A cost-utility analysis comparing second-line chemotherapy schemes in patients with metastatic breast cancer

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined second-line chemotherapy in metastatic breast cancer. In particular, docetaxel (a single agent taxane/taxoid), paclitaxel (a single agent taxane/taxoid), combined vinorelbine and mitomycin C (VRM), and mitomycin plus vinblastine (MV). MV is current standard second-line chemotherapy, while the alternatives were the comparators. No further details about the treatments were given.

Type of intervention
Secondary prevention

Economic study type
Cost-utility analysis.

Study population
The study was concerned with female patients aged 18 to 70 years who had been diagnosed with breast cancer, with at least one site of metastatic cancer. In addition, the patients had to have developed progressive disease after first-line chemotherapy.

Setting
The study was based on hypothetical patients. Therefore, a setting was not explicitly stated. However, given the hospital perspective used, it can be inferred that the setting was secondary care.

Dates to which data relate

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of completed studies. These were augmented by assumptions and estimates made by the authors.

Modelling
A decision analytic model was used to assess cost-utility. At baseline, patients received one of the four treatments (paclitaxel, docetaxel, VRM or MV) for 12 cycles. As the model time horizon was 12 months each cycle lasted 1 month. The model was used to depict the course of the disease over concurrent cycles of chemotherapy to define possible patient outcomes, and the cost of each outcome, for each of the four treatments. Treatment-associated toxicities (such as febrile neutropenia), treatment effects, patient utilities and the probability of changing health states
were incorporated into the model.

**Outcomes assessed in the review**
The outcomes of interest for input into the model were the toxicity death rate, treatment-limited death rate, chemotherapy response rate and outcome probabilities.

**Study designs and other criteria for inclusion in the review**
The efficacy data were obtained from two phase III clinical trials and one phase II trial. Further details of the study design were not reported. No inclusion or exclusion criteria were reported.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
The heterogeneity of baseline patients was evaluated by comparing their average age, prior treatment history, the number and sites of metastatic cancer, and performance status. No further attempts to ensure the validity of the primary studies were reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
The efficacy data were extracted from three studies.

**Methods of combining primary studies**
The authors did not combine the results from the individual primary studies. One study provided data on the efficacy of docetaxel and MV, another provided data for paclitaxel, and another data for VRM.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The outcomes for toxicity death rate and treatment-limited death rate were not reported.

The chemotherapy response rate was:

29% (95% confidence interval, CI: 23 - 36) for paclitaxel, 33% (95% CI: 26 - 40) for docetaxel, 45% (95% CI: 32 - 59) for VRM and 12% (95% CI: 7 - 17) for MV.

The median time to progression was 4.2 months for paclitaxel, 4.4 months for docetaxel, 6.2 months for VRM and 2.6 months for MV.

The median survival was 11.7 months for paclitaxel, 11.4 months for docetaxel, 13.2 months for VRM and 8.7 months for MV.

The outcome probabilities were calculated on the basis of the clinical efficacy data, but were not reported.
Methods used to derive estimates of effectiveness
The authors used some assumptions to supplement their efficacy data.

Estimates of effectiveness and key assumptions
The authors clearly stated that they made the following assumptions:

the patients would be hospitalised in the case of febrile neutropenia and that febrile neutropenia would only occur during the first 3 months;
non-response patients developed disease in the next interval and this would in turn lead to death in the following period;
dose reduction was ignored (due to lack of detailed data); and
non-responders contributed more to death rates than responders by a ratio of 3:1.

Measure of benefits used in the economic analysis
QALYs and QAPFYs were used for the economic analysis. The utility values (used to calculate QALYs and QAPFYs) were collected from the literature. After considering the alternatives available, the authors chose a "six-country average utility" as the basic source of utility data. The method of valuation used by this source was not reported. The utility of each time interval was multiplied by the number of life-years (or progression-free life-years) in each time interval to estimate the number of QALYs (or QAPFYs).

Direct costs
The costs were estimated from the perspective of the hospital. The cost analysis focused on the costs of cytostatics and other drugs (wholesale prices were used), the cost of hospitalisation, and follow-up costs. The authors, appropriately, did not carry out discounting due to the short time horizon of the study (12 months). The costs were not reported separately from the quantities. The drug costs were taken from Pharmaceutical Compass 1998. Other costs were collected from two studies published in 1997 and 1998. The price year was stated to be 1998.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
The authors stated that only the direct costs were considered in the analysis, but gave no justification for this. However, the median survival of patients was relatively short, suggesting that the actual patients in this situation might not be economically productive. This would make the indirect costs (if based on productivity) irrelevant.

Currency
US dollars ($).

Sensitivity analysis
One-way sensitivity analyses were performed to assess the impact of changing clinical efficacy, treatment costs (by changing the dose delivery) and utility data. These parameters appear to explore both uncertainty in the data inputted into the model, and the generalisability of the results, although this was not explicitly stated by the authors.

Estimated benefits used in the economic analysis
The number of life-years gained (LYG), the number of progression-free life-years, the total QALYs and the total
QAPFYs were estimated for each treatment alternative.

For paclitaxel, the number of LYG was 0.7595, the number of progression-free life-years was 0.3950, the total QALYs was 0.35 and the total QAPFYs was 0.19.

For docetaxel, the number of LYG was 0.7591, the number of progression-free life years was 0.4458, the total QALYs was 0.34 and the total QAPFYs was 0.23.

For VRM the number of LYG was 0.8466, the number of progression-free life years was 0.5326, the total QALYs was 0.43 and the total QAPFYs was 0.29.

For MV, the number of LYG was 0.7008, the number of progression-free life years was 0.3241, the total QALYs was 0.29 and the total QAPFYs was 0.15.

The incremental QALYs were estimated for paclitaxel, docetaxel and VRM versus MV. These were 0.07 for paclitaxel, 0.05 for docetaxel, and 0.14 for VRM.

Cost results
The total costs per patient were estimated for each treatment alternative (no breakdown of the costs was provided). These were $10,594 for paclitaxel, $16,911 for docetaxel, $7,359 for VRM and $4,037 for MV.

The incremental costs were estimated for paclitaxel, docetaxel and VRM versus MV. These were $6,557 for paclitaxel, $12,873 for docetaxel and $3,322 for VRM.

Synthesis of costs and benefits
The costs and the benefits were combined to estimate the average cost per QALY for each alternative. The costs per QALY were $30,270 for paclitaxel, $49,739 for docetaxel, $17,114 for VRM and $13,922 for MV.

The incremental costs per QALY were estimated for paclitaxel, docetaxel and VRM versus MV. These were $99,547 for paclitaxel, $256,304 for docetaxel and $23,046 for VRM.

The authors reported the results of the sensitivity analysis. They drew the readers' attention to the impact of a higher response rate of paclitaxel treatment, suggesting that a 37% increase led to an increase in QAPFYs of 32%, an increase in costs of 12% and an increase in the cost per QALY ratio of 13%. When this response rate increased by 47% there was a fall in the cost per QAPFY for this treatment alternative. The authors also reported that changing the utility values had an "important" impact on the QALYs, QAPFYs and cost-effectiveness ratios.

Authors' conclusions
The combined vinorelbine and mytomycin C (VRM) therapy cost relatively little and provided a high number of quality-adjusted life-years (QALYs). In addition, this treatment showed the lowest incremental cost-effectiveness ratio. Docetaxel was reported to be most expensive with lower efficacy. Mytomycin plus vinblastine (MV) was the cheapest approach, but offered the least number of life-years gained (LYG).

CRD COMMENTARY - Selection of comparators
The comparators were stated explicitly at the outset and were appropriate for the study objective. They were chosen as they have been shown to be effective second-line chemotherapy regimens. The baseline comparator was MV since it represented standard practice.

Validity of estimate of measure of effectiveness
The effectiveness data were collected from a review of published material. However, the authors did not state that they were carrying out a systematic review. Data from the primary studies were not combined, suggesting that perhaps the
authors used data from the available studies selectively. The authors clearly identified the sources of their estimates, thus enabling the reader to refer to these sources and independently assess their quality.

**Validity of estimate of measure of benefit**
The measures of benefit used were the QALYs and QAPFYs. These were estimated from survival data generated by the decision analytic model, and from utility data obtained from published material. The authors took the utility data from a single paper, despite several papers providing relevant data. Their reason for this was that this paper provided a "six-country average utility". The authors discussed some limitations of the other potentially relevant utility papers, which leads to the conclusion that it would have been inappropriate to try to combine the data from the relevant papers to generate a combined utility estimate. Some details of the decision model, such as the number of hypothetical patients treated, were not reported.

**Validity of estimate of costs**
A hospital perspective was adopted. The authors included the costs of drugs, follow-up and hospitalisation. The drug costs may not have been incurred by the hospital. Given the costs actually included, the third-party payer perspective may have described the study more appropriately. Details of the costs included in each category were not reported. Therefore, it not possible to assess objectively whether all the relevant costs were covered in the analysis. The costs and the quantities were not reported separately.

**Other issues**
The authors made good comparisons with numerous earlier studies and provided reasons for differences in the results. The concept of generalisability was not explicitly discussed. However, the authors carried out a sensitivity analysis that covered different costs, and also used a "six-country average utility". Both these efforts potentially increase the generalisability of the study to locations beyond the USA. The authors do not appear to have presented their results selectively. The study compared four possible second-line chemotherapy regimens and this was reflected in the conclusion of the study. The authors highlighted the limitations of their study, discussing three sources. First, the assumptions made in the model. Second, the differences in the methodology and patients used in the utility papers reviewed. Third, the lack of efficacy data. Although the authors reported incremental cost-effectiveness ratios, these were calculated for each alternative relative to MV. It may have been preferable to rank alternatives by cost (or effect), to exclude dominated alternatives, and to calculate incremental ratios in order increased the cost (or effect).

**Implications of the study**
The authors do not make any recommendations with respect to changes in policy or practice. They do not explicitly state a need for further research, although possible research is implied within the discussion.

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None stated.

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**Other publications of related interest**


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