Economic evaluation of chemotherapy with mitoxantrone plus prednisone for symptomatic hormone-resistant prostate cancer: based on a Canadian randomized trial with palliative endpoints


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
Initial mitoxantrone and prednisone (M+P) was compared to prednisone alone (P) in patients with symptomatic hormone-resistant prostate cancer (HRPC).

Type of intervention
Palliative care.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with symptomatic HRPC and pain. No further inclusion or exclusion criteria were reported.

Setting
The setting was tertiary care. The economic study was carried out in Canada.

Dates to which data relate
The dates during which the effectiveness evidence and resource use data were collected were not reported. The authors collected resources from a chart review conducted between June 1996 and October 1996. The price year was 1996.

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

Link between effectiveness and cost data
Retrospective costing was carried out on the same patient sample as that used to collect the effectiveness evidence.

Study sample
No power calculations were reported. The method of sample selection was not reported. There was no clear evidence that the initial study sample was appropriate for the clinical study question. A total of 161 patients with pain were initially randomised to M+P or P alone. This paper reported the findings from the three centres that enrolled the bulk of the patients (n=114; 61 in the M+P group and 53 in the P group). Forty-seven patients were excluded from this economic study because they were enrolled from 8 other centres across Canada. Non-responding patients who were randomised to the P arm could receive M subsequently and 29 patients subsequently crossed over from the P alone
Study design
This study used a multi-centre (three Canadian hospitals) crossover, randomised, controlled, trial design. Patients were followed-up from the start of treatment until death. The median survival follow-up time was 11 months. The authors did not report whether any patients were lost to follow-up in this economic study. At the time of resource collection, six of the 114 patients were alive (4 in the M+P group and 2 in the P group). The authors did not report the method used to mask participants (health care professionals and patients) or health care investigators to treatment allocation for the assessment of outcomes.

Analysis of effectiveness
The basis for the analysis of the clinical study (intention to treat or treatment completers only) was not stated. The primary health outcome was a palliative response, which was measured by a two-point reduction in a six-point scale completed by the patients without an increase in analgesic medication, and maintained for two consecutive evaluations at least three weeks apart.

The groups were comparable in terms of survival and baseline patient characteristics. There was a tendency for the M+P group to have a higher baseline analgesic score, (p<0.003).

Effectiveness results
The M+P group were more likely to have a palliative response (23 of the 80 patients (29%), 95% CI: 19 - 40 patients) compared to the P group (10 of the 81 patients (12%), 95% CI: 6 - 22 patients, p<0.01).

Eleven of the 50 patients initially randomised to the P group responded after the addition of mitoxantrone.

Clinical conclusions
The authors concluded that M+P results in a clinically and statistically significant proportion of patients with HRPC achieving pain relief.

Modelling
Survival curves were reported for the two treatment arms.

The mean cumulative costs for the two initially randomised groups were plotted as a function of time. This was necessary because the study used a crossover design and the two treatment arms did not have comparable time periods. The authors explained that in this trial there was no fixed time period at which the two treatment arms could be compared without the confounding effect of the crossover.

Measure of benefits used in the economic analysis
Quality-adjusted life years (QALYs) were used as the measure of benefit in the economic analysis. Patients in the trial completed the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 global quality of life rating scale questionnaire every three weeks. The quality of life scale was transformed to give an estimate of utility using a published transformation formula: utility = 1.07 x rating scale value (R) for R<0.95, 1.00 x R for R>0.95. This transformation was used to account for the lower utility obtained when a person described quality of life without risking any possible loss to that individual.

Direct costs
Quantities and costs were not reported separately. The time horizon started from randomisation until death (n=108 patients) or last recorded follow-up (n=6 patients who were still alive at the end of the study). The direct costs included
were: days of inpatient admissions (cancer centre, intensive care unit, community hospital, hospice); outpatient clinics; day care; chemotherapy; radiation therapy; hormonal therapy; outpatient drugs; diagnostic and laboratory investigations. Homecare costs and costs to patients and their families were not included in the analysis. The estimation of the quantities was based on a chart review and was recorded by date, which could be related to the randomisation date. The estimation of each of the direct costs was based on: admission to a cancer centre in the Princess Margaret Hospital in Toronto using the hotel method; physician services with the Ontario Health Insurance Plan (OHIP) fee schedule; OHIP fee schedule for investigations; Ontario Drug Benefit formulary; published review of external beam radiation; blood products from the Canadian Red Cross Society; and OHIP for surgery staff costs.

The quantity of resources was measured between June and October 1996. The price year was 1996. Costs were corrected to 1996 prices using the Statistics Canada Consumer Price Index for all items. Discounting was, appropriately, not carried out, due to the short time-frame (less than one-year) of the study.

**Statistical analysis of costs**
Costs were analysed using Student's t test, a log transformation and non-parametric statistical tests. The authors only reported the Student's t tests because the results with each type of test were similar.

**Indirect Costs**
Indirect costs were not reported.

**Currency**
Canadian dollars (Can$). The baseline analysis was repeated using cost estimates derived from an American academic centre and Canadian costs were converted to US$, using the 1996 exchange rate (US$0.73 = Can$1).

**Sensitivity analysis**
One-way sensitivity analyses were carried out using the following input parameters: inpatient and outpatient costs (varied by 25%); laboratory and diagnostic costs (varied by 50%); surgery costs (varied by 500%).

**Estimated benefits used in the economic analysis**
There was a mean of 41.5 quality-adjusted weeks associated with the M+P group and 28.2 quality-adjusted weeks associated with the P group.

The incremental benefits were 13.3 quality-adjusted weeks per patient for the strategy of initial mitoxantrone (M+P).

**Cost results**
The mean total cost from randomisation to death was Can$27,300 (US$ 21,900) for patients randomised to the M+P group.

The mean total cost from randomisation to death was Can$29,000 (US$ 23,350) for patients randomised to the M+P group.

**Synthesis of costs and benefits**
The M+P group resulted in an overall cost saving of Can$1,700 per patient (95% CI: -Can$9,200 to +Can$5,800) and an additional 13.3 quality-adjusted weeks. It was therefore not relevant to calculate an incremental cost-utility ratio for the baseline analysis.

An incremental analysis was performed for the upper 95% CI for the cost estimate (Can$5,800) of the M+P strategy and the value was Can$19,700 per QALY gained.
Changing the input parameters for the costs estimates did not alter the overall reduction associated with the M+P group.

Authors’ conclusions
The authors concluded that the use of M+P in symptomatic HRPC seems to be an appropriate use of resources in regions with costs and health systems similar to Canada.

CRD COMMENTARY - Selection of comparators
The authors did not provide any justification for the choice of the comparator (P) in this study. It would appear that P alone was a relevant comparator for the treatment of symptomatic HRPC in Canada. You, as a user of the database, should decide if this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a cross-randomised controlled trial, which was appropriate for the study question. The study sample was representative of the study population. The patient groups were comparable at analysis, with the exception of initial pain levels, which were higher in the M+P group.

The approach used to analyse the effectiveness data, in terms of treatment completers or intention to treat, was not reported. The study did not report any power calculations. It was therefore not possible to determine if the study sample was adequate to detect statistical differences in effectiveness.

Validity of estimate of measure of benefit
The summary measure of benefit was quality-adjusted life weeks. The value of survival was estimated as utility, which was based on transformed quality-adjusted life year valuations and appeared to be appropriate for the study question.

Validity of estimate of costs
All categories of costs relevant to the study perspective were included in the analysis. The authors explained that costs to the family doctor and homecare costs were omitted from the analysis because it was not possible to value them accurately. Indirect costs were also omitted from the analysis. The authors did not suggest whether this omission would affect the conclusions reached from the results of the study.

Costs and quantities were not reported separately. It is not clear if unit costs or charges were used to value costs. The study included a statistical analysis of cost data. The authors suggest that the study sample was based on a clinical outcome measure rather than cost data and that the study may not have been large enough to detect a statistical difference in costs. The authors compared two approaches for the analysis of the cost data because these were positively skewed and presented the results of a parametric test, the Student’s t test. Fieller’s theorem was used to estimate 95% confidence intervals around the cost and utility data. An alternative approach would have been to use non-parametric bootstrapping but the economic literature is not clear regarding which approach should be used. A sensitivity analysis of costs was conducted using appropriate ranges of the input parameters. The study did not explore the sensitivity of the results to utility estimates, which may affect the generalisability of the benefit measure. The authors explored the impact of using North American rather than Canadian price estimates. All costs were incurred over one year and discounting was, therefore, unnecessary.

Other issues
The authors made appropriate comparisons of their findings with those from other studies and the issue of generalisability to other settings was addressed. The authors suggested that the results of this study should only be generalised to other settings with a health care system similar to Canada. The methods and results of the randomised controlled trial were published in a separate paper. The authors pointed out that optimisation of analgesia was a requirement of entry to the trial. It is possible that further methods of pain control could prevent future hospitalisations but the study did not address this issue. The authors’ conclusions reflected the scope of the analysis.
Implications of the study
The authors suggested that the decision to use M+P in a patient with pain from HRPC should be based on clinical and not economic considerations. The authors suggested that future studies could assess measures of palliation and economic issues in a comparison of treatment versus best supportive care co-ordinated by a palliative care physician.

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