A. **Final version.**

B. **Details of review team**

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C. **Full title of research question**

Docetaxel for the treatment of hormone-refractory metastatic prostate cancer.

D. **Clarification of research question and scope**

This review will examine the clinical effectiveness and the cost-effectiveness of docetaxel (Taxotere®, Aventis Pharma Ltd) for hormone-refractory metastatic prostate cancer. Randomised controlled trials comparing docetaxel with other chemotherapy regimens based on mitoxantrone or estramustine or active supportive care (which may include radiotherapy, corticosteroids, oxygen, antibiotics and analgesics) to treat patients with hormone-refractory metastatic prostate cancer will be included. A broader range of studies will be considered in the assessment of cost effectiveness including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

E. **Report methods**

1. Search strategy

Refer to Appendix 1 for details of the sources to be searched and the draft search strategy for MEDLINE. No language restrictions will be applied to the search strategy.

2. Inclusion and exclusion criteria

Two reviewers will independently screen all titles and abstracts. Full paper manuscripts of any titles/abstracts that may be relevant will be obtained where possible and the relevance of each study assessed according to the criteria below. Studies that do not fulfil all of the criteria will be excluded and their bibliographic details listed with reasons for exclusion. Any discrepancies will be resolved by consensus and if necessary a third reviewer will be consulted.

a. Study designs

- Randomised controlled trials (RCTs)
- Cost-effectiveness evaluations, including cost minimisation and cost consequence analyses
- Cost-utility analyses
- Cost-benefit analyses.

b. Intervention

- Docetaxel (Taxotere®, Aventis Pharma Ltd).

c. Comparators

- Chemotherapy regimens based on mitoxantrone or estramustine
- Active supportive care (which may include radiotherapy, corticosteroids, oxygen, antibiotics and analgesics).

d. Participants

- Men with hormone-refractory metastatic prostate cancer.

e. Outcomes

- Overall survival
- Progression-free survival
- Response rate (including complete and partial response)
- PSA decline
- Adverse effects of treatment
- Pain
- Health-related quality of life
- Costs from an NHS and Personal Social Services perspective

Where the evidence allows, the appraisal will identify subgroups of men with hormone-refractory metastatic prostate cancer for whom docetaxel is particularly appropriate or inappropriate.

3. Data extraction strategy

Data relating to both study design and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. If time constraints allow, attempts will be made to contact authors for missing data. Data from multiple publications of the same study will be extracted and reported as a single study.

4. Quality assessment strategy

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted.

The quality of the clinical effectiveness studies will be assessed according to criteria based on NHS CRD Report No.4.[1] The quality of the cost-effectiveness studies will be assessed according to a checklist updated from that developed by Drummond et al.[2] See Appendix 3 for further details. This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Clinical Excellence.[3] This information will be tabulated and summarised within the text of the report.

5. Methods of analysis/synthesis

Details of the extracted data and quality assessment for each study of clinical effectiveness will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Where

sufficient data are available, treatment effects will be presented as relative risks for dichotomous data, weighted mean differences for continuous data or as hazard ratios where appropriate. Relative risks will be presented as Forest plots but only pooled when this is statistically and clinically meaningful. Studies will be grouped according to the intervention and comparator used. Heterogeneity between the included studies will be assessed by considering differences in (a) study population (b) intervention (c) outcome measures (d) study quality and (e) comparator. In addition, where pooling seems appropriate, chi-squared tests of heterogeneity will be performed. Where feasible, the possibility of publication bias will also be investigated using funnel plots and Egger's test.

Methods of analysis for economic studies

Details of each identified published economic evaluation, together with a critical appraisal of its quality will be presented in structured tables. This will cover both studies based on patient-level data and decision models and will include any studies submitted to NICE by the manufacturers.

Patient-level data

For analyses based on patient-level data, the validity of the studies will be assessed for the source of resource use and effectiveness data, the valuation methods used to cost the resource use and value patient benefits, the methods of analysis and generalisability of results. Studies will be classified as follows:

I. Prospective resource use and patient outcome data.
II. Mixed prospective and retrospective data.
III. Retrospective data.

These categories will be further subdivided as follows:

A. RCT
B. Controlled trial (quasi- or no randomisation)
C. Cohort study with concurrent controls
D. Cohort study with historical controls

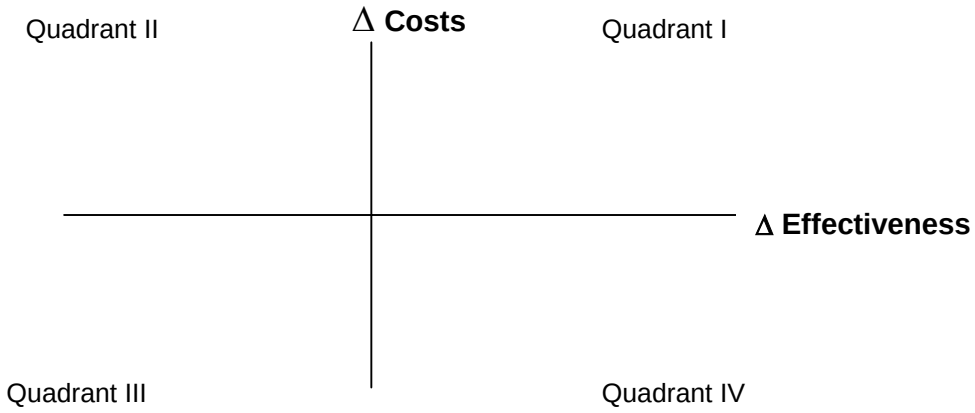
Decision models

Critical appraisal will be based on a range of questions including:

i. Structure of model
ii. Time horizon
iii. Details of key input parameters and their sources
iv. Methods of analysis (e.g. handling uncertainty).

Part of the assessment process will involve the location of each study in the appropriate quadrant of the cost-effectiveness plane (shown in Figure 1). This indicates the direction of the differential costs and effects of the alternative treatment options considered, but does not address the uncertainty surrounding these estimates. Where possible, indications of the uncertainty underlying these estimates will be assessed and an appropriate statistic such as confidence intervals around costs and effects or the incremental cost-effectiveness ratio, or cost-effectiveness acceptability curves will be presented. These will be produced from either published analyses, Monte Carlo simulation or per patient data on total costs and effects.

Figure 1. Cost-effectiveness plane and quadrants



Key to Quadrants:
Quadrant I. Intervention increases costs and effectiveness. Incremental analysis required to assess cost-effectiveness compared with other interventions.
Quadrant II. Intervention is dominated as it increases costs and reduces effectiveness.
Quadrant III. Intervention reduces costs and effectiveness. Incremental analysis required.
Quadrant IV. Intervention is dominant as costs are reduced and effectiveness increased.

F. **Handling the company submission**

All data submitted by the drug manufacturers will be considered if received by the review team no later than 12 April 2005. Data arriving after this date will only be considered if time constraints allow. If the data meet the inclusion criteria for the review it will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission will be assessed. This will include a detailed analysis of the appropriateness of the parametric and structural assumptions involved in any models in the submission and an assessment of how robust the models are to changes in key assumptions. Following this analysis, if the existing models (company or published) are not sufficient, de novo or modified versions of any models may be developed. Clarification on specific aspects of the model may be sought from the drug manufacturer. Any 'commercial in confidence' data taken from a company submission will be clearly marked in the NICE report (by underlining) and removed from the subsequent submission to the NCCHTA.

G. **Project management**

a. **Timetable/milestones** - submission of:
Draft protocol: 24 January 2005
Final protocol: 7 February 2005
Consultees' meeting: 11 February 2005
Industry submission to NICE: 6 April 2005
Review team receive industry submission: 12 April 2005
Progress report: 19 April 2005
Draft report to NICE and external reviewers (provisional): 24 June 2005
Assessment Report: 14 July 2005

b. **Competing interests**
None of the research team has any competing interests to declare. Any competing interests relating to the external reviewers will be declared in the final report.

c. **External review**
The Technology Assessment Report will be subject to external review by at least two experts acting on behalf of the NHS HTA Programme. These referees will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that the NICE secretariat and Appraisal Committee will undertake methodological review. In addition, an external methodological referee will be asked to review the report on behalf of the HTA Programme. Referees will review a complete and near final draft of the TAR and will understand that their role is part of external quality assurance. Referees will be required to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking, which we will hold on file. Comments from referees and the Technical lead, together with our responses will be made available to NCCHTA in strict confidence for editorial review and approval. In addition, the review team will invite an external expert to advise on the clinical content of the review.

H. **Appendices**

Appendix 1: Search procedure

Sources to be searched
The following databases were searched to inform the scope of the TAR and the protocol.

MEDLINE (OVID)
CENTRAL (on The Cochrane Library)
EMBASE (OVID)
National Research Register
Clinical Trials.gov
Controlled Trials.com
NHS Economic Evaluation Database

For the full review, update searches will be run as necessary on the databases above.
In addition the following databases will be searched:

BIOSIS
Cochrane Database of Systematic Reviews
CINAHL
Database of Abstracts of Reviews of Effects
HTA database
Index to Scientific and Technical Proceedings (ISTP)
Science Citation Index
Office of Health Economics Health Economic Evaluations Database (HEED)
Inside Conferences

We will also search the websites of relevant conferences and cancer organisations, e.g. ASCO.

Search strategy
The following draft strategies were developed for Medline and were adapted with relevant subject indexing to run on other databases. They will be revised as required on acceptance of the protocol and adapted to run effectively on the other databases listed above. The searches for the information to inform the economic model will be developed in collaboration with the health economist assigned to the project and will be designed pragmatically to capture relevant information to inform all the model parameters.

Strategy for Docetaxel for hormone refractory prostate cancer
Database: Ovid MEDLINE(R)

The search was conducted for the period <1966 to November Week 3 2004>
Records retrieved: 153

Limits:

- No date limits were applied
- Animal-only studies were excluded
- No study design limits or language limits were applied

Database: Ovid MEDLINE(R) <1966 to November Week 3 2004>

---

1. prostatic neoplasms/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. animals/
5. human/
6. 4 not (4 and 5)
7. 3 not 6
8. Docetaxel.ti,ab.
9. Asodecel.ti,ab.
10. Dolectran.ti,ab.
11. Donataxel.ti,ab.
12. Doxetal.ti,ab.
13. Doxmil.ti,ab.
14. Neocel.ti,ab.
15. Plustaxano.ti,ab.
16. Texot.ti,ab.
17. Trazoteva.ti,ab.
18. Trixotene.ti,ab.
19. Daxotel.ti,ab.
20. NSC-628503.mp.
21. RP-56976.mp.
22. 114977-28-5.mp.
23. L01cd02.mp.
24. Taxotere.ti,ab.
25. or/8-24
26. 7 and 25

Strategy for Estramustine for hormone refractory prostate cancer
Database: Ovid MEDLINE(R)

The search was conducted for the period <1966 to November Week 3 2004>
Records retrieved: 696

Limits:

- No date limits were applied
- Animal-only studies were excluded
- No study design limits or language limits were applied

Database: Ovid MEDLINE(R) <1966 to November Week 3 2004>

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1. prostatic neoplasms/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. animals/
5. human/
6. 4 not (4 and 5)
7. 3 not 6
8. Estramustine.ti,ab.
9. ESTRAMUSTINE/
10. Estracyt.ti,ab.
11. BP 2003.mp.
12. Amsupros.ti,ab.
13. Emcyt.ti,ab.
14. Cellmustin.ti,ab.
15. Multosin.ti,ab.
16. Prostamustin.ti,ab.
17. Fosfato sodico de estramustina.ti,ab.
18. Nsc 89199.mp.
19. "Ro 21 8837 001".mp.
20. "Ro 22 2296 000".mp.
21. 2998 57 4.mp.
22. "4891 15 0".mp.
23. 52205 73 9.mp.
24. L01xx11.mp.
25. Estramustinphosphate.ti,ab.
26. Leo-275.mp.
27. Estramustinephosphate.mp.
28. Emcyte.mp.
29. emp.mp.
30. or/8-29
31. 7 and 30

Strategy for Mitoxantrone for hormone refractory prostate cancer
Database: Ovid MEDLINE(R)

The search was conducted for the period <1966 to November Week 3 2004>
Records retrieved: 153

Limits:

- No date limits were applied
- Animal-only studies were excluded
- No study design limits or language limits were applied

Database: Ovid MEDLINE(R) <1966 to November Week 3 2004>

---

1. prostatic neoplasms/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. animals/
5. human/
6. 4 not (4 and 5)
7. 3 not 6
8. Mitoxantrone.mp.
9. MITOXANTRONE/
10. Mitozantrone.ti,ab.
11. Mitoxantrone hydrochloride.ti,ab.
12. BP 2003.mp.
13. USP 27.mp.
14. Novatrone.ti,ab.
15. Onkotrone.ti,ab.
16. Batinel.ti,ab.
17. Micraleve.ti,ab.
18. Mitoxgen.ti,ab.
19. Mitoxmar.ti,ab.
20. Novatron.ti,ab.
21. Misostol.ti,ab.
22. Mitoxal.ti,ab.
23. Neotalem.ti,ab.
24. Genefadrone.ti,ab.
25. Formyxan.ti,ab.
26. Mitroxone.ti,ab.
27. Serotron.ti,ab.
28. Pralifan.ti,ab.
29. CL 232315.mp.
30. DHAD.ti,ab.
31. Dihydroxyanthracenedione dihydrochloride.ti,ab.
32. Hidrocloruro de mitoxantrona.ti,ab.
33. Mitoxantroni hydrochloridum.ti,ab.
34. Mitrozantrone hydrochloride.ti,ab.
35. Nsc 301739.mp.
36. 65271 80 9.mp.
37. 70476 82 3.mp.
38. L01db07.mp.
39. Novantrone.mp.
40. or/8-39
41. 7 and 40

Appendix 2: Data extraction form

Clinical effectiveness data where available will be extracted under the following headings:

Study Details

- Name of trial {trial name, I.D. or 'not stated'}
- Endnote reference {endnote reference number}
- Primary source [database, handsearching, company submission]
- Author {i.e. Jones et al}
- Date {i.e. year of publication or date of interim data collection}
- Type of report [abstract, full manuscript, interim report]
- Type of study phase [phase II, phase III…., not stated]
- Comparison group included [placebo, alternative drug, unclear, not stated]
- Intervention 1 {i.e. drug(s) name(s)}
- Dose of intervention 1 {dose}
- Number of cycles of intervention 1 {number}
- Length per cycle of intervention 1 {length}
- Intervention 2 {i.e. drug(s) name(s)}
- Dose of intervention 2 {dose}
- Number of cycles of intervention 2 {number}
- Length per cycle of intervention 2 {length}
- Comments about interventions {summary of comments or 'none'}

1. Participants

- Disease characteristics {summary of disease characteristics}
- Previous treatment {summary of drugs or other treatments such as debulking, radiotherapy etc., or 'not applicable'}
- Age or age range of participants {age(s)}
- Other participant characteristics {summary of characteristics}
- Comments about participants {summary of comments or 'none'}

2. Numbers in conditions

- Number recruited or accrued {summary or 'not stated'}
- Length of follow-up after treatment finishes {summary or 'not stated'}
- Number and times of follow-up measurements {summary or 'not stated'}
- Attrition intervention 1 {summary of number involved and reasons for loss}
- Attrition intervention 2 {summary of number involved and reasons for loss}
- Per protocol analysis performed [yes, no, not stated, unclear]
- Comments {summary of comments or state 'none'}

Results (data for all outcomes specified in the protocol will be entered in the following format)

- Outcome 1 {description of outcome measure}
- Intervention 1 baseline data {data for outcome 1}

- Intervention 2 baseline data {data for outcome 1}
- Intervention 1 follow-up data {data for outcome 1}
- Intervention 2 follow-up data {data for outcome 1}
- Comments on outcome 1 {summary of comments}
- Overall comments {summary of comments}

Economic evaluation data will be extracted and entered into an Access form under the following headings:

[ ] indicates a list of options included in a pull down box
( ) indicates a click on/off button, where on represents 'yes' and off 'no'
{ } indicates free text entered in a box

- Endnote reference {in the form of xyz, no '#'}
- Primary source [database, handsearching, company submission]
- Author {i.e. Jones et al}
- Date {i.e. year of publication or date of interim data collection}
- Type of economic evaluation [cost effectiveness analysis, cost utility analysis, cost benefit analysis]
- Currency used [$US, $AS, £Sterling …., not stated]
- Year to which costs apply {enter year or not stated}
- Perspective used {e.g. health service, societal, hospital, third party payer, patient, unclear}
- Study population {describe the population characteristics}
- Intervention 1 {description of intervention 1}
- Intervention 2 {description of intervention 2}
- Source of effectiveness data [single study, review/synthesis of previous studies, expert opinion, not stated]
- Source of resource use data [single study, review/synthesis of previous studies, expert opinion, not stated]
- Source of unit cost data [literature, data from actual source, combination of literature and data from actual source, not stated]
- Link between cost and effectiveness data [prospective/concurrent, retrospective/disconnected…]
- Clinical outcomes measured and methods of valuation used {summary of outcomes and valuation methods used}
- Cost data handled appropriately {summary of methods used to e.g. discount, inflate}
- Modelling {summary of models used, type of model, purpose of model, components of model, key input parameters and model outputs}
- Outcome measures used in economic evaluations {summary of outcome measures used in economic evaluations e.g. incremental cost-effectiveness ratio, net benefit, cost-effectiveness acceptability curve }
- Direction of result with appropriate quadrant location
- Statistical analysis for patient-level stochastic data {summary of analyses used}
- Appropriateness of statistical analysis {comment on appropriateness}
- Uncertainty around cost-effectiveness expressed

- Appropriateness of method of dealing with uncertainty around cost-effectiveness
- Sensitivity analysis {list summary of analysis}
- Appropriateness of sensitivity analysis {comment on appropriateness}
- Modelling inputs and techniques appropriate
- Author's conclusions {list as in publication}
- Implications for practice {summary of implications}
- Comments {summary of comments}

Appendix 3: Quality Assessment Scale

Studies of clinical effectiveness will be assessed using the following criteria, based on CRD Report No. 4[1]

Was the method used to assign participants to the treatment groups really random?
(Computer generated random numbers and random number tables will be accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates and days of the week)
Was the allocation of treatment concealed?
(Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially-numbered identical containers, on-site computer based systems where the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque).
Was the number of participants who were randomised stated?
Were details of baseline comparability presented in terms of <insert prognostic factors>?
Was baseline comparability achieved in terms of <insert prognostic factors>?
Were the eligibility criteria for study entry specified?
Were any co-interventions identified that may influence the outcomes for each group?
Were the outcome assessors blinded to the treatment allocation?
Were the individuals who administered the intervention blinded to the treatment allocation?
Were the participants who received the intervention blinded to the treatment allocation?
Was the success of the blinding procedure assessed?
Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
Were the reasons for withdrawals stated?
Was an intention to treat analysis included?

Items will be graded in terms of yes (item properly addressed), ✕ no (item not properly addressed), /✕ partially (item partially addressed), **?** unclear or not enough information, or **NA** not applicable

Studies of cost effectiveness will be assessed using the following criteria, which is an updated version of the checklist developed by Drummond[2]:

Study question

1. Costs and effects examined
2. Alternatives compared
3. The viewpoint(s)/perspective of the analysis is clearly stated *(e.g. NHS, society)*

Selection of alternatives

4. All relevant alternatives are compared *(including do-nothing if applicable)*
5. The alternatives being compared are clearly described *(who did what, to whom, where and how often)*
6. The rationale for choosing the alternative programmes or interventions compared is stated

Form of evaluation

7. The choice of form of economic evaluation is justified in relation to the questions addressed.
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?

Effectiveness data

9. The source(s) of effectiveness estimates used are stated
(e.g. single study, selection of studies, systematic review, expert opinion)
10. Effectiveness data from RCT or review of RCTs
11. Potential biases identified (especially if data not from RCTs)
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)

Costs

13. All the important and relevant resource use included
14. All the important and relevant resource use measured accurately (with methodology)
15. Appropriate unit costs estimated (with methodology)
16. Unit costs reported separately from resource use data
17. Productivity costs treated separately from other costs
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.

Benefit measurement and valuation

19. The primary outcome measure(s) for the economic evaluation are clearly stated
(cases detected, life years, QALYs, etc.)
20. Methods to value health states and other benefits are stated (e.g. *time trade off*)
21. Details of the individuals from whom valuations were obtained are given
(patients, members of the public, health care professionals etc.)

Decision modelling

22. Details of any decision model used are given (e.g. *decision tree, Markov model*)
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified
24. All model outputs described adequately.

Discounting

25. Discount rate used for both costs and benefits
26. Do discount rates accord with NHS guidance (1.5%-2% for benefits; 6% for costs)?

Allowance for uncertainty

Stochastic analysis of patient-level data

27. Details of statistical tests and confidence intervals are given for stochastic data
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).

Stochastic analysis of decision models

30. Are all appropriate input parameters included with uncertainty?
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?
32. Are the probability distributions adequately detailed and appropriate?
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).

Deterministic analysis

34. The approach to sensitivity analysis is given (*e.g. univariate, threshold analysis etc*)
35. The choice of variables for sensitivity analysis is justified
36. The ranges over which the variables are varied are stated

Presentation of results

37. Incremental analysis is reported using appropriate decision rules
38. Major outcomes are presented in a disaggregated as well as aggregated form
39. Applicable to the NHS setting

All items will be graded as either yes (item adequately addressed), ✕ no (item not adequately addressed), **?** unclear or not enough information, NA not applicable or NS not stated.

Appendix 4: Background

Prostate cancer is the most common male cancer, excluding non-melanoma skin cancer, in the UK, with approximately 27,000 new cases per annum and an age-standardised incidence rate of 80.4 per 100,000 men in England (2000 data).[4] In 2002 there were 8,969 deaths from the disease in England and Wales and 9,937 deaths in the UK, accounting for 6% of all UK cancer deaths and 12% of male cancer deaths.[4] Prostate cancer was responsible for 39,283 hospital episodes in 2003-4.[5] The 5-year survival rate in the UK was around 65% for patients diagnosed in the period 1996-1999.[6] Although incidence rates have increased, mortality from the disease has remained largely unchanged. Survival rates have been improving for the last two decades, partly due to the impact of detecting clinically unapparent, more slowly growing tumours as a result of more widespread prostate specific antigen (PSA) screening.[7] With an increased ageing population, there will be further increases in the rate of diagnosis.[8]

Aetiology

The primary risk factor for prostate cancer is increasing age, with 90% of all cases occurring in men over 60 and 42% in men over 75.[5] The highest worldwide rates are observed in Afro-American men, with much lower rates seen in men of Asian origin.[9] It is likely that multifactorial environmental and genetic factors are implicated. Diets high in animal fats and dairy products appear to be associated with increased risk.[9] As prostate cancer does not occur in castrated men, the male sex hormone testosterone is thought to be implicated in prostate cancer aetiology. High levels of insulin-like growth factor (IGF-1) a protein involved in cell metabolism may also be involved.[10] About 9% of cases are thought to have a genetic component, which is particularly important in cases developing at an early age where around 40% of cases of men under 55 years may have a genetic predisposition.[11]

Staging

The extent of prostate cancer is classified into stages I - IV. In Stage I and II the disease is confined to the prostate. In stage III disease the tumour is more locally advanced and in stage IV it is either locally advanced and invading local adjacent structures, or has associated distant metastases. Approximately 22% of cases will be diagnosed at stage IV.[12]

Prognosis

The most important prognostic factor is the growth pattern or grade of the tumour, assessed using the Gleason scoring system. Gleason scores range from <4 for less aggressive to 8-10 for more aggressive tumours. Other important prognostic factors are PSA level and the extent of local tumour spread.[12]

Treatment

There is no current agreement about gold standard treatment for early prostate cancer. Options include active monitoring, radical prostatectomy or radical radiotherapy (external beam radiation or brachytherapy). Hormonal therapy may also be used in conjunction with radical treatment or as sole therapy. The choice of treatment depends on life expectancy, tumour characteristics and patient preference. Locally advanced tumours are treated with hormone therapy, and radiotherapy may also be employed although its role is less certain. Metastatic disease is treated with hormone therapy, either through orchidectomy or by the

administration of LHRH antagonists and /or anti-androgens.[12] Treatment in this setting is aimed at improvement of symptoms and control rather than cure.

Hormone-refractory prostate cancer

The majority of prostate cancers respond initially to hormone therapy. However, in the majority of patients the cancer will become resistant to hormonal treatment and will progress. The median response duration to first-line hormonal therapy in metastatic disease is around 18 months.[13] Response rates to second-line hormonal therapy range from 35-45%.[14] Survival is not expected to exceed between 9 and 12 months after developing hormone resistant disease.[15] Treatment for hormone-refractory metastatic prostate cancer is palliative, and while pain reduction and improvements in quality of life are achieved in substantial proportions of patients (up to 80%), survival does not appear to be prolonged.[15] Treatment options include radiotherapy, either external beam radiotherapy or strontium-89, chemotherapy and bisphosphonates.[12]

Current service provision for hormone-resistant metastatic prostate cancer

Current guidance from the National Institute for Clinical Excellence (NICE) states that chemotherapy should be considered and trials of chemotherapy supported, while palliative radiotherapy should also be considered as a treatment option.[12]

Description of intervention

Docetaxel is a member of a class of drugs known as taxanes and is marketed as Taxotere® by Aventis Pharma Ltd. It is derived from precursor extracted from the needles of the European yew tree, *Taxus baccata*.[16] Docetaxel is a mitotic inhibitor, which acts by disrupting the microtubular network that is essential for mitotic and interphase cellular functions. It promotes the assembly of tubulin into stable microtubules and inhibits microtubule depolymerisation, causing inhibition of cell division and cell death.[17, 18]

Docetaxel is licensed for use in combination with prednisone (prednisolone). It is administered as a one-hour infusion once every three weeks. The recommended dose is 75mg/m2, while prednisone (prednisolone) should be administered daily at 5mg p.o. b.i.d.[19]

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