

A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer

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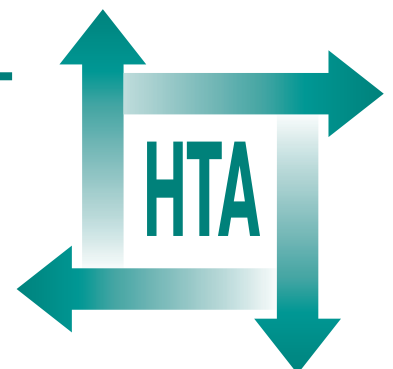
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Executive summary

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Executive summary

Background

Prostate cancer is the most common male cancer, excluding non-melanoma skin cancer, in the UK, accounting for around 13% of male cancer deaths. In 2001, there were 26,027 new cases in England and 1746 in Wales, giving age-standardised incidence rates of 89.8 and 92.6 per 100,000 men, respectively. The majority of patients are diagnosed with early disease and have a good prognosis. However, approximately 22% of cases will be diagnosed with advanced or metastatic disease, with an additional 25% developing metastases throughout the course of the disease. The majority of prostate cancers initially respond to hormone therapy, with a median response duration in metastatic disease of around 18 months. However, in most patients the cancer will become resistant to hormonal treatment and will progress. After developing hormone-resistant disease, survival is not expected to exceed 9–12 months. Treatment for metastatic hormone-refractory prostate cancer (mHRPC) is palliative and current advice issued by the National Institute for Health and Clinical Excellence states that chemotherapy should be considered and trials of chemotherapy supported, and palliative radiotherapy should also be considered as a treatment option. The use of chemotherapy for mHRPC is widespread in the UK. New trials assessing the effectiveness for the treatment of mHRPC of docetaxel, which is licensed for use in combination with prednisone/prednisolone in the UK, have emerged. The cost of a course of up to 10 cycles of docetaxel at the recommended dose is approximately £11,000. Therefore the evidence must be appraised by a systematic review and economic model.

Objectives of the review

A systematic review was undertaken and an economic model constructed to evaluate the clinical effectiveness and cost-effectiveness of docetaxel (Taxotere[®], Sanofi-Aventis) in combination with prednisone/prednisolone for the treatment of mHRPC.

The main comparators considered were other established chemotherapy regimens and best supportive care.

Methods

Search strategy

A scoping search was conducted which identified a study of docetaxel plus prednisone versus mitoxantrone (Novantrone[®], Wyeth) plus prednisone. The scoping search did not identify any trials comparing docetaxel plus prednisone/prednisolone with any of the other relevant treatments. However, trials comparing mitoxantrone with other chemotherapies and corticosteroids (used as best supportive care) were identified. Therefore, in order to allow for a comparison between docetaxel and other relevant treatments, the clinical effectiveness and cost-effectiveness of mitoxantrone, the common comparator, were also reviewed.

Twenty-one resources (including MEDLINE, EMBASE and The Cochrane Library) were searched to April 2005 for randomised controlled trials (RCTs) and systematic reviews of the clinical effectiveness of docetaxel and mitoxantrone and economic evaluations of the cost-effectiveness of docetaxel and mitoxantrone.

Inclusion/exclusion criteria

Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full text of any study judged to be relevant by either reviewer was obtained and assessed for inclusion or exclusion. Disagreements were resolved through discussion. For the assessment of clinical effectiveness, RCTs that compared docetaxel in combination with prednisone/prednisolone with any chemotherapy regimen or best supportive care (which may include radiotherapy, corticosteroids, oxygen, antibiotics and analgesics) or placebo were included. RCTs that assessed mitoxantrone in combination with a corticosteroid compared with any chemotherapy regimen or best supportive care or placebo were also eligible for inclusion. For the assessment of cost-effectiveness, a broader range of study designs were considered. Only full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analysis) were included.

Data extraction and quality assessment

Data from included studies were extracted by one reviewer and independently checked for accuracy by a second reviewer. Individual studies were assessed for quality by one reviewer and independently checked for accuracy by a second reviewer.

Methods of analysis/synthesis

The results of the data extraction and quality assessment for each study of clinical effectiveness are presented in structured tables and as a narrative summary. Where appropriate, outcomes were synthesised using formal analytic approaches. For the cost-effectiveness section of the report, details of each identified published economic evaluation, together with a critical appraisal of its quality, are presented in structured tables. A new cost-effectiveness model was developed in order to establish the cost-effectiveness of docetaxel compared with a range of potential comparators. The model was developed to estimate costs from the perspective of the UK NHS and health outcomes in terms of life-years gained and quality-adjusted life-years (QALYs) for the full range of relevant treatment strategies. A simple two-state Markov model was constructed to calculate mean survival and to account for discounting. The model was run for a time horizon of 15-years in order to obtain a robust estimate of mean survival. A separate review was undertaken to identify sources of utility data required to estimate QALYs. Sensitivity analyses were also undertaken to explore the robustness of the main analysis to alternative assumptions related to quality of life. Monte Carlo simulation was used to propagate uncertainty in input parameters through the model in such a way that the results of the analysis could be presented with their uncertainty. The impact of uncertainty surrounding the decision was established using value of information and implementation approaches.

Handling the company submissions

No substantive additional clinical effectiveness data were presented in the company submission. The economic evaluation included in the company submission was assessed and used to inform the development of the new model.

Results

A total of 1065 titles and abstracts were screened for inclusion in the review of clinical effectiveness and cost-effectiveness and 267 records were

ordered as full papers. Seven RCTs were identified that met our inclusion criteria. Three of these trials used docetaxel compared with mitoxantrone plus prednisone, three trials used mitoxantrone plus a corticosteroid compared with a corticosteroid and one trial used mitoxantrone plus prednisone compared with mitoxantrone plus prednisone plus clodronate.

Clinical effectiveness

We found one large, good-quality trial ($n = 1006$) that assessed the intervention under consideration: docetaxel plus prednisone; this was in comparison with mitoxantrone plus prednisone (TAX 327). No other trials were found that assessed the clinical effectiveness of docetaxel plus prednisone. The results of this trial showed statistically significant improvements with 3-weekly docetaxel plus prednisone compared with mitoxantrone plus prednisone, in terms of overall survival [hazard ratio (HR) for death = 0.76 [95% confidence interval (CI): 0.62 to 0.94]], quality of life [relative risk (RR) = 1.67 (95% CI: 1.14 to 2.45)], pain response [RR = 1.58 (95% CI: 1.1 to 2.27)] and prostate specific antigen (PSA) decline [RR = 1.41 (95% CI: 1.14 to 1.73)]. Tumour response rate was higher for the 3-weekly docetaxel plus prednisone group than the mitoxantrone plus prednisone group, but this difference was not statistically significant. The improved outcomes for docetaxel plus prednisone were associated with more grade 3–4 adverse events; however, this had no detrimental effect on quality of life, which was significantly improved in the 3-weekly docetaxel group. Progression-free survival was not assessed in this trial.

Since docetaxel plus prednisone is only compared with mitoxantrone plus prednisone, it was considered important to consider other evidence which would inform a comparison against other potentially relevant comparators (e.g. other chemotherapy-based treatments and best supportive care). Therefore, we searched for all other treatments that were compared with mitoxantrone plus a corticosteroid.

We found three trials comparing mitoxantrone plus prednisone with another chemotherapy regimen: one trial that compared mitoxantrone plus prednisone with docetaxel plus prednisone plus estramustine, one trial that compared mitoxantrone plus prednisone with docetaxel plus estramustine, and one trial that compared mitoxantrone plus prednisone with mitoxantrone plus prednisone plus clodronate. Both treatments that included docetaxel were superior to

mitoxantrone plus prednisone in terms of overall survival (although the difference was not statistically significant for docetaxel plus prednisone plus estramustine), response rate (although the difference was not statistically significant for docetaxel plus estramustine) and progression-free survival (although this was only assessed for docetaxel plus estramustine in comparison with mitoxantrone plus prednisone). Docetaxel plus estramustine was associated with more adverse events compared with mitoxantrone plus prednisone. No significant differences were found between mitoxantrone plus prednisone plus clodronate and mitoxantrone plus prednisone without clodronate.

In addition, we found three trials that compared mitoxantrone plus a corticosteroid with best supportive care, using corticosteroids. Two of these used prednisone (5 mg twice daily) as the comparator and one compared mitoxantrone plus hydrocortisone with hydrocortisone (40 mg given in two divided doses daily). One of the trials included men with asymptomatic mHRPC, another included men with symptomatic mHRPC, with symptoms including pain and disease progression and the third included all men with progressive mHRPC. One trial allowed patients to cross over during the trial, which resulted in 50 out of 81 patients randomised to prednisone receiving additional mitoxantrone; the other two trials did not allow crossovers.

The combined result of these three trials showed very little difference between mitoxantrone plus corticosteroids compared with corticosteroids alone in terms of overall survival [HR = 0.99 (95% CI: 0.82 to 1.20)]. Other outcomes could not be pooled because they were measured differently in the three trials. However, in the two studies that measured health-related quality of life and pain responses, the mitoxantrone groups had statistically significant improvements compared with the corticosteroid groups. High losses to follow-up for these outcomes dictate that these results should be interpreted cautiously.

An adjusted indirect comparison was performed to estimate the relative efficacy of docetaxel plus prednisone versus corticosteroids. The results of the indirect comparison showed that docetaxel plus prednisone seems to be superior to prednisone alone in terms of overall survival. However, this is based on an indirect comparison using one good-quality trial comparing docetaxel plus prednisone with mitoxantrone plus

prednisone (TAX 327) and three trials comparing mitoxantrone plus corticosteroids with corticosteroids, that differed in terms of patient population and methodology.

In summary, a direct comparison of docetaxel plus prednisone versus mitoxantrone plus prednisone in an open-label randomised trial showed improved outcomes for docetaxel plus prednisone. Two other chemotherapy regimens that included docetaxel: docetaxel plus estramustine and docetaxel plus prednisone plus estramustine, also showed improved outcomes in comparison with mitoxantrone plus prednisone. Three trials that compared mitoxantrone plus a corticosteroid with a corticosteroid alone were identified and their results for overall survival were combined, which showed very little difference between the two groups. Mitoxantrone plus prednisone plus clodronate showed no significant differences in comparison with mitoxantrone plus prednisone. Our review of the data suggests that docetaxel plus prednisone is the most effective treatment for men with mHRPC.

Cost-effectiveness

The systematic literature search identified only one study which met the criteria for inclusion in the cost-effectiveness review. A separate cost-effectiveness analysis was also submitted by the manufacturer (Sanofi-Aventis).

Of the cost-effectiveness evidence reviewed, only the manufacturer's submission was considered directly relevant from the perspective of the NHS. The review of this evidence highlighted potential limitations within the submission in its use of data, the range of comparators considered and the lack of quality adjustment in the final outcome. These limitations led to the development of a new model with the aim of providing a more comprehensive range of comparators (including a comparison with other chemotherapy regimens and prednisone/prednisolone alone) for the analysis of the cost-effectiveness of docetaxel plus prednisone/prednisolone from the perspective of the NHS. Two separate analyses were undertaken based on different sets of potentially relevant comparators. Despite the use of separate analyses, the estimates of cost-effectiveness provided in both analyses were similar. This model indicated that mitoxantrone plus a corticosteroid dominates a corticosteroid alone (i.e. it is cheaper and more effective). Compared with mitoxantrone plus prednisone/prednisolone, the use of docetaxel plus prednisone/prednisolone (3-weekly) appears cost-effective as long as the NHS is willing to pay

£33,000 per QALY. A range of sensitivity analyses were undertaken to test the robustness of the model to alternative assumptions regarding discount rates, quality of life estimates and the impact of side-effects. The incremental cost-effectiveness ratio associated with docetaxel plus prednisone (3-weekly) remained fairly robust to these variations with estimates ranging from £28,000 to £33,000 per QALY. Value of information analysis revealed that further research is potentially valuable. Given a maximum acceptable ratio of £30,000 per QALY, the expected value of information was estimated to be approximately £13 million. This represents the maximum amount that a decision-maker should be willing to pay for additional evidence to inform this decision in the future and can be used as a benchmark to establish the potential efficiency of further primary research.

Conclusions

Clinical effectiveness

The evidence demonstrates that docetaxel plus prednisone is superior to mitoxantrone plus prednisone, in terms of overall survival, quality of life, pain, and PSA decline. Docetaxel plus prednisone seems to be superior to corticosteroids alone in terms of overall survival. However, this is based on an indirect comparison; therefore, the results need to be interpreted with some caution. Our review of the data suggests that docetaxel plus

prednisone seems to be the most effective treatment for men with mHRPC.

Cost-effectiveness

The results from the assessment group model suggest that treatment with docetaxel plus prednisone/prednisolone is cost-effective in patients with mHRPC as long as the health service is willing to pay £33,000 per additional QALY. Sensitivity analysis demonstrated the robustness of the estimate of cost-effectiveness to these variations.

Research recommendations

Future research should include the direct assessment of quality of life and utility gain associated with different treatments including the effect of adverse events of treatment, using generic instruments, which are suitable for the purposes of cost-effectiveness analyses.

Publication

Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al.* A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer. *Health Technol Assess* 2007;**11**(2).

NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

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