, the data from the uncontrolled studies on their own were inadequate due to clinical diversity, statistical heterogeneity and lack of precision. This was in addition to the fact that uncontrolled studies provide a lower level of evidence due to the biases and lack of rigour that are inherent in such studies.

Economic data

The economic data included in the review were not comparable with the effectiveness data (that is, the same interventions were not assessed). Four economic evaluations were included in the review. Three examined vinorelbine, docetaxel and paclitaxel and one compared capecitabine, vinorelbine, 5-fluorouracil and gemcitabine. The three economic evaluations of vinorelbine, docetaxel and paclitaxel were fairly well conducted. For the remaining economic evaluation, there was insufficient information to properly judge the overall quality of the analysis because it was only available as an abstract.

Only one economic evaluation (based in Canada) comparing vinorelbine, docetaxel and paclitaxel found vinorelbine to be the dominant treatment (more effective and less costly than paclitaxel and docetaxel). The average cost per quality-adjusted progression-free year was Can$31,220 for vinorelbine, Can$59,096 for paclitaxel and Can$110,072 for docetaxel. One economic evaluation (based in the UK) found vinorelbine to be less effective and less expensive than both docetaxel and paclitaxel for the treatment of ABC. Docetaxel was found to be more effective and more expensive than vinorelbine and paclitaxel. The incremental cost per quality-adjusted life-year for docetaxel were £14,500 compared with vinorelbine and £1990 compared with paclitaxel. However, it was noted that the economic evaluation was sponsored by Aventis, who manufacture docetaxel. The third economic evaluation (based in France) found docetaxel to be dominant, and vinorelbine, when compared to docetaxel, was found to have higher costs and poorer outcomes. When generalising these data to the UK, vinorelbine is usually considered as an alternative to taxane therapy for patients who cannot tolerate intensive treatment, rather than a replacement for it.

In the comparison of capecitabine, vinorelbine, 5-fluorouracil and gemcitabine, capecitabine was reported to be the most cost-effective therapy for the treatment of anthracycline-resistant MBC with a cost-effectiveness ratio of Can$1436 and a marginal cost-effectiveness ratio of Can$687 per quality-adjusted life month with 5-fluorouracil as the reference therapy. However, capecitabine is not currently licensed in the UK for MBC, which limits the generalisability of the findings to the NHS.

Conclusions

According to the evidence derived from RCTs, vinorelbine monotherapy as first-line, second-line or subsequent therapy for ABC, may be more effective in terms of progression-free survival and survival than melphalan. However, melphalan is not representative of conventional treatment for MBC, which limits the generalisability of the findings to the clinical setting. Vinorelbine monotherapy was not found to be more effective than other chemotherapy regimens in terms of response rates. In addition, the poor quality of the data on which these findings were based should be borne in mind.

Vinorelbine as combination therapy with doxorubicin, 5-fluorouracil or mitoxantrone ▶

did not appear to be more effective than alternative combinations of chemotherapy in the treatment of MBC. Vinorelbine plus mitoxantrone may be associated with less nausea/vomiting and alopecia than FAC/FEC, but may result in more febrile neutropenia.

The evidence from RCTs show that there were no data to support the use of vinorelbine either as a single agent or in combination over standard first-line chemotherapy with anthracyclines or other non-taxane containing regimens. The efficacy and toxicity profiles were similar, with no suggestion of superiority over existing treatments. Vinorelbine may be one possible option when an alternative agent is required.

The evidence from uncontrolled Phase II studies appeared to indicate that vinorelbine has anti-tumour activity and an acceptable toxicity profile, but may be associated with leukopenia, granulocytopenia, nausea/vomiting and constipation when used as monotherapy and neutropenia, alopecia and nausea/vomiting when used in combination. The data from the uncontrolled studies on their own were inadequate due to the clinical diversity, statistical heterogeneity and lack of precision. This was in addition to the fact that uncontrolled studies are of a lower level of evidence due to the biases and lack of rigour that are inherent in such studies.

The economic studies included in the review tended to compare vinorelbine with taxane therapy. When comparing the cost-effectiveness of vinorelbine, paclitaxel and docetaxel one economic evaluation 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.

Implications for further research

The review identified the following areas for future research.

1. Further large well-conducted RCTs are required to investigate the use of vinorelbine alone or in combination with other chemotherapy agents.
2. Further cost-effectiveness analyses of vinorelbine used in the same combinations as examined in the included trials are required.

Publication

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NHS R&D HTA Programme

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