Cost-utility analysis of the GC versus MVAC regimens for the treatment of locally advanced or metastatic bladder cancer


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 two alternative treatments for patients with locally advanced or metastatic bladder cancer, gemcitabine and cisplatin (GC) versus methotrexate, vinblastine, doxorubicin and cisplatin (MVAC). For the 28-day cycle of GC, the dosages were 1,000 mg/m² gemcitabine on days 1, 8 and 15, and 70 mg/m² cisplatin on day 2. For the 28-day cycle of MVAC, the dosages were 30 mg/m² methotrexate on days 1, 15 and 22, 3 mg/m² vinblastine on days 2, 15 and 22, 30 mg/m² doxorubicin on day 2, and 70 mg/m² cisplatin on day 2.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with measurable (or assessable) and histologically proven locally advanced (T4b, N2, N3) or metastatic (M1) bladder cancer. The patients had a Karnofsky performance status of at least 70, adequate bone marrow reserve and renal function, and an estimated life expectancy of at least 12 weeks. Adequate bone marrow reserve was indicated by a white blood cell count of at least 3.5 x 10⁹/L, platelet levels of at least 100 x 10⁹/L, and a haemoglobin level of at least 10 g/dL. Adequate renal function was indicated by a measured creatinine clearance of at least 60 mL/minute. Patients with non-malignant systemic disease that precluded them from receiving study therapy, or patients who were pregnant, were not eligible. Also excluded were patients with central nervous system metastases, second primary malignancy (except in situ carcinoma of the cervix or adequately treated basal cell carcinoma of the skin), or clinically significant pleural effusions or ascites, and patients who used any investigational agent one month before treatment initiation.

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

Dates to which data relate
The dates during which the effectiveness and resource use data were gathered were not reported. The authors stated that the enrolment period was November 1996 to September 1998. The price year is likely to have been 2001.

Source of effectiveness data
The effectiveness evidence was derived from a single study, the main details of which have been published elsewhere (von der Maase et al., see Other Publications of Related Interest).
Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were performed in the planning phase of the study. These suggested that a sample of 400 patients (200 per arm) was required to detect a 33% difference in survival between the arms at a significance level of 5% and a power of 0.20. Of the 426 patients who entered the study, 405 were randomised to the two groups. There were 203 patients in the GC arm and 202 in the MVAC arm. In the GC arm, the median age was 63 years and 78.8% of the patients were male. In the MVAC arm, the median age was 63 years and 79.2% of the patients were male. However, 9 patients (3 in the GC arm and 6 in the MVAC arm) did not receive the study drugs. Of the 21 patients who were not randomised, 19 did not meet the protocol entry criteria, one died from bladder cancer, and one refused to participate for personal reasons.

Study design
This was a prospective, multi-centre and multi-national randomised, open-label, controlled (Phase III) trial. The method of randomisation was reported. The patients were stratified according to their performance status, stage, visceral metastases, alkaline phosphatase level, prior radiotherapy, measurable disease, and site. The patients were followed until they died. No loss to follow-up was observed. Independent blinded reviewers confirmed all investigator-determined responses.

Analysis of effectiveness
The basis for the analysis of the clinical study was intention to treat. The primary health outcome was survival (using the Kaplan-Meier approach). The secondary health outcomes were:

- objective tumour response;
- duration of responses;
- times to progressive disease;
- times to treatment failure;
- toxicity;
- changes in performance status and weight; and

evaluations of quality of life (QOL), as estimated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30.

Standard criteria were used for response classification. Hazard ratios (HRs for GC over MVAC) and corresponding confidence intervals (CIs) were calculated using the Cox’s proportional hazards model. A multivariate model was used to assess the impact of determined prognostic factors. The primary outcome measure was the one used in the present economic evaluation. The two groups were comparable at baseline, although more patients in the GC arm had adverse prognostic factors. However, the difference was not significant.

Effectiveness results
Overall survival was comparable in both arms (HR 1.04, 95% CI: 0.82 - 1.32; p=0.75).

There was no statistically significant difference in objective tumour response, duration of responses, times to progressive disease, or times to treatment failure.

The toxic death rate was 1% in the GC arm and 3% in the MVAC arm. Non haematologic toxic events were generally
more frequent in MVAC patients, while haematologic toxic events were generally more frequent in GC patients. The exception to the latter (haematologic toxic events) was neutropenia, which was more frequent in MVAC patients.

Weight improved more in GC patients than in MVAC patients, but the change in performance status was not statistically significant. QOL was maintained in both arms throughout the study.

Clinical conclusions
The effectiveness study showed that the two treatments were equally effective in most of the outcome measures used. However, the safety profile in GC patients was more favourable.

Measure of benefits used in the economic analysis
The summary benefit measure used in the economic analysis was the quality-adjusted life-years (QALYs). These were obtained by combining data on survival and utility weights. Survival was derived from the clinical trial. Utility weights were estimated from a pilot study, which was based on preferences elicited from health care professionals with experience in medical oncology, by means of the time-trade off approach. No discounting was applied due to the short survival of patients with bladder cancer.

Direct costs
Discounting was not applied since the costs per patients were incurred during a short time. The unit costs and the quantities of resources used were not presented separately. The health services included in the economic evaluation were grouped into categories. More specifically, study medications, inpatient administrations, outpatient administrations, hospitalisations, medical procedures, blood transfusions, health professional visits, and concomitant medications. The cost/resource boundary of the NHS was adopted. Resource use was estimated from individualised actual data referring to the same patients as those involved in the effectiveness study. The costs were estimated from the latest NHS sources, manufacturers and the British National Formulary. The price year was 2001.

Statistical analysis of costs
Bias-corrected bootstrapping (based on 2,000 simulations) was used to estimate the cost distribution of the mean cost per patient. The costs were presented as mean values (95% and 68.4% CIs).

Indirect Costs
The indirect costs were not considered.

Currency
UK pounds sterling (€).

Sensitivity analysis
One-way sensitivity analyses were performed to assess the impact of variations in some variables on the estimated cost-effectiveness ratio. The costs varied were inpatient and outpatient chemotherapy administration, and the treatment of adverse events. The variations ranged from +/-25% from the baseline value. The utility weights were also varied.

Estimated benefits used in the economic analysis
The incremental QALYs gained with GC over MVAC were 0.130 (95% CI: 0.105 - 0.188).

Cost results
The mean total cost per patient was 12,609 with GC and 9,633 with MVAC.
The cost difference was largely attributable to the cost of the study medications, which were not completely offset by the fewer resources associated with inpatients hospitalisations and the use of concomitant medications.

The incremental cost of GC over MVAC was 2,976 (95% CI: 2,427 - 3,526).

**Synthesis of costs and benefits**
An incremental cost-effectiveness ratio was calculated to combine the costs and benefits of the study interventions.

The incremental cost per QALY with GC over MVAC was 22,925 (95% CI: 12,911 - 33,589).

The sensitivity analysis showed that the estimated cost-effectiveness ratio was sensitive to variations in inpatient and outpatient administration costs and the cost of treating febrile neutropenia.

No substantial variations were observed in the other sensitivity analyses.

**Authors' conclusions**
Given the currently used threshold of 30,000 per quality-adjusted life-year (QALY), the gemcitabine-cisplatin (GC) regimen was a cost-effective intervention for the treatment of patients with bladder cancer in the UK.

**CRD COMMENTARY - Selection of comparators**
The authors stated that MVAC represented the most commonly used combination therapy for bladder cancer throughout the USA, Europe, Canada and Japan, while GC therapy represented a more recent and less toxic alternative. Phase III trials directly comparing the two treatments had not been published. Therefore, the choice of the comparators appears to have been appropriate. You should decide whether they are valid treatments in your own setting.

**Validity of estimate of measure of effectiveness**
The internal validity of the effectiveness analysis is likely to have been high due to the study design, which was robust and appropriate for the study question. Most of the details on the methods and results were reported in the primary study. Careful attention was given to stratification and baseline comparability of the study groups. Statistical models were applied to assess the impact of potential confounding factors on the effectiveness results. The study sample is likely to have been representative of the study population. Power calculations were performed in the preliminary phase of the study and these justified the sample size. A further strength was the use of intention to treat as the basis for the analysis of the clinical study.

**Validity of estimate of measure of benefit**
The choice of the summary benefit measure (QALYs) was appropriate since the two treatments had a substantial impact on both quality and length of life for patients with bladder cancer. The utility weights were derived from the values of health care professionals. The basic method used to elicit preferences for health states was reported. No discounting was applied due to the short life expectancy of patients with bladder cancer. The use of QALYs means that it is possible to draw comparisons with the benefits of other health care interventions.

**Validity of estimate of costs**
The authors explicitly stated the perspective adopted in the study. It appears that all the relevant categories of costs have been included in the economic evaluation. Details of the unit costs were presented separately from the quantities of resources used, which enhances the possibility of replicating the study in other settings. Reflation exercises are also possible as the price year was implicitly reported. The costs were treated stochastically by using a bootstrapping approach. The estimated costs were then presented as mean values with CIs. The unit costs of some variables were varied in the sensitivity analysis.
Other issues
The authors made some comparisons of their findings with those from other studies. It was also noted that, as only a small fraction of the patients enrolled in the effectiveness study were selected from UK centres, the study has limited external validity. In addition, only limited sensitivity analyses were performed. The study referred to patients with locally advanced or metastatic bladder cancer and this was reflected in the conclusions of the analysis. The authors discussed some limitations of the analysis.

Implications of the study
The authors suggest that the information provided in the current economic evaluation might be helpful in informing the decision-making process.

Source of funding
None stated.

Bibliographic details

Other publications of related interest


Indexing Status
Subject indexing assigned by CRD

MeSH
Acyclovir /administration & dosage /therapeutic use; Alopecia; Anemia; Anti-Bacterial Agents /administration & dosage /therapeutic use; Antifungal Agents /administration & dosage /therapeutic use; Antiviral Agents /administration & dosage /therapeutic use; Ciprofloxacin /administration & dosage /therapeutic use; Cisplatin /adverse effects /administration & dosage /therapeutic use /pharmacology /economics; Clinical Trials as Topic; Costs and Cost Analysis; Diarrhea; Doxorubicin /adverse effects /administration & dosage /therapeutic use /pharmacology /economics; Drug Costs; Erythropoietin, Recombinant /administration & dosage /therapeutic use; Fluconazole /administration & dosage /therapeutic use; Granulocyte Colony Stimulating Factor, Recombinant /administration & dosage /therapeutic use; Humans; Methotrexate /adverse effects /administration & dosage /therapeutic use /pharmacology /economics; Neoplasm Metastasis /prevention & control /drug therapy; Neutropenia; Quality-Adjusted Life Years; Sepsis; Urinary Bladder Neoplasms /prevention & control /drug therapy; Vinblastine /adverse effects /administration & dosage /therapeutic use /pharmacology /economics

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