Two systematic reviews and meta-analyses of the effects of docetaxel and bisphosphonates for advanced prostate cancer

Protocol

Conducted by the Systemic Treatment Options in Cancer of the Prostate (STOpCaP) Meta-analyses Steering Group

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Introduction

Prostate cancer is a major health problem world-wide and is the second most common cancer in men. In 2012, it was estimated that 1.1 million men worldwide were diagnosed with prostate cancer (15% of all cancers diagnosed in men) and that there were 307,000 deaths, making it the fifth leading cause of death from cancer in men (1). The highest rates of prostate cancer are observed in Australia/New Zealand, Northern America and in Western and Northern Europe, where prostate specific antigen (PSA) testing and subsequent biopsy is widespread.

The initial (first line) treatment for locally advanced or metastatic prostate cancer is androgen deprivation therapy (ADT), also known as hormone therapy. This is achieved either surgically with bilateral orchidectomy, or medically with LHRH agonists/antagonist or oral anti-androgens alone (2).

ADT produces responses in up to 95% of patients, but it is not curative and disease recurs in virtually all patients (2). Recent data from the STAMPEDE trial indicated that the median failure free survival time following initiation of ADT was in the region of 11 months (3).

An increasing number of treatments are being given following relapse after primary ADT, including further hormonal manipulations (4), bisphosphonates (5), cytotoxic chemotherapy (6) and new hormone therapies (7), for example, abiraterone, docetaxel, enzalutamide and radium-223. However, there is little evidence to indicate which provide the best response, how they may be combined or scheduled or whether any might have a role in first-line treatment.

Docetaxel is a cytotoxic drug, which disrupts mitotic cell division and prevents cancer cell progeny. Following results of a number of RCTs showing that three-weekly docetaxel improved survival, it was approved by the FDA (USA) and NICE (UK) for treatment of men with castrate-refractory prostate cancer (CRPC) that was no longer responsive to ADT (8, 9). Subsequently, there has been increased interest and a number of RCTs investigating docetaxel chemotherapy in patients with hormone-sensitive prostate cancer embarking on first-line therapy, when they may be fitter and more able to tolerate such treatment. These trials have randomised men with both metastatic and localised prostate cancer to receive docetaxel (alone or in combination with other agents) alongside ADT or ADT alone. Recent results from two of these trials in metastatic, hormone sensitive disease have been conflicting. The CHAARTED trial (10) showed a significant improvement in overall survival whereas the GETUG-15 trial (11, 12) showed no difference in overall survival with the addition of docetaxel to ADT.

The bisphosphonates are a class of drugs that act to reduce the formation, inhibit activity and induce apoptosis of osteoclasts. They can therefore help to control hypercalcaemia and prevent skeletal complications associated with malignant disease. In randomised controlled trials, the first generation bisphosphonate, clodronate, when given at the same time as hormone therapy was initiated, was found to delay time to progression in men with bone metastases. There was also some evidence that it may improve survival (13). More recently, newer (third generation) bisphosphonates, notably zoledronic acid, have been
found it to be effective in reducing the risk of skeletal complications (for example, fractures) in patients with bone metastases from breast cancer and CRPC (14). In the wake of these results, a number of randomised trials have gone on to investigate whether there is a role for bisphosphonates in men with both metastatic and localised hormone-sensitive prostate cancer, who are about to commence ADT.

We aim to systematically review the current evidence from randomised controlled trials comparing ADT alone either with docetaxel or with a bisphosphonate (given at a therapeutic dose* rather than bone preserving dose).

*see table below.

**General Methods**

**Objective**

The primary aim is to assess the effects of both docetaxel and bisphosphates in combination with ADT in combination for advanced or metastatic hormone-sensitive prostate cancer.

The treatment comparisons are

- ADT versus with ADT + docetaxel
- ADT versus with ADT + bisphosphonate

A secondary aim is to assess whether any effect of these agents varies by the characteristics of the trials or patients

**Methods**

**Eligibility Criteria**

**Types of studies**

Only randomised controlled trials (RCTs) will be included

**Types of participants**

RCTs should have aimed to randomise men with high-risk localised or metastatic (stage III, IV), hormone-sensitive (i.e. not castrate refractory) prostate cancer. Men who have failed first-time hormone therapy are not eligible.

**Types of Intervention**

Participants should have been randomised to receive

- ADT alone versus ADT + docetaxel
- ADT alone versus ADT + bisphosphonate (at therapeutic rather than a bone preserving dose*)
*Therapeutic doses for bisphosphonates

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>4mg</td>
<td>Monthly</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>4mg</td>
<td>3 monthly</td>
</tr>
<tr>
<td>Clodronate</td>
<td>2080mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Risedronate</td>
<td>30mg</td>
<td>Daily</td>
</tr>
</tbody>
</table>

Comparisons should not be confounded by the use of additional treatment(s) in the control arm only.

Outcomes

Primary
Overall survival

Secondary
Failure-free survival

Identification of trials

Electronic Databases
- MEDLINE 1966-2015 will be searched using the Cochrane Highly Sensitive Search Strategy for identifying randomised trials(15), supplemented with MeSH and free text terms specific to the review (Appendix A) to specifically retrieve RCTs of hormone therapy in prostate cancer.
- EMBASE 1982-2015 will be searched using a best optimisation of sensitivity and specificity combination strategy(16), supplemented with MeSH and free text terms specific to the review (Appendix A).
- LILACS will be searched using a highly sensitive search strategy(17).
- CENTRAL 1966-2015 will be searched using the main search terms only e.g. “prostatic neoplasms”, and “chemotherapy”.

Trial Registers
ClinicalTrials.gov

Conference Proceedings

Conference proceedings searched electronically:
Proceedings of ASCO GU 2009-2015
Proceedings of the European Society of Medical Oncology (ESMO) 1990-2015
American Urological Association (AUA) 2008-2015
European Association of Urology (EAU) 2006-2015
European Society for Therapeutic Radiation Oncology (ESTRO) 2002-2015
American Society for Radiation Oncology (ASTRO) 2002-2015
Conference proceedings searched by hand:
Proceedings of the American Society of Clinical Oncology (ASCO) 1990-2003

Additional hand searches
Bibliographies of the reports of all identified trials and review articles will be screened for further trials. All Advisory Group members will be asked to review and where possible supplement our provisional list of eligible trials.

Selection of studies
All relevant abstracts will be assessed by three independent reviewers (CV, LR, SB). Full papers will be obtained, for those deemed potentially eligible, and the three reviewers will agree the final set of RCTs.

The risk of bias for eligible trials will be assessed (18, 19), with a low risk of bias being desirable for sequence generation, allocation concealment and completeness of outcome data reporting.

Data extraction and management
Data on patient characteristics, interventions and outcomes will be extracted from publications and presentations into predesigned forms. Where insufficient data is available from publications, it may be sought directly from investigators.

Patient/Trial characteristics
Trial accrual period
Patient age (median, range)
Patient ethnicity
Performance status
M status
T Category
N Category
Gleason Score
PSA at start of ADT (median, range)

Treatment characteristics
Prior treatment
Control arm details (e.g. type of ADT used)
Chemotherapy dose / duration
Bisphosphonate type / dose / duration

Outcomes
(Primary)
Overall Survival
Time from randomisation to death
(Secondary)
Failure-free survival
Time from randomisation to clinical or biochemical failure or death

Analysis

For meta-analyses of time-to-event outcomes, where available, the hazard ratio (HR) and associated statistics will be extracted directly from the trial reports. Where not reported, they will be estimated from Kaplan Meier curves or other summary statistics using published methods(20-22). Where insufficient data are available, supplementary data may be sought directly from the trial investigators.

The main meta-analysis will be of all trials with available data. However, the effect of treatment may vary across trials in the meta-analysis, for example, if they have delivered the treatment in different ways. Therefore, in addition to the main analyses, analyses are planned whereby trials, or arms within trials, will be grouped according to:

For both comparisons:

- Metastatic status of patients in trials
  - M0
  - M1
- Previous treatment / no previous treatment
- Previous local treatment
  - surgery
  - radiotherapy
  - surgery and radiotherapy
  - No previous treatment
- Planned RT / no planned RT
- Type of ADT
  - Anti-androgen
  - Castration
  - Combined therapy
- Length of time on ADT allowed prior to randomisation (maximum)
  - <=12 months
  - >12 months

For docetaxel comparison:

- Total planned dose of docetaxel
  - <75mg^2 / 3 weeks / 6 cycles
  - 75mg^2 / 3 weeks / 6 cycles
- >75mg2 / 3 weeks / 6 cycles
• Additional agents on docetaxel arm only
  o None
  o Estramustine
  o Prednisone
  o Zoledronic Acid
  o Other

For bisphosphonates comparison:

• Type of bisphosphonate
  o Zoledronic acid
  o Risendronate
  o Sodium clodronate

• Dose of Zoledronic acid
  o 4mg / monthly
  o 4mg / 3 monthly

All of these trial group analyses will be based on the primary outcome of survival. A hazard ratio will be calculated for each trial and a pooled hazard ratio calculated for each trial group. If there are insufficient numbers of trials or patients within any trial group, groups may be combined. A chi-square test for interaction and the F-ratio will be used to investigate if there are any substantial differences in the effect of treatment between trial groups. In particular, if there are differences in the effect of treatment by metastatic status, the other trial group analyses will be carried out separately in M0 and M1 trials. The random effects model will be used to establish the robustness of all results to the choice of model.

Analyses by patient level characteristics
Providing there are sufficient data available, we will investigate whether any observed treatment effect is consistent across well-defined patient subgroups based on the primary outcome of survival:

<table>
<thead>
<tr>
<th>For all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Performance Status*</td>
</tr>
<tr>
<td>T category</td>
</tr>
<tr>
<td>N category</td>
</tr>
<tr>
<td>Metastases</td>
</tr>
<tr>
<td>Gleason Score</td>
</tr>
<tr>
<td>Timing of entry into trials</td>
</tr>
<tr>
<td>Prior ADT</td>
</tr>
</tbody>
</table>
Additional analyses for M1 patients only

Location of metastases
- Bone, other, both, not assessed

Volume of metastases
- High (any visceral and/or 4+ bone) / Low (no visceral and <=3 bone)

Volume of bone metastases
- 0-3 / 4-9 / >9

Project Management

The data extraction and analysis will be carried out by the Project Management at the MRC CTU at UCL and any presentation or publication of results would be on behalf of the STOpCaP Steering Group (i.e. the Project Management and International Advisory Group).
Appendix A –

Search Strategies

MEDLINE Search strategy

Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE: sensitivity and precision
maximising version (2008 revision)(15); Ovid format

RCT filter MEDLINE

2. controlled clinical trial.pt.
3. "randomi*ed".ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
9. exp animals/ not humans.sh.
10. 8 not 9

AND

Terms specific to prostate cancer:

11. exp Prostatic Neoplasms/
12. (prostat$ adj3 adeno$).mp.
13. (prostat$ adj3 malignan$).mp.
15. (prostat$ adj3 carcinoma$).mp.
17. (prostat$ adj3 neoplas$).mp.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17

AND

Terms specific to Androgen deprivation Therapy (ADT)

19. ((androgen$ or hormon$) adj3 (ablat$ or block$ or withdraw$ or depriv$ or suppress$)).mp.
20. exp Antineoplastic Agents, Hormonal/tu [Therapeutic Use]
21. exp Androgen Antagonists/
22. (luteinizing hormone releasing hormone or LHRH).mp.
23. Orchiectomy.mp.
24. 19 or 20 or 21 or 22 or 23

AND

Terms specific to drug therapy:

25. exp Drug Therapy/
26. (multimodal$ or adjuvant or adjunct$).mp.
27. (together or plus or concurrent or combi$ or add$ or conjunct$).tw.
28. 25 or 26 or 27

AND

Terms specific to chemotherapy

29. ((chemotherapy or antineoplastic or anticancer) adj3 (agent$).tw.
30. exp chemotherapy adjuvant/
31. exp Antineoplastic agents/
32. docetaxel.tw.
33. taxotere.tw.
34. 29 or 30 or 31 or 32 or 33

AND

Terms specific to bisphosphonates:

35. exp diphosphonates/
36. exp bisphosphonates/
37. (bisphosphonate$ or disphosphonat$).af.
38. zoledron$.af.
39. zometa.af.
40. aclasta.af.
41. 35 or 36 or 37 or 38 or 39 or 40

COMBINE ALL

42. 10 and 18 and 24 and 28
43. 34 or 41
44. 42 and 43

/ means all subheadings were selected
pt = publication type
mp = free text search for a term
tw term in a title/abstract
af term in all fields
EMBASE Search strategy

Best Optimisation of Sensitivity and Specificity Search(16); Ovid format

RCT filter EMBASE

1. randomi:.tw.
2. placebo:.mp.
3. double-blind:.tw.
4. 1 or 2 or 3
AND

Terms specific to prostate cancer:

5. exp Prostatic Neoplasms/
6. (prostat$ adj3 adeno$).mp.
7. (prostat$ adj3 malignan$).mp.
8. (prostat$ adj3 canc$).mp.
9. (prostat$ adj3 carcinoma$).mp.
11. (prostat$ adj3 neoplas$).mp.
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
AND

Terms specific to Androgen deprivation Therapy (ADT)

13. ((androgen$ or hormon$) adj3 (ablat$ or block$ or withdraw$ or depriv$ or suppress$)).mp.
14. exp Antineoplastic Agents, Hormonal/tu [Therapeutic Use]
15. exp Androgen Antagonists/
16. (luteinizing hormone releasing hormone or LHRH).mp.
17. Orchiectomy.mp.
18. 13 or 14 or 15 or 16 or 17
AND

Terms specific to drug therapy:

19. exp Drug Therapy/
20. (multimodal$ or adjuvant or adjunct$).mp.
21. (together or plus or concurrent or combin$ or add$ or conjunct$).tw.
22. 19 or 20 or 21
AND

Terms specific to chemotherapy
23. ((chemotherapy or antineoplastic or anticancer) adj3 (agent$).tw.
24. exp chemotherapy adjuvant/
25. exp Antineoplastic agents/
26. docetaxel.tw.
27. taxotere.tw.
28. 23 or 24 or 25 or 26 or 27

AND

Terms specific to bisphosphonates:

29. exp diphosphonates/
30. exp bisphosphonates/
31. (bisphosphonate$ or disphosphonat$).af.
32. zolatedr$.af.
33. zometa.af.
34. aclasta.af.
35. 29 or 30 or 31 or 32 or 33 or 34

COMBINE ALL

36. 4 and 12 and 18 and 22
37. 28 or 35
38. 36 and 37
LILACS Search strategy

Search Strategy 1
Highly Sensitive Search Strategy(17); Lilacs format

ENTERED AS:

(Tw estud$ OR Tw clinic$ OR AB grupo$ OR CT COMPARATIVE STUDY OR Tw placebo$ OR Tw random$ OR Ti compara$ OR Ti tratamiento OR Tw control$ OR MH/dt) AND NOT ((CT ANIMALS FEMALE OR CT ANIMALS MALE OR CT CATS OR CT CATTLE OR CT CHICK EMBRYO OR CT DOGS OR CT GUINEA PIGS OR CT IN VITRO OR CT MICE OR CT RABBITS OR CT RATS) OR (MH Prevalence OR MH Practice Guidelines OR MH Diagnosis, Differential OR MH Cross-Sectional Studies OR MH predictive value of tests) OR (Ti clinical AND case OR Ti updat$ OR Ti Epidemiol$ OR Ti clinical$ AND case$ OR Ti caso AND clinico OR Ti review OR Ti diagno$ AND treatment OR Ti descrip$ OR Ti consenso OR Ti caso$ AND control$ OR Ti analisis AND critico) OR (AB retrospectiv$ and stud$ OR AB estudio AND retrospectivo OR AB revis$ AND ficha$ OR AB revision AND bibliograf$ OR AB estud$ AND descrip$ OR AB presenta AND caso OR AB describe AND caso OR AB serie AND clinica OR AB puesta AND al AND dia OR AB tratamiento AND diagnostic$ AND revis$ OR AB experien$ AND caso$ OR AB analisis AND critico) OR (PT case reports OR PT review) AND NOT (Tw estud$ OR AB grupo$ OR Tw control$ OR Tw random$)) [Words]

And

(Mh prostatic neoplasms/) or (tw prostat$ AND (Tw carcinoma$ or Tw canc$ or Tw tumo$ or Tw neoplas$)) [Words]

And

(Mh Drug therapy/) or (Tw chemotherapy) [Words]

(Mh prostatic neoplasms/) or (tw prostat$ AND (Tw carcinoma$ or Tw canc$ or Tw tumo$ or Tw neoplas$))

And (Mh Drug therapy/) or (Tw chemotherapy)
Search Strategy 2

Sensitive search strategy to retrieve CLINICAL TRIALS in the LILACS database

(((PT:"Ensaio Clinico Controlado Aleatorio" OR PT:"Ensaios Clinicos Controlados Aleatorios como Assunto" OR MH:"Ensaios Clinicos Controlados como Assunto" OR MH:"Ensaios Clinicos como Assunto" OR PT:"Estudo Multicentrico" OR MH:"Distribucio Aleatoria" OR MH:"Metodo Duplo-Cego" OR MH:"Metodo Simples-Cego") OR ((MH:"Grupos Controle" OR MH:"Estudos Cross-Over" OR MH:"Estudos de seguimento" OR MH:"Estudos prospectivos") AND PT:"Estudo comparativo") OR PT:"Estudos de avaliação") AND ((tw:ensaios $ or tw:ensayos $ or tw:trial$ or tw:estudios $ or tw:estudio$ or tw:study or tw:studies) AND (tw:azar or tw:acaso or tw:enmascarado or tw:placebo$ or tw:control$ or tw:aleat$ or tw:random$ or tw:dobleciego or tw:simpleciego or (tw:simple$ or tw:single or tw:duplo$ or tw:doble$ or tw:mask$)) AND tw:clinic$)) OR ((tw:ensaios $ or tw:ensayos $ or tw:trial$) AND (tw:azar or tw:acaso or tw:enmascarado or tw:placebo$ or tw:control$ or tw:aleat$ or tw:random$ or tw:dobleciego or tw:simpleciego or (tw:simple$ or tw:single or tw:duplo$ or tw:doble$ or tw:mask$)) AND tw:clinic$)) AND NOT (MH:animais OR MH:ratos OR MH:camundongos OR MH:gatos OR MH:primatas OR MH:coelhos OR MH:suinos OR PT:"in vitro")

Controlled Clinical Trials / Ensaios Clinicos Controlados / Ensayos Clinicos Controlados

((PT:"randomized controlled trial" OR PT:"controlled clinical trial" OR PT:"multicenter study" OR MH:"randomized controlled trials as topic" OR MH:"controlled clinical trials as topic" OR MH:"multicenter studies as topic" OR MH:"random allocation" OR MH:"double-blind method" OR MH:"single-blind method") OR ((ensaio $ OR ensayo$ OR trial$) AND (azar or acaso or placebo OR control$ or aleat$ OR random$ OR enmascarado$ OR simpleciego$ OR (simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask$)) AND临床)) AND NOT (MH:animals OR MH:rabbits OR MH:rats OR MH:primates OR MH:dogs OR MH:cats OR MH:swine OR PT:"in vitro")

(MH:prostatic neoplasms) or (tw prostat$ AND (Tw carcinoma$ or Tw canc$ or Tw tumo$ or Tw neoplas$)) And (Mh Drug therapy/) or (Tw chemotherapy)
From Brazilian Cochrane Center website (March 2014)

Search Strategy 3
Ensaios clinicos randomizados (23, 24)

((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascara$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal)))

(MH:prostatic neoplasms) or (tw prostat$ AND (Tw carcinoma$ or Tw canc$ or Tw tumo$ or Tw neoplas$)) And (Mh Drug therapy/) or (Tw chemotherapy)
References


