Capecitabine plus docetaxel combination therapy

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
Two treatment options for patients with anthracycline-pretreated metastatic breast carcinoma were examined. The options were capecitabine (CAP) plus docetaxel (DOC) combination therapy and DOC alone. In the former (CAP+DOC), oral capecitabine (1,250 mg/m² twice daily) was given on days 1 - 14, followed by a 7-day rest period, with docetaxel (75 mg/m²) administered as a 1-hour intravenous (i.v.) infusion on the first day of each 3-week cycle. In the latter, DOC (100 mg/m²) was administered as a 1-hour i.v. infusion on the first day of each 3-week cycle.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised patients with anthracycline-pretreated metastatic breast carcinoma.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were derived from a single study published in 2002. The price year appears to have been 2001, although some costs came from sources published in 2003.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the clinical study.

Study sample
Limited information on the methods used to select the sample and the design of the primary study was reported in the current pharmacoeconomic study. An overall sample of 511 patients was included in the analysis, of which 255 were in the CAP+DOC group and 256 in the DOC group. The median age of the patients was 52 years (age range: 26 - 79) in the CAP+DOC group and 51 years (age range: 25 - 75) in the DOC group.
Study design
This was a prospective, multi-centre, randomised, Phase III clinical trial. The evidence came from 75 centres in 16 countries. Patients were followed up to a maximum of 2.9 years when less than 20% of individuals were still alive. Tumour responses were assessed at 6-week intervals until week 48 and at 12-week intervals thereafter. No other information was given.

Analysis of effectiveness
The outcome measures used in the effectiveness analysis were:

- the reduction in the risk of death,
- the median overall survival,
- the incidence of treatment-related adverse events,
- the global health score,
- the duration of time to disease progression, and
- the duration of post-disease progression survival.

The study groups were comparable at baseline in terms of their demographic and clinical characteristics.

Effectiveness results
Patients receiving combination therapy had a 23% reduction in the risk of death compared with single-agent DOC.

The median overall survival was 14.5 months in the combination arm and 11.5 months in the DOC arm. The hazard ratio was 0.775 (95% confidence interval: 0.634 - 0.947; p=0.0126).

The incidence of treatment-related adverse events was similar in the combination and single-agent arms (98% versus 94%, respectively).

The proportion of patients that experienced Grade 3 treatment-related adverse events was higher in the combination arm than in the single-agent DOC arm (71% versus 49%). Further, 25% of patients in the combination arm experienced Grade 4 treatment-related adverse events compared with 31% in the single-agent DOC arm.

The difference in the global health score between groups did not reach statistical significance.

Clinical conclusions
The effectiveness analysis showed that, in general, better outcomes were associated with the combination treatment.

Modelling
A Markov model was constructed to assess the economic impact of the two treatments over a period of 2.9 years (which represented the last observed follow-up time in the clinical trial) in a cohort of patients with anthracycline-pretreated metastatic breast carcinoma. No further details on the decision model were reported.

Measure of benefits used in the economic analysis
The summary benefit measures used were the expected survival and quality-adjusted life-years (QALYs). The utility weights were derived from published clinical trials (three Phase II and III studies) because they were not gathered alongside the clinical trial. Patient preferences were elicited using both the standard gamble technique and the visual analogue scale. Other details of the published sources were reported. A value of 0.73 was attributed to disease.
progression-free survival, while a value of 0.48 was given to weight survival after disease progression. An annual rate of 3% was used to discount the expected (quality-adjusted) survival.

Direct costs
The authors stated that the cost analysis was performed from the perspectives of the payer and the patient. However, only the direct medical costs were included in the analysis. The health services considered were hospital admissions (including admission diagnosis and length of stay), study medication (including cumulative dose, infusion duration and frequency), treatments for adverse events (medicines and procedures) and outpatient consultations. Out-of-pocket non-medical expenses were excluded. The unit costs were presented separately from the quantities of resources used for most items. Resource use was mainly derived from the clinical trial. The costs came from average wholesale prices, Medicare reimbursement rates and hospital statistics. Discounting was relevant since the costs were incurred during 2.9 years, thus an annual discount rate of 3% was applied. The price year might have been 2001.

Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not considered in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
A series of univariate sensitivity analyses were performed to assess the robustness of the cost-effectiveness and cost-utility estimates to variations in the model inputs. For example, medical resource use cost, duration of disease progression-free survival and survival after disease progression, utility for each health state, and discount rate. The alternative values were either derived from the literature or set by the authors. A two-way sensitivity analysis was also carried out on time to disease progression and overall survival times. A Monte Carlo simulation was used to derive a cost-effectiveness distribution, assigning a probability distribution to all model inputs.

Estimated benefits used in the economic analysis
After discounting, the mean duration of survival was 1.38 years with CAP+DOC combination therapy and 1.16 years with DOC alone (difference 0.22 years). The estimated discounted QALYs were 0.81 with CAP+DOC and 0.66 with DOC alone (difference 0.15 years).

Cost results
The estimated total costs per patient were $24,475 with CAP+DOC combination therapy and $22,477 with DOC alone (difference $1,998, 8.9%).

The extra cost of CAP was offset, in part, by the reduced dose of DOC in the combined therapy and the reduced hospitalisation costs for adverse events.

Small additional costs for consultations and medications for treatment of adverse events were observed in the combination arm.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine the costs and benefits of the
two treatments.

The incremental cost per life-year gained with CAP+DOC combination therapy over DOC alone was $9,163.

The incremental cost per QALY gained with CAP+DOC combination therapy over DOC alone was $13,558 (+/- 6,742) (interquartile range: 16,432 - 25,211).

The sensitivity analysis showed that variations in the cost of DOC or CAP had the greatest impact on the model result, with the cost per QALY ranging from cost-saving to more than $50,000 when the two extreme values of the published confidence interval were used. Variations in the other model inputs did not alter substantially the conclusions of the base-case analysis, and the incremental cost-effectiveness ratio remained lower than $25,000 per QALY in all cases. The Monte Carlo simulation revealed that the probability of the cost-effectiveness ratio being $26,000 or more was less than or equal to 25%.

Authors' conclusions
The survival benefit with the combined regimen was achieved at a small incremental cost. In addition, the cost per quality-adjusted life-year (QALY) compared favourably with that of other commonly implemented oncologic interventions.

CRD COMMENTARY - Selection of comparators
The rationale for the selection of the comparators was clear. The two interventions were chosen as they had been the treatments examined in the primary clinical trial used to provide the data. The dosages were reported. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data came from a clinical trial, which was appropriate for the study question. The use of a randomised and multi-centre design ensures a high internal validity. Further, the study groups were comparable at baseline. However, the trial had been published elsewhere, and limited information on the design of the study was provided.

Validity of estimate of measure of benefit
The benefit measures used in the analysis were appropriate as they capture the impact of the interventions on the most relevant dimensions of care (i.e. survival and quality of life). The use QALYs and expected survival enables comparisons with the benefits of other health care interventions. Some information on the source used to derive the utility weights was provided. Discounting was applied, as recommended by US guidelines. The impact of different discount rates and utility weights was investigated in the sensitivity analysis.

Validity of estimate of costs
The cost analysis was carried out from the perspective of the payer, and some patient costs appear not to have been included in the analysis. The unit costs were presented separately from the quantities of resources used for most items, which enhances the possibility of replicating the results of the analysis in other settings. The source of the cost data was reported and was consistent with the perspective of the study. The cost estimates were treated deterministically but were varied in the sensitivity analysis. Different discount rates were also applied. The price year was not totally clear, which limits the possibility of performing reflation exercises in other time periods.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies, although they reported the results of a meta-analysis of oncology studies where the median cost per QALY of the oncology intervention was estimated to be around $20,000. The combination therapy under investigation was estimated to be
associated with a cost-effectiveness ratio more favourable than approximately 85% of the oncology cost-effectiveness ratios reported in the meta-analysis. The issue of generalisability of the study results to other settings was not explicitly addressed, although extensive sensitivity analyses were performed. These enhance the external validity of the study. The authors stated that the resource use data were not collected after disease progression, which might represent a limitation of the study. However, it appears that resource consumption associated with subsequent care of patients was similar across the study groups. A justification was provided for the time horizon used in the model.

**Implications of the study**
The study results supported the use of the CAP+DOC combination in comparison with standard single-agent DOC. The authors stated that improvements in patient education could play an important role in helping patients to recognise side effects and their severity, permitting them to reduce the impact of severe toxicity. This could also reduce the number of consultations, thus making the combination therapy even more cost-effective.

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