Population-based pharmacoeconomic model for adopting capecitabine/docetaxel combination treatment for anthracycline-pretreated metastatic breast cancer

Verma S, Ilersich A L

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 use of capecitabine (Xeloda; Hoffman-La Roche)-docetaxel combination therapy for the treatment of anthracycline-pretreated metastatic breast cancer (MBC). The regime used was 21-day cycles of oral capecitabine (1,250 mg/m² twice daily on days 1 to 14) plus docetaxel (75 mg/m² on day 1).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised female patients with anthracycline-pretreated MBC. The patients had to be over 18 years and have histologically or cytologically confirmed breast cancer with unresectable locally advanced and/or metastatic disease. The authors stated the inclusion criteria clearly. Patients were ineligible if they had received a docetaxel-containing regimen in either the adjuvant or advanced disease setting, or if they had received three or more chemotherapy regimens for advanced or metastatic disease. The authors clearly stated further exclusion criteria.

Setting
The setting was secondary care. A specific study setting was not reported since the study was multi-centred. The base-case analysis was set in Ontario, Canada.

Dates to which data relate
The authors reported the "clinical cut off for the study analysis was 15 February 2001". They also reported that a minimum follow-up of 15 months had been reached. Resource use was measured during the same time as the clinical trial. The health care costs related to patients diagnosed with breast cancer in 1995. A price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The medical resource use data were collected prospectively for the same sample of patients as that used in the effectiveness study.

Study sample
There was very little information on the study sample. Most of the following information was obtained from the original effectiveness paper (see Other Publications of Related Interest).

The authors reported that they required 454 patients in order to achieve 80% power to detect significant differences between the treatments. They therefore aimed to recruit 500 patients so as to allow for a 10% dropout. The method of sample selection was not described. The initial sample was appropriate for the clinical study question as it included female patients with MBC. A total of 511 patients were recruited. Of these, 255 patients received the capecitabine-docetaxel combination and 256 received docetaxel alone. The median age was 52 years (range: 26 - 79) in the combination group and 51 years (range: 25 - 75) in the single-agent group. The authors did not report any refusal to participate, or specific exclusions.

**Study design**

There was very little information on the study design. Most of the following information was obtained from the original effectiveness paper (see Other Publications of Related Interest).

The analysis was based on a randomised, controlled clinical trial. The patients were randomised by country, using a block size of four, via a computer-assisted, touch-tone, central randomisation service located in Houston (TX, USA) and Brussels (Belgium). The patients were stratified according to whether they had received prior paclitaxel therapy. The patients were recruited from 75 centres in 16 countries. A minimum follow-up of 15 months was achieved in all patients. There was no loss to follow-up. Copies of the X-rays and computed tomography scans were given to a panel of radiologists for independent review. The radiologists were blinded to the study treatment, the clinical condition of the patient, and the investigator's evaluation.

**Analysis of effectiveness**

The basis of the analysis was intention to treat. The primary health outcome was tumour response. This was assessed at 6-week intervals until week 48 and then at 12-week intervals until disease progression. The best overall response achieved was reported. The patients were classified as achieving stable disease if, at the first tumour assessment after study treatment, there was neither disease progression nor a response that was later confirmed. Survival rates were also recorded. The authors reported that the baseline characteristics were well balanced between the two treatment groups.

**Effectiveness results**

The median time to disease progression was 6.1 months (95% confidence interval, CI: 5.4 - 6.5) in the combination arm and 4.2 months (95% CI: 3.4 - 4.5) in the single therapy arm. Therefore, combination therapy resulted in a significantly superior time to disease progression than single-agent therapy (logrank p=0.0001; hazard ratio 0.625, 95% CI: 0.545 - 0.780).

The hazard ratio translates into a 35% decrease in the risk of disease progression with combined therapy.

The median survival was 14.5 months (95% CI: 12.3 - 16.3) in the combination arm and 11.5 months (95% CI: 9.8 - 12.7) in the single therapy arm.

The 12-month survival was 57% (95% CI: 51 - 63) in the combination arm and 47% (95% CI: 41 - 53) in the single therapy arm.

**Clinical conclusions**

The authors concluded that combination therapy resulted in "significantly superior efficacy, including a significantly higher tumour response rate".

**Modelling**

Statistics Canada's Population Health Model was used to estimate the direct health care cost associated with the lifetime
management of breast cancer in Canada.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions for the model.

**Estimates of effectiveness and key assumptions**
The authors assumed that patients with human epidermal growth factor receptor 2+ MBC receiving trastuzumab would not be eligible for capecitabine-docetaxel therapy and that all other anthracycline-docetaxel-pretreated patients would be eligible for capecitabine-docetaxel therapy. Patients with progressive disease following capecitabine-docetaxel therapy were assumed to be eligible for further salvage treatment with vinorelbine.

**Measure of benefits used in the economic analysis**
The summary measures of health benefit were the number of patients projected to be alive at 1 year and the number of life-months gained. The cost-effectiveness ratios used the number of life-years gained (LYG), which were derived from the above.

**Direct costs**
The Canadian public health care system was used as the base-case perspective for the analysis. It was reported that the model considered all the medical costs during treatment and the treatment costs after subsequent disease progression. The authors also reported that the perspective of the analysis was restricted to the costs that would be accumulated at the hospital level and, in the case of oral therapy, at the drug benefit programme level. Discounting was not carried out, which was appropriate as the time horizon extended for 1 year only. The unit costs were estimated using actual data collected from published list prices and published studies. Resource use was collected during the trial up to 15 February 2001, which ended 15 months' follow-up. A price year was not reported.

**Statistical analysis of costs**
The costs were treated stochastically.

**Indirect Costs**
The authors stated that the indirect costs and direct non-medical costs were not included in the analysis.

**Currency**
Canadian dollars (Can$).

**Sensitivity analysis**
One-way sensitivity analyses were carried out to assess the impact of disparities between the trial setting and current clinical practice in Ontario. In particular, the dose of docetaxel and the costs associated with treating adverse events were varied.

**Estimated benefits used in the economic analysis**
The percentage of patients projected to be alive at 1 year multiplied by the Ontario population (n=542) was 251 for docetaxel and 309 for capecitabine-docetaxel. The difference was 59. The total number of life-months gained was 6,016 for docetaxel and 7,425 for capecitabine-docetaxel. The difference was 1,409.

**Cost results**
The total cost per patient was $13,659 for treatment with capecitabine-docetaxel and $12,833 for treatment with docetaxel. The difference was $826.

**Synthesis of costs and benefits**

The incremental cost for capecitabine-docetaxel combination therapy compared with single-agent docetaxel therapy was $3,691 per LYG.

When the dose of docetaxel monotherapy was reduced by 25%, the cost-effectiveness ratio increased to $12,961 per LYG.

When the costs of treating adverse events were discarded, the cost-effectiveness ratio became $12,444 per LYG.

**Authors' conclusions**

The cost-effectiveness ratio compared favourably with proposed cut-offs for cost-effectiveness. "Capecitabine/docetaxel therapy is a highly active and cost-effective new treatment option for women with anthracycline-pretreated MBC (metastatic breast cancer)."

**CRD COMMENTARY - Selection of comparators**

The authors compared single-agent docetaxel therapy with the capecitabine-docetaxel combination therapy. The choice of the comparator was justified through a discussion of the relative merits of combining treatments. Single-agent treatment with docetaxel was reported to be one of the most active therapies available.

**Validity of estimate of measure of effectiveness**

The analysis used a randomised controlled trial, which was appropriate for the study question. Few details of the study design and study sample were reported in the published economic evaluation; reference was only made to the original clinical paper. It was therefore impossible to evaluate the validity of the clinical evidence from this paper. The quality of the effectiveness data was described in the original paper (see Other Publications of Related Interest).

**Validity of estimate of measure of benefit**

The summary measure of health benefit was the LYG. These were obtained through modelling.

**Validity of estimate of costs**

The authors stated that the study was carried out from the perspective of the Canadian Health care system. The analysis included the costs of chemotherapy, infusion, hospitalisation for adverse events, consultations and treatment for adverse events. All the relevant costs seem to have been included. The authors were explicit about not including non-medical and indirect costs. The unit costs and the quantities were not reported separately. The price year was not reported.

**Other issues**

The authors made appropriate comparisons of their findings with those from other studies. They highlighted the ability to adapt the model to enable the generalisability of the results across countries. The results were not presented selectively. The authors' conclusions accurately reflected the nature of the patients enrolled in the study. A number of limitations were presented. For example, not using a measure of patient utility, the assumptions made, and the failure to account for any potential prolonged use of capecitabine or its use in patients who have not received taxane treatment before. The authors presented the results of their analysis clearly and gave a valuable discussion of reasons for the results obtained.

**Implications of the study**
The authors did not make any recommendations for policy or practice, although the preference for using combination therapy was clear. Further analysis using a crossover design was suggested, in order to explore the issue of sequencing treatments versus choosing an effective combination.

**Source of funding**
None stated.

**Bibliographic details**

**PubMedID**
12773745

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Antibiotics, Antineoplastic /economics /therapeutic use; Antibodies, Monoclonal /administration & dosage /economics; Antibodies, Monoclonal, Humanized; Antimetabolites, Antineoplastic /administration & dosage /economics; Antineoplastic Agents, Phytogenic /administration & dosage /economics; Antineoplastic Combined Chemotherapy Protocols /economics /therapeutic use; Breast Neoplasms /drug therapy /economics /mortality; Bridged Compounds /administration & dosage /economics; Budgets; Capecitabine; Cost-Benefit Analysis /economics; Deoxycytidine /administration & dosage /economics; Dose-Response Relationship, Drug; Female; Fluorouracil /analogs & derivatives; Follow-Up Studies; Humans; Neoplasm Metastasis; Ontario; Paclitaxel /administration & dosage /analogs & derivatives /economics; Population Surveillance; Survival Analysis; Taxoids; Trastuzumab; Treatment Outcome; Vinblastine /administration & dosage /analogs & derivatives /economics; Women's Health

**AccessionNumber**
22003009514

**Date bibliographic record published**
31/07/2004

**Date abstract record published**
31/07/2004