Is combined androgen blockade with bicalutamide cost-effective compared with combined androgen blockade with flutamide

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Health technology
The study examined combined androgen blockade (CAB) in the treatment of men with Stage D2 prostate cancer. CAB comprised a luteinising, hormone-releasing, hormone (LHRH) agonist plus an androgen receptor blocker, either bicalutamide 50 mg or flutamide 250 mg.

Type of intervention
Treatment.

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

Study population
The study population comprised a hypothetical cohort of patients with Stage D2 prostate cancer.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data and most resource use data were derived from studies published in 1997 and 2000. Some costs were estimated in 2004, but the price year was not stated clearly.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of studies and authors' assumptions.

Modelling
A decision model was constructed to assess the costs and benefits of the two combination treatments. A simplified version of the model was reported. Two time horizons, 5 and 10 years, were chosen. Patients in either arm could experience moderate or severe diarrhoea. Patients in the flutamide arm with severe diarrhoea were switched to bicalutamide. Bicalutamide was discontinued in patients with severe diarrhoea, although patients continued taking the LHRH agonist indefinitely. The outcome states included stable disease, disease progression and death. Other adverse events were not considered because they did not significantly affect quality of life and were not significantly different between groups, as the head-to-head clinical trial had shown.

Outcomes assessed in the review
The outcomes estimates from the literature were the time to prostate cancer progression, the utility values associated
with specific health states, and the probabilities of moderate or severe diarrhoea with the two drugs.

**Study designs and other criteria for inclusion in the review**
A review of the literature does not appear to have been carried out to identify primary studies. A head-to-head clinical trial of flutamide and bicalutamide was used to derive data on treatment efficacy. Details of the other sources of data were not given.

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

**Criteria used to ensure the validity of primary studies**
The use of a clinical trial should have ensured the validity of the primary estimates.

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

**Number of primary studies included**
The clinical data were mainly derived from two primary studies.

**Methods of combining primary studies**
The primary estimates were not combined.

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

**Results of the review**
The median time to prostate cancer progression in the analysis was 97 weeks for the bicalutamide plus LHRH group versus 77 weeks for the flutamide plus LHRH group.

The base utility for late-stage prostate cancer was 0.800 (range: 0.600 - 0.900).

The utility decrement (additive) was 0.180 (range: 0.120 - 0.250) for severe diarrhoea and 0.120 (range: 0.000 - 0.200) for moderate diarrhoea.

The utility values were: 0.400 (range: 0.200 - 0.480) in the month of death; 0.650 (range: 0.325 - 0.780) 6 months before death; 0.600 (range: 0.300 - 0.720) 5 months before death; 0.550 (range: 0.275 - 0.660) 4 months before death; 0.500 (range: 0.250 - 0.600) 3 months before death; and 0.450 (range: 0.225 - 0.540) 2 months before death.

With bicalutamide, the probability of severe diarrhoea was 0.005 (range: 0.004 - 0.006) and the probability of moderate diarrhoea was 0.115 (range: 0.092 - 0.138).
With flutamide, the probability of severe diarrhoea was 0.060 (range: 0.048 - 0.072) and the probability of moderate diarrhoea was 0.200 (range: 0.160 - 0.240).

**Methods used to derive estimates of effectiveness**
The authors made some assumptions that were used to model the outcomes in the two arms of the model.

**Estimates of effectiveness and key assumptions**
It was assumed that the occurrence of diarrhoea during flutamide therapy did not correlate with the likelihood of diarrhoea when taking bicalutamide. Utility decrements for side effects were assumed to be additive to the utility effects of stable and progressive metastatic prostate cancer.

**Measure of benefits used in the economic analysis**
The summary benefit measures used were the life-years (LYs) and quality-adjusted life-years (QALYs). These were estimated using a modelling approach. There was limited information on the calculation of QALYs and the approach used to derive the utility weights. An annual discount rate of 3% was applied.

**Direct costs**
The cost analysis took the perspective of the health insurer. The health services considered were drugs, diarrhoea treatment, doctor visits, and health care in the 6 months before death. The unit costs were presented separately from the quantities of resources used for most items. However, the costs of health care during the last 6 months of a patient's life were presented as a macro-category. Resource use was estimated from published data, while the costs came from average wholesale prices, Medicare reimbursement rates and a published study. Discounting was relevant as the costs were incurred during a long timeframe. The price year was not explicitly stated, although the drug costs were estimated using 2004 prices.

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

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

**Currency**
US dollars ($).

**Sensitivity analysis**
Univariate and multivariate sensitivity analyses were carried out to assess the robustness of cost-utility estimates to variations in the model inputs. Ranges of values were either derived from the literature or set by the authors. The multi-way analysis was displayed as a cost-effectiveness acceptability curve.

**Estimated benefits used in the economic analysis**
The benefits associated with the two interventions were not reported.

**Cost results**
The total costs were not reported.
**Synthesis of costs and benefits**

Incremental cost-effectiveness and cost-utility ratios were calculated to combine the costs and benefits of the alternative combination therapies.

After 5 years, the incremental cost per LY gained with bicalutamide versus flutamide was $20,000 and the incremental cost per QALY gained was $22,000. The results at 10 years showed modest improvements in comparison with 5-year data.

The sensitivity analysis showed that the cost of bicalutamide and differences in survival were the main drivers of the model results. At the lowest limit of survival for CAB with bicalutamide, the incremental cost per QALY gained was approximately $45,000. As the price of bicalutamide fell to the minimum of its range, bicalutamide became the dominant strategy (lower cost and increased survival) compared with flutamide.

Changes in other model inputs did not affect the cost-effectiveness of bicalutamide.

The cost-effectiveness acceptability curve showed that the value of the ceiling ratio ($13,637) at a probability of 0.5 was the median cost per QALY for bicalutamide plus an LHRH agonist.

**Authors' conclusions**

Bicalutamide was cost-effective in comparison with flutamide when used as part of combined androgen blockade (CAB) for men with advanced prostate cancer. The results of the sensitivity analysis confirmed the robustness of the base-case results but also highlighted the importance of the acquisition cost of bicalutamide.

**CRD COMMENTARY - Selection of comparators**

The rationale for the choice of the comparators was clear as the two most commonly used anti-androgens were selected. The dosages were clearly reported. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness data were estimated from published studies. It was not stated whether a systematic review of the literature was undertaken to identify the primary studies, which might have been included selectively. The evidence on treatment efficacy came from a head-to-head clinical trial, which had a high internal validity due to its randomised design and long follow-up. However, details on the design and patients' characteristics were not reported. There was also limited information on the study used to estimate other clinical inputs. The authors made some assumptions because of the lack of published evidence or because of the uncertainty in some data. The reasons for the exclusion of some adverse events were clear. The issue of variability in the data was addressed in the sensitivity analysis.

**Validity of estimate of measure of benefit**

QALYs and LYS are the most appropriate benefit measures because they capture the impact of the intervention on both quality of life and survival, which are the most relevant dimensions of care for patients with prostate cancer. Details of the approach used to derive utilities were not reported. The use of QALYs allows comparisons with the benefits of other health care interventions. Discounting was applied, as recommended by economic evaluation guidelines.

**Validity of estimate of costs**

The cost analysis was consistent with the perspective adopted in the study. The unit costs were presented separately from the quantities of resources used for most items. Only the costs of cancer care were presented using a macro-category, which is quite common for consumption of health care resources in patients with cancer. Since such costs were derived from a previous study, no details of the items and unit costs were provided. The source of the data for the other cost categories was reported. The cost estimates were varied in the sensitivity analysis, but statistical analyses of the costs were not performed. The price year was not explicitly stated, which limits the possibility of reflating the cost results in other time periods.
Other issues
The authors stated that few economic evaluations of CAB for advanced prostate cancer had been published, thus they could not make extensive comparisons with the results from other studies. The issue of the generalisability of the study results to other settings was not explicitly addressed. However, the use of a sensitivity analysis enhances the external validity of the study results. The study referred to patients with advanced prostate cancer and this was reflected in the authors' conclusions. The results of the analysis were reported selectively. The authors noted that the main limitation of the analysis was the uncertainty around some model inputs, but the sensitivity analysis led to the identification of the most relevant model drivers.

Implications of the study
The study results suggested that CAB with bicalutamide is a cost-effective strategy for the treatment of patients with advanced prostate cancer.

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