Estimating the cost effectiveness of total androgen blockade with flutamide in M1 prostate 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
Combined androgen blockade with flutamide plus medical or surgical castration.

Type of intervention
Treatment.

Economic study type

Study population
Hypothetical cohorts of 70 year old men with newly diagnosed, untreated metastatic prostate cancer with good performance status.

Setting
Secondary care.

Dates to which data relate
The effectiveness data was taken from a trial published in 1989. 1993 prices were used.

Source of effectiveness data
Based on a review/synthesis of previously completed studies.

Link between effectiveness and cost data
No attempt was made to count individual patient's charges or the true cost of care. For each health state the costs of ongoing care were based on Medicare payments.

Modelling
A decision analysis model using a Markov model was used to model the prognosis of men followed as a large cohort over time.

Outcomes assessed in the review
The outcomes assessed were the time to progression, and average and median survival.
Study designs and other criteria for inclusion in the review
The effectiveness analysis was based on the results of the Intergroup 0036 trial, and for the sensitivity analysis a meta-analysis in addition.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

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

Number of primary studies included
One 'large' controlled US trial: the Intergroup 0036 trial. A meta-analysis synthesizing the results of 9 trials was also used in the sensitivity analysis.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.

Results of the review
The trial found a 26% improvement in median survival among men treated with flutamide and leuprolide compared to leuprolide and placebo. Subsequent follow-up of the original report after 77% of all patients had died found a 20% improvement in median survival.

Measure of benefits used in the economic analysis
The outcome measure used in the economic analysis was life years gained. Future benefits were discounted at 5%. A decision analysis model using a Markov process was used to model the prognosis of the men over time. The model calculated the cumulative value of outcomes for the men: the prognosis for each group was determined by the movement between health states over time. In the model transitions occurred at 3 month intervals until a finite follow-up period or until all patients died. The Markov model used a 3 month cycle, since this is the common interval after which response to initial therapy is determined and follow-up occurs in stable patients. After the initial 3 months, patients will move to one of four health states: response with therapy, no progression, progression, or death from disease progression or other causes. A patient's subsequent diagnosis depends on the state of health at the start of the next cycle. The sensitivity analysis included the evaluation of quality-adjusted life-years gained, albeit based on arbitrary quality-of-life scores.

Direct costs
Costs were considered from a third-party payer perspective (specifically, all direct health care costs paid by Medicare or the Department of Veterans Affairs). This perspective assumes that medication such as flutamide has small out-of-pocket cost. The cost for orchiectomy was based on typical 1993 Medicare reimbursements assuming it was an outpatient procedure. The cost for goserelin, leuprolide acetate and flutamide were based on the 1994 average wholesale price, a survey of local pharmacies, and included an office visit for LHRH analogues. Costs were
discounted at 5% and for ongoing care adjusted to a 1993 base year.

**Currency**
US dollars ($).

**Sensitivity analysis**
Single variable changes were carried out for all variables and selected results. Analysis of extremes, probabilistic and threshold sensitivity analysis were performed for some variables.

**Estimated benefits used in the economic analysis**
For severe disease, after 7 years 96% of patients in the monotherapy cohort (orchiectomy or LHRH) had died with the median and average survivals of 29.5 and 34.4 months, respectively. Using a relative efficacy of 25%, the flutamide cohort (orchiectomy/LHRH + flutamide) had a median and average survival of 34.3 and 39.2 months. For minimal disease, after 10 years 94% of the monotherapy cohort (orchiectomy or LHRH) had died with the median and average survivals of 42.3 and 50.0 months. Using a relative efficacy of 25%, the flutamide cohort (orchiectomy/LHRH + flutamide) had a median and average survival of 49.4 and 56.9 months.

**Cost results**
When used as monotherapy, the costs to progression of LHRH analogues were greater than if an orchiectomy was done by $3810 - $6540 for severe disease and $8510 - $14,050 for minimal disease. Using the baseline flutamide efficacy of 25% the total care costs to progression of flutamide and orchiectomy were similar to using leuprolide alone ($10,280 versus $10,100) in severe disease patients and was actually lower in minimal disease patients ($15,030 versus $18,180). Compared to orchiectomy alone, total costs to progression of leuprolide plus flutamide were $15,590 to $26,960 greater.

**Synthesis of costs and benefits**
The costs per additional life-year with flutamide ranged from $13,700 to $25,300 if castration was an orchiectomy. For flutamide with LHRH analogues the cost per life year gained ranged from $18,600 to $32,200. Sensitivity showed the most important variable was the range of flutamide efficacy. Using a preliminary overview estimate of 10% efficacy from all flutamide trials (predominantly in patients with severe disease) the benefit is 1.5 months for severe and 1.9 months for minimal disease patients at an incremental cost ranging from $47,500 to $60,900 per year. If such a modest benefit is observed in larger, continuing trials then the general use of flutamide would be very expensive. Changes in the cost and duration of flutamide use greatly affected the cost-effectiveness ratio. Reducing the costs of flutamide by 50% the incremental cost per year decreased to $10,300 (severe disease) and $13,000 (minimal disease).

**Authors' conclusions**
Flutamide has an incremental cost-effectiveness more favourable than most accepted therapies. If drug costs are covered under health care reform, flutamide should be initiated and covered for all good performance status patients.

**CRD Commentary**
As the authors noted, there is a lack of consensus on the efficacy of first line hormonal therapy and flutamide, and further trial results are required before a firmer assessment of cost-effectiveness can be made. Adverse effects of flutamide (diarrhoea and hepatotoxicity) were not considered in the model and the model therefore slightly over-estimated the cost-effectiveness of flutamide as there may be additional costs incurred because of these adverse effects (e.g. additional investigations, liver function monitoring).

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