Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostate cancer

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Authors' objectives
To assess the relative effectiveness of alternative strategies for androgen suppression as treatment of advanced prostate cancer. There were three separate assessments within the review:

1. The relative effectiveness of the available methods for monotherapy (orchidectomy, luteinising hormone-releasing hormone (LHRH) agonists, and antiandrogens).

2. The effectiveness of combined androgen blockade versus monotherapy.

3. The effectiveness of immediate versus deferred androgen suppression.

Searching
MEDLINE, EMBASE, and Cancerlit were all searched from 1966 to 1998 (search terms listed). The Cochrane Controlled Trials Register and the CENTRAL Register were searched, and the yield from this search was checked against the table of contents/list of trials compiled by the Prostate Cancer Trialists' Collaborative Group (1995) and the trials cited in the MetaWorks meta-analysis (1997) (see Other Publications of Related Interest no.1) to determine if any relevant trials had been omitted. In addition, Current Contents was searched until 1998, and abstracts presented at the 1998 meetings of the American Urological Association and the American Society for Clinical Oncology were examined.

Study selection
Study designs of evaluations included in the review
Primarily, randomised controlled trials (RCTs) were included. For adverse event data, both RCTs and non-randomised phase II studies were included if they reported the frequency of patients withdrawing from therapy due to adverse events. For quality of life data, all identified reports were included.

Specific interventions included in the review
For review part 1 (relative effectiveness of monotherapies), trials were included if patients in one arm received a LHRH agonist (e.g. leuprolide, goserelin, or buserelin), a non-steroidal antiandrogen (e.g. flutamide, nilutamide, or bicalutamide), or the steroidal antiandrogen cyproterone acetate. Patients in the second arm of the trial had to be treated with orchidectomy or diethylstilbestrol (DES). Trials were also included if two different monotherapies were compared or if orchidectomy was compared with DES. Trials were excluded if they compared different dosages of a single drug or if they compared DES or orchidectomy with steroidal drugs other than cyproterone.

For review part 2 (combined androgen blockade versus monotherapy), trials were included if they made any of the following comparisons: orchidectomy alone versus orchidectomy plus an antiandrogen; a LHRH agonist alone versus a LHRH agonist plus an antiandrogen; orchidectomy alone versus a LHRH agonist plus an antiandrogen; or either orchidectomy or a LHRH agonist alone versus either orchidectomy or a LHRH agonist plus an antiandrogen.

For review part 3 (immediate versus deferred androgen suppression), trials were included if they allocated patients to receive androgen suppression therapy that was deferred until the appearance of symptoms of disseminated disease (primarily bone pain) or at first signs of disseminated disease (bony or distant soft tissue metastases) versus initiation of therapy at an earlier point, including any of the following: when patient diagnosed with asymptomatic stage C or D1 disease; when patients originally given definitive treatment for localised disease demonstrated biochemical evidence of recurrence (defined by rising prostate-specific antigen (PSA)); or when patients originally given definitive treatment for localised disease showed signs of progression other than PSA.
Participants included in the review
Trials comparing different options for monotherapy, or comparing monotherapy with combined androgen blockade, were included if they enrolled men with advanced prostate cancer who had not been previously treated with hormonal therapy for prostate cancer. Advanced prostate cancer was defined as either those with disseminated and/or symptomatic metastases (defined as stage D1/D2, N+ or M1 disease), or those with asymptomatic or minimally advanced disease (defined as stage C or T3-4NxMO disease). For trials comparing immediate and deferred initiation of androgen suppression only, a third patient group was included; those with a rising PSA or other signs of progression, after surgery or radiotherapy for early stage disease.

Outcomes assessed in the review
Trials were included if they reported at least one of the following: overall survival; cancer-specific survival; progression-free survival; time to hormone refractory status; time to treatment failure; adverse effects of treatment; quality of life; patient preference or satisfaction.

How were decisions on the relevance of primary studies made?
Titles and abstracts of identified references were examined against the review's selection criteria by one reviewer, and references were categorised as 'include', 'exclude', and 'uncertain'. All references categorised as 'include' were retrieved. All references categorised as 'exclude' were examined by a second reviewer. If the second reviewer categorised any of these as 'include', they were retrieved. References categorised as 'uncertain' were reconsidered by both reviewers with a bias towards being inclusive. When full articles were retrieved, each reviewer evaluated all articles against the inclusion and exclusion criteria. Disagreements were resolved by consensus.

Assessment of study quality
The following criteria were used: method of randomisation; blinding of the randomisation process during patient recruitment; blinding of the investigator and patient to treatment allocation prior to breaking the randomisation code (except when patient underwent surgical castration); reporting of withdrawals and handling of them in the analysis; use of intention-to-treat analysis; reporting of power analysis; whether adherence with treatment was monitored; and descriptions of treatment protocols, including concurrent treatments. Studies of higher quality were defined as those which had used double-blinding or those where blinding was not applicable, and those where an intention-to-treat analysis was performed on the outcome of interest. Two reviewers independently assessed the validity of each eligible study, and disagreements were resolved by consensus.

Data extraction
Data were extracted on trial identifiers, study methods (including enrolment and withdrawal numbers), patient characteristics, outcomes (including the proportion of patients surviving at 1 year, 2 years, 5 years, and 10 years, and median survival durations), and comments. Where survival data were not reported, the reviewers estimated the values from curves that were available in the published reports. Two reviewers independently collected data for each eligible study, and disagreements were resolved by consensus.

Methods of synthesis
How were the studies combined?
A narrative summary was performed. In addition, hazard rates for overall survival were combined using a random-effects model.

How were differences between studies investigated?
Sensitivity analyses were used to test for heterogeneity of methods (including the effect of including studies of lower methodological quality), participants, and interventions. For the meta-analysis of combined androgen blockade, sensitivity analysis was also used to test whether studies that reported 5-year survival differed from studies reporting 2-year survival. An initial analysis was performed to determine whether the results of castration and administration of DES are comparable and thus whether it is valid to pool studies in which the control arms used either of these monotherapies. Separate analyses were carried out to compare the available monotherapies, compare monotherapy with combined androgen blockade, and compare the outcomes of immediate androgen suppression with those of...
Results of the review

For part 1 (relative effectiveness of monotherapies), 24 trials with over 6,600 patients were included. For part 2 (combined androgen blockade compared to monotherapy) 27 trials (n=7,987) were included. For review part 3 (immediate versus deferred androgen suppression) three trials (n= 1,209) were included.

Review part 1 (relative effectiveness of monotherapies):

A meta-analysis based on 10 trials (n=1,908) comparing a LHRH agonist to orchidectomy or to DES showed that 2-year survival with a LHRH agonist is equivalent to orchidectomy (hazard ratio 1.1262; 95% CI 0.915, 1.386). No statistically significant differences in survival were found among patients treated with different LHRH agonists. The hazard ratio for non-steroidal antiandrogens relative to orchidectomy was 1.2158 for non-steroidal antiandrogens as a class (95% CI 0.988, 1.496), compared to 0.9835 for DES (95% CI 0.764, 1.267), and 1.1262 for LHRH agonists (95% CI 0.915, 1.386). Withdrawals occurred less often among patients treated with a LHRH agonist (0-4%) than among patients treated with non-steroidal antiandrogens (4-10%). Impotence was more common among patients treated with orchidectomy or LHRH agonists compared to patients treated with non-steroidal antiandrogens, but the available data were too inconsistent to quantify the differences. Hot flushes were more common and gynaecomastia was less common among patients treated with LHRH agonists than among those treated with non-steroidal antiandrogens. Among the LHRH agonists, local pain, reactions, hypersensitivity, or development of a mass at the injection site were very infrequent. There was insufficient evidence to compare the effects of the various monotherapies on quality of life.

Review part 2 (combined androgen blockade compared to monotherapy):

The hazard ratio for monotherapy versus combined androgen blockade in overall survival at 2 years was 0.970 (95% CI: 0.866, 1.087). There was an advantage in overall survival for combined androgen blockade at 5 years (hazard ratio 0.871; 95% CI 0.805, 0.942). For patients with good prognosis, no statistically significant difference in survival was found between combined androgen blockade and monotherapy. The meta-analysis found that combined androgen blockade using flutamide or nilutamide appeared to be equivalent. Patients randomised to combined androgen blockade withdrew from treatment due to adverse effects more frequently than patients randomised to monotherapy.

Review part 3 (immediate versus deferred androgen suppression):

No evidence was available from RCTs to compare androgen suppression initiated immediately upon PSA rise after definitive therapy to androgen suppression deferred until clinical signs or symptoms of progression. The meta-analysis found no significant difference between immediate primary hormonal therapy and deferred therapy for survival at 5 years (hazard ratio 0.914; 95% CI 0.815, 1.026). For patients with locally advanced or asymptomatic metastatic prostate cancer who underwent radiotherapy, the evidence suggested a longer duration of survival after androgen suppression initiated at the same time as radiation therapy and continued for several years than after radiation therapy alone followed by androgen suppression initiated at progression. The meta-analysis found a significant difference in 5-year overall survival in favour of radiation therapy plus continued androgen suppression compared to radiation therapy alone (hazard ratio 0.631; 95% CI 0.479, 0.831). Patients who undergo immediate hormonal treatment will have a longer duration of therapy in which they experience the adverse effects of androgen suppression. There is scant data on duration of androgen therapy, risk of adverse effects, and effect on quality of life.

Cost information

The cost-effectiveness of androgen suppression strategies for patients with advanced prostate cancer was evaluated using a decision analysis model. The model incorporated benefits and harms of the interventions, captured a broad range of costs, and accounted for quality of life effects. The model was constructed from a societal perspective, with all costs and benefits discounted at 3%.

The cost-effectiveness analysis showed that the extra benefit from orchidectomy and DES is small, even after accounting for differential toxicities. The results were sensitive to the quality of life associated with orchidectomy. For
patients whose quality of life would diminish substantially if they underwent orchidectomy, the use of LHRH agonists or non-steroidal antiandrogens may represent reasonable alternatives. The cost per QALY of combined androgen blockade with a LHRH agonist was estimated at US$100,000. It was estimated that efficacy of this intervention would have to increase by 20% compared to orchidectomy before this drug combination could be considered cost-effective. Combined androgen blockade with an orchidectomy must increase efficacy by 10%.

For patients with locally advanced or asymptomatic metastatic cancer at the time of diagnosis, initiating antiandrogen therapy early, when patients enjoy a good quality of life, would result in higher costs with no added benefit, but possible harm, compared to deferring therapy. Findings changed little when uncertain values entered into the model were varied over wide ranges in one-way sensitivity analyses.

**Authors' conclusions**

**Review part 1 (relative effectiveness of monotherapies):**

There was no statistically significant difference in survival for patients treated with a LHRH agonist compared to patients treated with orchidectomy or DES, or among patients treated with different LHRH agonists. The evidence showed a trend towards lower survival after non-steroidal antiandrogens used as monotherapy than after orchidectomy, DES, or LHRH agonists. LHRH agonists and non-steroidal antiandrogens differ in their adverse effects. The evidence on differences in adverse effects among the agents within each class is limited, but does not suggest that one agent is superior to the others. There is insufficient evidence to compare the effects of the various monotherapies on quality of life.

**Review part 2 (combined androgen blockade compared to monotherapy):**

There was no statistically significant difference in survival at 2 years between patients treated with combined androgen blockade or monotherapy. Meta-analysis of the limited data available showed a statistically significant difference in survival at 5 years in favour of combined androgen blockade. However, the magnitude of this difference was of questionable clinical significance. For patients in a subgroup with good prognosis, there was no statistically significant difference in survival between combined androgen blockade and monotherapy. Non-steroidal antiandrogens may be more effective than cyproterone for combined androgen blockade. There was no statistically significant difference in survival among patients given combined androgen blockade with different non-steroidal anti-androgens. The evidence comparing adverse effects was limited, but favoured monotherapy over combined androgen blockade. Evidence comparing quality of life was available from only one study and also favoured monotherapy.

**Review part 3 (immediate versus deferred androgen suppression):**

No evidence was available from RCTs to compare androgen suppression initiated immediately upon PSA rise after definitive therapy to androgen suppression deferred until clinical signs or symptoms of progression. For patients newly diagnosed with locally advanced or asymptomatic metastatic disease, the evidence is insufficient to determine whether primary androgen suppression initiated immediately at diagnosis improves outcomes compared to androgen suppression deferred until clinical signs or symptoms of progression. For patients with locally advanced or asymptomatic metastatic prostate cancer who undergo radiotherapy, the evidence suggested a longer duration of survival after androgen suppression initiated at the same time as radiation therapy and continued for several years than after radiation therapy alone followed by androgen suppression initiated at progression. Patients undergoing immediate hormonal treatment will have a longer duration of therapy in which they experience the adverse effects of androgen suppression. There was scant data on duration of androgen therapy, risk of adverse effects, and effect on quality of life.

**CRD commentary**

This is a rigorously conducted systematic review of the relative effectiveness of alternative strategies for androgen suppression as treatment of advanced prostate cancer. The review addressed three separate questions: comparison of monotherapies; combined androgen blockade versus monotherapy; and timing of androgen suppression. The selection criteria for primary studies are explained in detail. The search strategy is thorough, but the language restriction used is not explained. If this was restricted to English language only, it is possible that relevant papers could have been missed. A rigorous validity assessment was conducted, and sensitivity analyses on the basis of methodological quality...
were conducted and presented in the report. Individual study details are provided in tables. Methods used for pooling data are appropriate, and differences between studies are investigated through sensitivity analyses and subgroup analyses. Study selection, validity assessment, and data extraction were conducted by two independent reviewers. The detailed conclusions presented by the authors appear to follow on from the evidence provided.

A journal paper which summarises the first review question (relative effectiveness of different monotherapies) has been identified (see Other Publications of Related Interest no.2).

A journal paper which summarises the second review question (relative effectiveness of different monotherapies) has been identified (see Other Publications of Related Interest no.3).

Implications of the review for practice and research
Practice: The authors stated that there is a large body of RCTs showing that orchidectomy and the available LHRH agonists are equally effective, and no LHRH agent is superior when adverse effects are considered. Combined androgen blockade has not been demonstrated to be of greater benefit than monotherapy for the aggregate population of patients with advanced prostate cancer or for the sub-population of patients with good prognostic factors. Other patient subgroups that might benefit more from combined androgen blockade than monotherapy have not been well defined.

Research: The authors stated that future trials on prostate cancer should use consensus definitions for patient enrolment criteria, subgroup characteristics and trial end points, such as those developed by the World Health Organization.

The hypothesis that combined androgen blockade provides a greater benefit than monotherapy either for all men with advanced prostate cancer or for a subgroup of patients with good prognostic factors are not supported by the available evidence and do not merit continued investigation.

RCTs are needed to assess the efficacy of various strategies for the timing of androgen suppression. The most urgent priorities for future research includ the following.

Immediate treatment at biochemical progression for relapse after definitive therapy for clinically localised disease.

Intermittent androgen suppression initiated with rising PSA levels and withdrawn when PSA levels return to baseline.

Short-term neoadjuvant androgen suppression prior to definitive therapy for localised disease with a higher risk of relapse based on extent and grade of tumour.

Evidence collected from patients on the effects of various androgen suppression therapies on the quality of life is urgently needed. The information obtained should be incorporated into patient-education materials and used in shared decision-making. Its impact on patients' treatment choices should also be evaluated.

The cost-effectiveness analysis points to the need for data on patient utilities associated with life after orchidectomy; re-evaluation of the risk of lower doses of DES as method of androgen suppression; and collection of economic data from RCTs as additional priorities for future research.

Bibliographic details

Original Paper URL
http://www.ahrq.gov/clinic/epcsums/prossumm.htm

Other publications of related interest

Indexing Status
Subject indexing assigned by CRD

MeSH
Androgen Antagonists /therapeutic use; Prostatic Neoplasms /drug therapy

AccessionNumber
12000008340

Date bibliographic record published
31/08/2001

Date abstract record published
31/08/2001

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.