ORIGINAL RESEARCH ARTICLE

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# Cost Effectiveness of Treatment Options in Advanced Breast Cancer in the UK

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## Abstract

**Objective:** To compare clinical and economic study data for docetaxel, paclitaxel and vinorelbine in the treatment of anthracycline-resistant advanced breast cancer.

**Study design and methods:** A Markov decision-analysis model to simulate the clinical course of a 'typical' patient with advanced breast cancer during salvage chemotherapy was updated with response rates and adverse effect rates from phase III clinical trial data for docetaxel, paclitaxel and vinorelbine. Costs were taken from UK national databases and hospitals. Utilities were estimated from 30 oncology nurses in the UK using the standard gamble method.

**Perspective:** National Health Service.

**Results:** When compared with other chemotherapeutic agents, docetaxel has been shown to increase response rate, time to progression and survival in patients with advanced breast cancer. In the base-case analysis, the incremental cost-utility ratio for docetaxel versus paclitaxel was £1995 per quality-adjusted life year (QALY) gained (1998 values). The incremental cost-utility ratio for docetaxel versus vinorelbine was £14 055 per QALY gained. In the comparison with vinorelbine, docetaxel provided the equivalent of an additional 92 days of perfect health. Sensitivity analyses confirmed the robustness of the model and the validity of the base-case analysis results. Even in the worst case scenarios, docetaxel remained cost effective compared with paclitaxel and vinorelbine.

**Conclusions:** These findings support the use of the taxoids, notably docetaxel, in the management of advanced breast cancer.

There is currently no standard salvage chemotherapy regimen for use in patients with locally advanced or metastatic breast cancer after therapy with anthracyclines and alkylators has failed.[1] Treatment options have included cyclophosphamide, methotrexate and fluorouracil; continuous-infusion fluorouracil; methotrexate and fluorouracil/leucovorin; doxorubicin; mitomycin and vinblastine either as single agents or in combination; and platinum combinations. However, these salvage therapies have provided limited benefit and prognosis has remained poor.[2] As a consequence, the search for new drugs and treatment strategies continues in the hope of improving antitumour activity, time to disease progression, tolerability and survival.

More recently, promising agents have become available, namely the taxoids paclitaxel and docetaxel, and the vinca alkaloid, vinorelbine. The efficacy and acceptable tolerability of these agents

have been confirmed in randomised phase III clinical trials.[1,3-6] Docetaxel, paclitaxel and vinorelbine are licensed for use in advanced breast cancer within the UK, and are the three major salvage chemotherapy options for patients with disease progression following failure of adjuvant or first-line chemotherapy with anthracyclines. In addition, docetaxel can also be used after failure with alkylators.

An increased emphasis on evidence-based medicine and justification for the use of healthcare interventions on the basis of economic as well as clinical factors has led to a broader evaluation of new therapies. Advanced breast cancer is regarded as incurable and, despite treatment, total survival time is often less than a year.[7] For these patients, palliation of symptoms, minimising adverse effects of therapy and maximising quality of life are the major issues in selecting a treatment strategy. The restrictions of healthcare budgets and the importance of quality of life in terminally ill patients have led to the development of new methods for assessing the cost effectiveness of therapies. Since the thrust of drug development in oncology is in establishing improved efficacy and tolerability of novel agents, the collection of empirical cost-effectiveness data tends to be neglected. However, this information may be derived using decision-analysis models that make use of available evidence and expert opinion.

In such circumstances economic evaluation requires an outcome measure which takes into account both survival and quality of life. This is provided by the 'utility' which measures an individual's preference for time spent in different health states with varying quality of life. The most commonly used measure of utility is the quality-adjusted life-year (QALY), which accumulates the patient's survival time, weighted by the utility associated with each different health state experienced by the patient. Utilities are measured on a 0 to 1 scale, where 1 is the best imaginable health state. Thus, unless the patient is maintained in perfect health the number of QALYs will always be less than the simple survival time. An advantage of a generalised outcome measure like the QALY is that it allows comparison of interventions within and across therapeutic areas in terms of cost per QALY gained.[8]

A computer-based decision-analysis model has estimated the cost utility of docetaxel versus

**Table I.** Outcome estimates for metastatic breast cancer treatment used in the base-case analyses

| Parameter | Docetaxel[a] | Paclitaxel[b] | Vinorelbine[c] |
|---|---|---|---|
| Overall response rate (%) | 41.7 | 28 | 16 |
| Evaluable patient response rate (%) | 41.7 | 28 | 16 |
| Progressive disease (%) | 23.8 | 21 | 38.4 |
| Time to progression in weeks | 24 | 21 | 12 |
| Median survival in weeks | 56 | 46 | 36 |
| Infection with hospitalisation and/or intravenous antibacterials (%) | 8.8 | 4 | 10 |
| Febrile neutropenia with hospitalisation (%) | 7.3 | 7 | 0[d] |
| Neutropenia without hospitalisation (%) | 10.7 | 10 | 0[d] |
| Death associated with infection or febrile neutropenia (%) | 1.2 | 0[d] | 0[d] |
| Severe neurotoxicity (%) | 5 | 9 | 2 |
| Severe oedema (%) | 4 | 0[d] | 0[d] |
| Severe skin condition (%) | 3 | 0[d] | 0[d] |
| Severe nail condition (%) | 3.4 | 0[d] | 0[d] |
| Time to response in weeks | 9 | 9 | 6 |
| Courses of chemotherapy | 6 (at 3-week intervals) | 6 (at 3-week intervals) | 12 (weekly) |

a Data were derived from randomised phase III clinical trials.[1,4,6]

b Efficacy data were derived from a randomised phase III clinical trial;[3] safety data were derived from Phase II clinical trials.[11-16]

c Data were derived from a randomised phase III clinical trial.[5]

d Data not reported in an appropriate trial – for the purposes of the model, a value of zero was assumed.

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paclitaxel based on phase II clinical trial data for these agents.[9] Since phase III clinical trial data are now available for docetaxel and paclitaxel,[1,3,4,6] an updated analysis incorporating these new data has been conducted. In addition, the aforementioned describes a cost-utility analysis of docetaxel versus vinorelbine using published phase III clinical trial data for these agents.[1,4-6]

The objectives of this study were to determine the incremental cost-utility ratios of docetaxel versus paclitaxel and docetaxel versus vinorelbine in the treatment of patients with advanced breast cancer within the UK-licensed indications. The first analysis compared the only two taxoids currently licensed in the UK for the treatment of advanced breast cancer. This comparison aimed to reflect a choice faced by oncologists practising in this area and other healthcare decision makers. The second analysis compared docetaxel, for which the most promising clinical data are available, with vinorelbine, another recently introduced agent. Despite poorer response and survival rates, vinorelbine tends to be used because its unit cost is less than that of the taxoids.

## Methods

### Data Sources and Management

The efficacy and safety profiles of docetaxel, paclitaxel and vinorelbine, as treatments for advanced breast cancer, have recently been compared.[10] These findings have been used in the current analysis.

#### *Docetaxel versus Paclitaxel*

Three randomised phase III clinical trials on the use of docetaxel in patients with advanced breast cancer were used to construct the base-case scenario for docetaxel.[1,4,6] For each trial, the response rate (complete and partial) and adverse effect rates were weighted by the number of patients randomised. These weighted values were then used to calculate weighted average efficacy (overall response rate) and adverse effect rates for docetaxel.

Only one randomised phase III clinical trial on the use of paclitaxel in patients with advanced breast cancer within the UK licensed indication has been published.[3] This trial examined both anthracycline-resistant (those with tumour progression in spite of anthracycline treatment) and anthracycline-naïve patients; this latter group falls outside the confines of the UK licence. While the report of this phase III clinical trial presented the overall response rates for the subgroups separately thus allowing use in the construction of the base-case scenario for paclitaxel, the safety data were aggregated and inappropriate for inclusion in the model. In the absence of phase III safety data for single-agent paclitaxel in anthracycline-resistant patients, weighted averages of the safety data from phase II clinical trials were calculated for the purposes of this study.[11-16] Weights were calculated based on the number of patients enrolled in each study as described above for docetaxel.

**Table II.** Health state utilities for metastatic breast cancer

| Health state | UK utility (SD) |
|---|---|
| Start of second-line therapy | 0.64 ± (0.15) |
| Partial/complete response | 0.84 ± (0.12) |
| Stable disease | 0.62 ± (0.22) |
| Progressive disease | 0.33 ± (0.24) |
| Terminal disease | 0.13 ± (0.12) |
| Peripheral neuropathy with partial/complete response | 0.62 ± (0.16) |
| Severe oedema with partial/complete response | 0.78 ± (0.15) |
| Severe skin condition with partial/complete response[a] | 0.56 |
| Febrile neutropenia and hospitalised | 0.24 ± (0.12) |
| Infection without hospitalisation | 0.48 |
| Death | 0 |

a Estimated from other toxicities.
**SD** = standard deviation.

#### *Docetaxel versus Vinorelbine*

The weighted average efficacy and adverse effect rates for docetaxel for use in the base-case analysis were those derived from the three randomised phase III clinical trials as described above.

Weighted average efficacy and adverse effect rates for construction of the base-case scenario for vinorelbine were calculated using data from the only published randomised phase III clinical trial

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designed to evaluate the use of single-agent vinorelbine in anthracycline-resistant advanced breast cancer.[5]

### Probabilities, Costs and Utilities

Probabilities of the occurrence of outcome variables in the base-case analysis were derived from clinical trial data and are shown in table I.

In healthcare, utilities are a measure of the patient's preferences for health states.[17] Prospective patient utilities were not collected during the trials. Consequently, the best option available was the use of proxy respondents. Proxy utility values were obtained from 30 oncology nurses from specialist cancer centres in the UK and from 150 nurses in four other Western European countries. The standard gamble method was used to obtain rankings of the health states based on utilities.[18] The utilities are presented in table II and are unique to the health states regardless of the treatment. The health states were defined without reference to particular chemotherapy treatment to enable blind estimates of preference. Nurses were unaware of the chemotherapies being compared and were not paid for participating in the study. The UK nurse mean responses were used in the basic analysis and sensitivity analyses were conducted on the range of responses and the mean responses from the 150 Western European nurses. As the patients in the model experience the different health states, the utilities increase or decrease as appropriate.

Cost variables for use in the model were developed in collaboration with leading oncologists so that they accurately reflected current treatment practices within the UK. For each health state specified in the model, the direct healthcare resource use was defined by one oncologist and reviewed by four other oncologists. The treatment pattern and resource use for each health state was defined by the overall views of the five oncologists. The treatment algorithms for the different health states were designed to reflect resource use during a 3-week period.

**Table III.** Resource costs used in the base-case analyses for metastatic breast cancer

| Resource | Unit cost[a] (£ sterling; 1999 values for drug costs, 1997/1998 values for other resources) |
|---|---|
| Docetaxel per 3-week course | 1150 |
| Paclitaxel per 3-week course | 1122 |
| Vinorelbine per 3-week course | 441 |
| Chemotherapy administration per visit (outpatient clinic) | 62 |
| Hospital day (i.e. 1 day in hospital) [regular] | 270 |
| Hospital day (i.e. 1 day in hospital) [intensive care] | 919 |
| GP consultation | 14 |
| Specialist consultation | 50 |
| **Combined resources** | **State cost (sterling)** [b] |
| Early progressive disease[c] (palliative medicines, GP visit, 50% with laboratory tests, x-ray, ultrasound) | 154 |
| Late progressive disease[c] (palliative medicines, weekly GP visit, 80% with nurse home visits twice weekly) | 267 |
| Stable disease[c] (palliative medicines, GP visit, 50% with laboratory tests and x-ray, 60% with outpatient visit) | 126 |
| Terminal disease[c] (palliative medicine, twice-weekly GP visit, 80% with nurse home visits twice weekly, nutritional supplements daily) | 372 |
| Neutropenia [7 days hospital; IV outpatient; oral antibacterial (depending on severity of neutropenia)] | 2470; 907; 42 |
| Severe neurotoxicity[c] (GP visit, 50% with laboratory tests, outpatient visit) | 124 |
| Severe oedema[c] [GP visit, 50% with hospital day (i.e. 1 day in hospital), specialist] | 284 |

a £1 = $US1.55.

b Refers to the total costs for the related Markov state.

c Cost per 3-week period.

**GP** = general practitioner; **IV** = intravenous.

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Unit prices were applied to convert the resource use patterns into costs for a 3-week period. Where possible, unit costs were taken from national databases; laboratory costs and costs of chest x-rays were provided by specific hospitals (Hospital Trust in Central England, personal communication, 1997). The National Health Service Hospital and Community Inflation Index was used to convert these costs to 1997/1998 prices.[19] Drug costs were calculated using prices taken from the Monthly Index for Medical Specialties[20] (1999 values) and were based on a nominal body surface area of 1.75$m^2$ and recommended dosages of 100 mg/$m^2$ for docetaxel, 175 mg/$m^2$ for paclitaxel and 30 mg/$m^2$ for vinorelbine. The updated costs of the health states in advanced breast cancer have recently been published.[7] The resource costs used in the model are shown in table III; indirect productivity costs were not included in the model.

## The Decision-Analysis Model

### *Model Design*

A previously reported decision-analysis model was used for the cost-utility analyses in this study.[9] The model was validated by a number of practising oncologists at leading cancer treatment centres in the UK to ensure that it accurately represented the care of patients with advanced breast cancer. The model used the Markov process to simulate the clinical course of a representative patient with advanced breast cancer through discrete disease states and toxicities. A 'typical' patient is difficult to define because of the highly complex nature of the disease and its treatment. Expert clinical advice was therefore sought to produce the definition and validate the disease states and toxicities that might be encountered in successive cycles of the model. A probability, a cost and a utility were determined for each disease state and toxicity.

The cost-utility analyses considered only direct medical costs over a time frame of 3 years from the initiation of salvage therapy. A discount rate of 6% was applied to all costs after the first year. This discount rate was based on the UK Treasury rate, and is the value commonly used in economic evaluations conducted in the UK following the Guidance on Good Practice in the Conduct of Economic Evaluations of Medicines.[21] Docetaxel and paclitaxel are each administered as a single dose every 3 weeks for a total of 6 chemotherapy cycles and vinorelbine is administered weekly for a total of 12 chemotherapy cycles. The model assumes that all patients achieving response receive the full drug dose. Treatment with paclitaxel involves a 3-hour dose infusion period while docetaxel is administered as a 1-hour infusion. Costs arising from differences in the administration schedules, which would increase the costs associated with paclitaxel more than those associated with docetaxel, were not included in the analyses. Indirect productivity costs such as patient time lost from working or in normal activities, were not included in the analyses except insofar as they were incorporated into the utilities.

### *Disease Process and Outcomes of Treatment*

The representative patient considered in the model had been diagnosed with advanced breast cancer and had disease progression (increasing tumour size) and metastases following first-line chemotherapy with anthracyclines. The patient entered the model and received chemotherapy with docetaxel, paclitaxel or vinorelbine according to the licensed dosage and administration schedules. After a course of the specified treatment, the patient had one of the following outcomes (classified according to World Health Organization criteria used in the clinical trials):[22] complete response, partial response, stable disease, or progressive disease.

As complete response is rare in patients with advanced breast cancer, complete and partial responses were combined for the purposes of the model to provide the overall response rate. Since patients with advanced breast cancer also have a poor prognosis, those with a response or stable disease eventually develop progressive disease leading to death.

The model also took into account various toxicities that might result from chemotherapy. The toxicities associated with chemotherapeutic agents are

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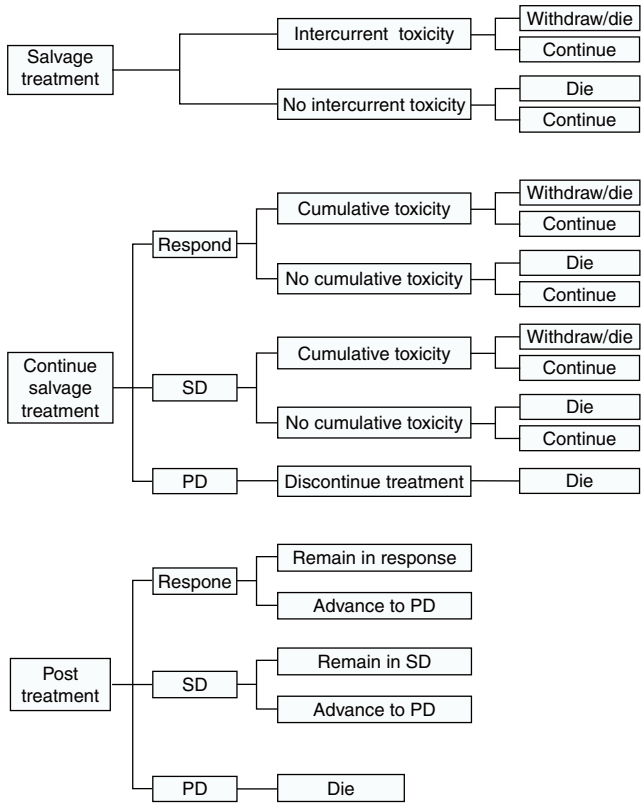


**Fig. 1.** Model structure. **PD** = progressive disease; **SD** = stable disease.

usually classified as immediate (occurring during or immediately after treatment), intercurrent (occurring between courses of treatment) or cumulative (occurring after several courses of treatment). Pre-medication is often used to reduce the incidence and severity of adverse effects of chemotherapy, and pre-medication was included in the treatment patterns used in the model to reflect current practice.

Immediate toxicities, such as nausea and vomiting, are assumed to discontinue after completion of each course of chemotherapy. Neutropenia is the most common intercurrent toxicity. Patients with neutropenia are at greater risk of succumbing to infection, which may culminate in sepsis and an increased risk of mortality. Patients who develop severe neutropenia with fever, indicating a risk of infection, may therefore be withdrawn from chemotherapy. The model assumed that the immediate toxicities occurred during cycles two and three. Cumulative toxicities that could be encountered with salvage chemotherapy and included in the model were severe fluid retention, severe peripheral neuropathy, arthralgia, myalgia and skin conditions. The model assumed that these conditions persisted for 9 weeks. Patients may be withdrawn from chemotherapy if these toxicities are severe.

### *Structure of the Model*

Diagrammatic representation of the model is shown in figure 1. Cycle length of the model was 3 weeks. This equated to the interval between courses of treatment for docetaxel and paclitaxel; a total of six courses of treatment was administered

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**Table IV.** Sensitivity analyses: docetaxel (D) versus paclitaxel (P)

| Analysis (costs discounted by 6% unless otherwise indicated) | Cost (£)/QALY gained | Incremental cost (D-P) | Incremental utility cost (D-P) |
|---|---|---|---|
| Base case | 1995 | 172 | 0.0862 |
| Base case, benefits and costs discounted | 2070 | 172 | 0.0831 |
| Paclitaxel survival same as docetaxel | 4550 | 251 | 0.0551 |
| Utility values for disease states pooled from 6 countries | 3220 | 172 | 0.0534 |
| Cost of stable disease reduced to £55 per 3-week period | 3666 | 316 | 0.0862 |
| Cost of progressive disease reduced to £100 per 3-week period | 6055 | 522 | 0.0862 |
| Cost of progressive disease increased to £300 per 3-week period | Docetaxel dominates[a] | 251 | 0.0862 |

a Docetaxel is more effective and less costly

**QALY** = quality-adjusted life year.

for these agents. Twelve courses of treatment of vinorelbine were administered during four cycles of the model. For each chemotherapeutic agent, the model estimated the quality-adjusted time a patient would spend in the discrete disease states (complete or partial response, stable disease, progressive disease) and toxicities during each cycle and the associated resource costs. Costs accumulated in the model as the patient progressed through the health states. The response rates and adverse effect profiles for each agent could then be assessed in terms of the costs and benefits that they imply. For a disease in which length of survival is not significantly increased by treatment, it is reasonable to assume that patients who respond to treatment incur a lower cost than patients who experience disease progression, since disease progression often involves additional therapy to alleviate symptoms and control disease. Similarly, patients who respond are assumed to have a better quality of life than patients who progress, since patients who respond spend longer in better states of health. Patients who experience adverse effects from therapy are assumed to have a reduced quality of life at that time and to incur additional costs related to clinical management of the adverse effect. Costs accumulate in the model as the patient progresses through the health states.

The model assumed that treatment response would be evident by the second cycle and confirmed by the fourth cycle. Patients who progressed at cycle 2 were withdrawn from therapy and developed early progressive disease. Those with a response or stable disease proceeded through cycle three to cycle four when the response was confirmed. Patients who were not withdrawn from therapy because of severe cumulative toxicities completed the courses of treatment. These patients remained in the response or stable disease states for the median duration of response and then developed progressive disease. The model took into account the median survival times for docetaxel, paclitaxel and vinorelbine, which were derived from clinical trial data (table I). Following treatment with docetaxel, paclitaxel or vinorelbine, half of the patients had died by 56, 46 or 36 weeks, respectively. The remainder of the patients died after these times.

## Analyses

The probabilities, utilities and costs presented in tables I, II and III, respectively, were used in the base-case analyses. The base-case scenarios represented the most likely events to result from treatment with docetaxel, paclitaxel and vinorelbine.

The output from this type of economic model is incremental cost effectiveness. This output provides an assessment of the extra costs and benefits of an intervention when compared with another treatment option. It incorporates the notions of choice and sacrifice faced in real-life clinical situ-

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ations, namely that if one therapy is chosen then another will not be used.

Sensitivity analyses form an important part of economic evaluations using models, especially where input variables have been estimated. To test the robustness of the model and the validity of the base-case cost-utility results, sensitivity analyses were performed using the following scenarios: discounting benefits (clinical outcomes) as well as costs at a rate of 6%; varying the utilities assumed for each of the health states; increasing and decreasing the costs applied to the disease states and toxicities experienced.

## Results

### Docetaxel versus Paclitaxel

In the base-case analysis, the total per-patient cost of using docetaxel was £7817. This compared with a total per-patient cost of £7645 for paclitaxel. The QALY values for the base-case scenario were 0.7347 for docetaxel and 0.6485 for paclitaxel. When compared with costs and benefits for paclitaxel, treatment with docetaxel resulted in an additional total cost of £172 per patient for an additional 0.0862 QALY, which is equivalent to an extra 31 days of perfect health. The incremental cost-utility ratio for docetaxel versus paclitaxel was therefore £172/0.0862 QALY or £1995 per QALY gained.

The results of the sensitivity analyses are presented in table IV. The model was sensitive to the costs associated with treatment, progressive disease, and stable disease. If the model costs were overestimated, the cost-effectiveness ratio would be higher. However, if the model costs were underestimated, the ratio would be lower, and docetaxel might become less expensive (dominate paclitaxel by being less costly and more effective).

The results of the analyses consistently showed that docetaxel resulted in higher health gain (increased QALYs) than paclitaxel. In most cases, docetaxel also resulted in greater healthcare costs. However, using the base-case scenario, the increased utility benefit was substantial and the additional cost per QALY gained was small, illustrating that docetaxel is a cost-effective therapy for use in patients with advanced breast cancer when compared with paclitaxel. Sensitivity analyses with the upper and lower bounds of utilities did not change the advantage of docetaxel over paclitaxel. Assuming the same survival for both agents results in higher cost per QALY for docetaxel.

The evidence used in the model was derived from three randomised phase III trials for docetaxel[1,4,6] and one randomised phase III trial for paclitaxel.[3] Although the agents were not compared head to head in these trials, models are disigned to overcome this problem. Criteria for making evidence-based decisions in the UK[23] suggest that randomised trials provide the highest quality evidence and, while adapting the criteria to cost-effectiveness studies may be open to debate, under their construct the model data are category I or II (table V). Docetaxel would be 'strongly recom-

**Table V.** Recommendations based on cost-utility estimates and the quality of evidence

| | Incremental cost per quality-adjusted life-year gained (£ × 1000) | | | |
|---|---|---|---|---|
| Quality of evidence[a] | <3 | 3-20 | >20 | negative |
| I | Strongly recommended | Strongly recommended | Limited support | Not supported |
| II | Strongly recommended | Supported | Limited support | Not supported |
| III | Supported | Limited support | Limited support | Not supported |
| IV | Not proven | Not proven | Not proven | Not proven |

a Categories are based on the quality of data from clinical trials and other clinical evidence (adapted from Stevens et al.[23]).

**I** = well-designed randomised controlled trials; **II** = controlled trials with pseudo-randomisation *or* no randomisation or prospective cohort studies with concurrent or historic controls *or* retrospective cohort studies with concurrent controls *or* case-control retrospective study; **III** = large differences from comparisons between times and/or places with and without intervention; **IV** = opinion of respected authorities based on clinical experience, descriptive studies and reports of expert committees.

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**Table VI.** Sensitivity analyses: docetaxel (D) versus vinorelbine (V)

| Analysis (costs discounted by 6% unless otherwise indicated) | Cost (£)/QALY gained | Incremental cost (D-V) | Incremental utility cost (D-V) |
|---|---|---|---|
| Base case | 14 055 | 3549 | 0.2525 |
| Base case, benefits and costs discounted | 14 800 | 3549 | 0.2398 |
| Vinorelbine survival same as docetaxel | 14 287 | 3486 | 0.2440 |
| Utility values for disease states pooled from 6 countries | 15 095 | 3549 | 0.2351 |
| Cost of stable disease reduced to £55 per 3-week period | 14 186 | 3582 | 0.2525 |
| Cost of progressive disease reduced to £100 per 3-week period | 15 030 | 3795 | 0.2525 |
| Cost of progressive disease increased to £300 per 3-week period | 12 970 | 3274 | 0.2525 |

**£** = pounds sterling.

mended' or 'supported' based on the cost-effectiveness ratio.

### Docetaxel versus Vinorelbine

In the base-case analysis, the total per-patient costs of using docetaxel and vinorelbine were £7817 and £4268, respectively. The QALY values for the base-case scenario were 0.7347 for docetaxel and 0.4822 for vinorelbine. When compared with costs and benefits for vinorelbine, treatment with docetaxel produced an additional 0.2525 QALY (equivalent to 92 days of perfect health) for an extra cost of £3549. The incremental cost-utility ratio for docetaxel versus vinorelbine was therefore £3549/0.2525 QALY or £14 055 per QALY gained.

The results of the sensitivity analyses are presented in table VI. The incremental cost-utility ratio for docetaxel versus vinorelbine did not vary greatly in any of the scenarios, thus confirming the robustness of the model and the validity of the results of the base-case analysis.

Docetaxel consistently produced higher health gains (increased QALYs) and higher healthcare costs than vinorelbine in the base-case analysis and in the sensitivity analyses. The results demonstrated that docetaxel is a cost-effective therapy for use in patients with advanced breast cancer when compared with vinorelbine. Once again, adopting the criteria on level of evidence in decision-making,[23] docetaxel would be 'strongly recommended' or 'supported' (table V).

## Discussion

This work updates the cost-utility analysis of docetaxel versus paclitaxel that has previously been published.[9] At the time of this earlier study, there were few published reports of clinical trials of docetaxel and paclitaxel, and data from phase II clinical trials were used to provide estimates of treatment effects. Since the publication of that study, phase III clinical trial data for docetaxel and paclitaxel have become available.[1,3,4,6] These randomised phase III trials recruited large numbers of patients and, as such, are considered to provide the strongest clinical evidence available on which to base an analysis of docetaxel versus paclitaxel. The original cost-utility analysis was therefore repeated using estimates of clinical outcomes based on the published phase III clinical trial data for docetaxel and paclitaxel. In addition, this reanalysis enabled resource costs to be updated according to current prices and extend the original analysis to vinorelbine. The inclusion of vinorelbine in this study was considered important for the analyses to be comprehensive and reflect the treatment choices for advanced breast cancer.

Decision-analysis modelling is a useful tool in situations where data are disparate and time constraints and financial restrictions preclude the prospective collection of cost-effectiveness data. Although the decision-analysis model employed in this study may appear complex, it represents a considerable simplification of the issues relating to the treatment of advanced breast cancer. The model necessitates the definition of a 'typical' patient,

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and such patients rarely exist. The results of analysis models should be interpreted with some caution since they often depend upon limited clinical data and they rely upon estimates for many of the parameters involved. Although we attempted to use comparable published trial data, the quality of data is limited by the absence of head to head comparisons of docetaxel and paclitaxel or vinorelbine. Patients may differ across trials and clinical outcomes may be reported differently. In addition, we had to rely upon nurses to estimate patient utilities. Using patient-derived utilities would strengthen the model.

Models are used in an attempt to overcome the absence of head to head comparisons and when carefully validated and supported by expert opinion, they can contribute to our understanding of the socioeconomic factors surrounding the treatment of diseases. The present study looked specifically at the treatment of anthracycline-resistant advanced breast cancer. It is important to note that the model did not take into account treatments received and healthcare costs incurred early in the course of the disease. The model also does not take into account the indirect costs associated with advanced breast cancer. Productivity losses incurred by patients with advanced breast cancer are likely to be high and may not be dependent to the chemotherapeutic agent used or the response achieved. In practice, even patients who respond to treatment experience long term adverse effects, such as peripheral neuropathy and bone pain. Consequently, their work productivity could decline regardless of chemotherapy or response to treatment.

The quality of the phase II and III clinical trial data for docetaxel in patients with advanced breast cancer exceeds that for other medicines licensed for this indication in the UK, such as paclitaxel and vinorelbine. Phase III clinical trials have compared docetaxel with mitomycin plus vinblastine, doxorubicin, and methotrexate plus 5-fluorouracil.[1,4,6] Docetaxel has been shown to increase response rate, time to progression, and survival in patients with advanced breast cancer when compared with other chemotherapeutic agents. Of particular note is the fact that docetaxel is the only chemotherapeutic agent to have produced a significantly higher response rate than doxorubicin in a randomised trial and the only agent to show a survival advantage.[4] Until these data were published, doxorubicin was widely considered to be the most active single chemotherapeutic agent for treatment of patients with advanced breast cancer.

Paclitaxel was the first taxoid to be licensed in the UK for advanced breast cancer. However, the results of the original cost-utility analysis[9] and of this updated analysis suggest that docetaxel is a more cost-effective alternative. In the original study, the incremental cost-utility ratio for docetaxel versus paclitaxel in the base-case analysis was calculated as £2431 per QALY gained. However, there was no discounting of costs in that study. In the present study, the incremental cost-utility for docetaxel versus paclitaxel in the base-case analysis was similar at a value of £1995 per QALY gained. The use of docetaxel is further supported by the results of the comparison with vinorelbine in the present study. Although the cost per QALY gained was greater for docetaxel in the comparison with vinorelbine than in the comparison with paclitaxel, the value still supported the use of docetaxel. When compared with vinorelbine, docetaxel provided the equivalent of an additional 92 days of perfect health.

More recently, anecdotal comments from the UK-based National Institute for Clinical Excellence indicate that between £20 000 and £30 000 is an acceptable range for cost per QALY within the UK context.[24]

Sensitivity analyses confirmed the robustness of the model. In the comparison of docetaxel and paclitaxel, increasing model treatment cost increased the cost-effectiveness ratio, while decreasing costs reduced the ratio so that docetaxel could dominate paclitaxel. In the comparison of docetaxel and vinorelbine, the cost-effectiveness ratio did not differ greatly in any of the scenarios. The use of pooled utility values from oncology nurses in six countries instead of the UK-derived values or the upper and lower bounds of utility values increased

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the cost per QALY, but not sufficiently to change the acceptability of the cost-effectiveness ratios. The utility values clearly have an important impact and using actual patient data rather than nurses as proxies would strengthen the analysis.

There are similarities between this study and two other studies using modelling techniques to examine the cost utilities of docetaxel, paclitaxel and vinorelbine in the treatment of anthracycline-resistant advanced breast cancer.[25,26] In the French study that compared docetaxel with vinorelbine, vinorelbine resulted in higher costs than docetaxel, principally because of high rates of hospitalisation of patients who were nonresponsive to therapy.[25] Paclitaxel was intermediate in terms of cost and benefit. Increasing the costs for progressive disease management in the UK results in docetaxel being less costly than vinorelbine and providing higher utilities. Similar results in support of docetaxel were obtained from a US comparison of docetaxel and paclitaxel,[26] that used data from the phase III trial comparing docetaxel with doxorubicin.[4] Docetaxel provided substantially greater utility benefits than paclitaxel at a small extra cost per QALY gained. In contrast to these findings, a Canadian study has reported that the most cost-effective agent was vinorelbine and the least cost-effective agent was docetaxel.[27] However, the number of patients considered in this study was small, and there was no significant difference in quality-adjusted progression-free survival days.

## Conclusions

Docetaxel provided greater utility benefits than paclitaxel or vinorelbine at slightly higher additional costs. The results of our study support the use of docetaxel in the management of advanced breast cancer.

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