Hormone therapy: Clinical question 4
Systematic review undertaken to address the clinical question:

What should be done for patients with rising PSA levels and normal testosterone levels following definitive radiotherapy or radical prostatectomy?

Methods

Initial Literature Search
There were 12 hormone therapy questions requiring systematic reviews. An initial literature search was undertaken to identify trials that might be relevant to those questions. Medline (1966 – October 2006), EMBASE (1988 – October 2006) and CINAHL (1982 – October 2006) databases were searched. The search contained keywords and subject headings, such as “antiandrogens.mp.” and “exp castration/” respectively. This search was coupled with keywords and subheadings aimed at identifying prostate cancer-based research, such as “exp prostatic neoplasms/”. The Cochrane Collaboration randomised controlled trial search filter was then applied. All citations from this search were reviewed for relevant articles. A complete list of the terms used for all search strategies are included as Appendix A. Reference lists of all articles obtained were reviewed for additional relevant clinical trials.

Guidelines and Systematic Reviews
Systematic reviews and relevant recent (2000 onwards) guidelines were found by scanning the citations resulting from the literature search, and searching the Cochrane Database of Systematic Reviews and the National Guideline Clearinghouse (www.guidelines.gov).

Inclusion Criteria
Included studies:

- Examined the intervention of hormone therapy;
- Employed a relevant randomised control group;
- Included patients with rising PSA levels post definitive local therapy and these patients either represented at least 80% of included patients or survival outcomes were reported separately for this group;
- Were published in English;
- Were published prior to April 1 2006.
Results

Results of Literature Search

The combined Medline, EMBASE and CINAHL database search identified 4169 citations. Titles and abstracts were examined and 367 articles were retrieved for more detailed evaluation. Only 9 of the articles retrieved were potentially relevant to question 4. The guidelines and systematic reviews searches identified an additional meta-analysis potentially relevant to question 4.

One trial met the inclusion criteria for question 4 and was included in the review for this question. Routine scanning of recent relevant journal article titles published after April 2006 identified no further articles.

The references and the reasons for exclusion of the excluded articles are included in Appendix B. In summary, most articles were excluded because they were reviews or because they did not meet the inclusion criteria requiring patients with rising PSA post local definitive therapy.
Figure 1. Process of inclusion and exclusion of studies for this systematic review

Study characteristics
Characteristics of the included study is described in table 1
### Table 1: Immediate vs deferred hormone therapy for men with detectable PSA levels post prostatectomy: study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Design</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andriole 1995</td>
<td>Radical prostatectomy in the past 10 years</td>
<td>RCT</td>
<td>Finasteride (10 mg/day) for 12 months</td>
<td>Placebo daily for 12 months</td>
<td>PSA levels</td>
<td>Double blinded for first 12 months</td>
</tr>
<tr>
<td>(North America)</td>
<td>PSA levels 0.6 – 10.0 ng/ml</td>
<td>Multi-centre</td>
<td>Followed by an offer to continue finasteride for another 12 months</td>
<td>Followed by an offer at 12 months of finasteride (10mg/day) for 12 months</td>
<td>Disease (clinical or biochemical) progression</td>
<td>Intention to treat analyses for 12 month data</td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td>No skeletal metastases on bone scan</td>
<td></td>
<td></td>
<td></td>
<td>Toxicity</td>
<td>Heterogeneous group of patients</td>
</tr>
<tr>
<td>Industry</td>
<td>Any palpable mass negative on biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time between surgery and study entry varied (median 2.8-2.9 years)</td>
</tr>
<tr>
<td>associations</td>
<td>No previous androgen deprivation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time between surgery and post-surgical detection of PSA varied</td>
</tr>
<tr>
<td></td>
<td>No radiotherapy less than 6 months before entry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment discontinued on clinical progression or during the first 12 months if PSA levels increased by 10ng/ml above baseline levels or during second 12 months if PSA levels rose to twice 12 month levels</td>
</tr>
<tr>
<td></td>
<td>N = 120</td>
<td>N = 54</td>
<td>N = 66</td>
<td>Maximum follow-up 24 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Study Quality for question 4

Table 2: Methodological quality of included randomised controlled trials from which data for survival outcomes was extracted (n = 1).

<table>
<thead>
<tr>
<th>Quality Category</th>
<th>At 12 months follow-up</th>
<th>At 24 months follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the study double-blinded?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Reasonably certain double-blind (e.g. identical placebo)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>b. Single-blind, objective outcomes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>c. Not blinded, not reported</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2. Concealment of treatment allocation schedule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Adequately concealed (e.g. central randomisation)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>b. Inadequately concealed (e.g. sealed envelopes)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>c. No concealment, not reported</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3. Inclusion of all randomised participants in analysis of majority of outcomes (i.e. ITT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. No exclusions, survival analysis used</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>b. Exclusions not likely to cause bias</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>c. Too many exclusions, not reported</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4. Generation of allocation sequences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Adequate (e.g. computer random number generator)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>b. Inadequate, not reported</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

ITT = intention-to-treat
Study Results

Table 3: Results for biochemical progression

<table>
<thead>
<tr>
<th>Study</th>
<th>Definition</th>
<th>Outcome</th>
<th>Intervention</th>
<th>Comparison Group</th>
<th>p value</th>
<th>Length of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate hormone therapy vs deferred hormone therapy</td>
<td>Increase in PSA level from baseline PSA level (ng/ml)</td>
<td>Median</td>
<td>~0.5</td>
<td>~1.5</td>
<td>≤ 0.01</td>
<td>12 months</td>
</tr>
<tr>
<td>Andriole 1995 (North America)</td>
<td>Subgroup analyses for patients with data at 18 months</td>
<td>~0.5</td>
<td>~1.5</td>
<td>NS</td>
<td></td>
<td>24 months</td>
</tr>
</tbody>
</table>

~ Approximate; NS = Not statistically significantly different
REFERENCES FOR INCLUDED STUDIES

Appendices
Appendix A

Search strategy:

1. exp prostatic neoplasms/
2. (prostat$ adj3 (cancer$ OR carcinoma$ OR malig$ OR tumo?r$ OR neoplas$ OR metastas$ OR adeno$)).mp
3. exp androgen antagonists/
4. exp antineoplastic agents, hormonal/tu
5. exp hormone antagonists/
6. antiandrogens.mp
7. exp antiandrogens/
8. anti androgens.mp
9. gonadotrophin releasing hormone analog$.mp
10. grha.mp
11. goserelin.mp
12. exp goserelin/
13. zoladex.mp
14. exp cyproterone acetate/
15. exp bicalutamide/
16. bicalutamide.mp
17. casodex.mp
18. exp estrogens/
19. exp estrogen/
20. oestrogen.mp
21. exp leuprolide/
22. exp leuprolol
23. eligard.mp
24. lupron depot.mp
25. viadur.mp
26. (leuprolide or enatone or lupron or tap-144).mp
27. exp flutamide/
28. eulexin.mp
29. nifitolid$.mp
30. nitulamide.mp
31. nilandron.mp
32. anandron.mp
33. exp diethylstilbestrol/
34. exp gonadorelin/
35. exp gonadorelin agonist/
36. (luteinizing hormone releasing hormone or LHRH).mp
37. exp gonadorelin antagonist/
38. exp progestins/
39. exp gonadorelin acetate/
40. exp megestrol/
41. exp megestrol acetate/
42. megestrol.mp
43. megestrol acetate.mp
44. exp finasteride/
45. proscar.mp
46. exp buserelin/
47. exp buserelin acetate/
48. orchiectomy.mp
49. exp orchiectomy/
50. exp castration/
51. randomized controlled trial.pt.
52. controlled clinical trial.pt.
53. randomized controlled trials/
54. random allocation/
55. double blind method/
56. single blind method/
57. or/51-56
58. animals/ not (animals/ and humans/)
59. 57 not 58
60. clinical trial.pt.
61. exp clinical trial/
62. (clinic$ adj25 trial$).tw
63. cross-over studies/
64. (crossover or cross over or cross-over).tw.
65. ((singl$ or doubl$ or treb$ or tripl$) adj25 (blind$ or mask$)).tw.
66. placebos/
67. placebo$.tw.
68. random$.tw.
69. research design/
70. or/60-69
71. 70 not 58
72. 59 or 71
73. 1 or 2
74. or/3-50
75. 73 and 74
76. 75 and 72
Appendix B: Excluded Publications

Hormone therapy – Question 4

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akduman 2003</td>
<td>Review</td>
</tr>
<tr>
<td>Davis 2003</td>
<td>Review</td>
</tr>
<tr>
<td>Loblaw 2004</td>
<td>No results reported specifically for this disease stage</td>
</tr>
<tr>
<td>Loblaw 2007</td>
<td>No results reported specifically for this disease stage</td>
</tr>
<tr>
<td>Marks 2003</td>
<td>Review</td>
</tr>
<tr>
<td>Ryan 2006</td>
<td>Review</td>
</tr>
<tr>
<td>Sciarra 2004</td>
<td>No outcomes of interest</td>
</tr>
<tr>
<td>Shipley 2002</td>
<td>Not randomized to salvage hormone therapy</td>
</tr>
<tr>
<td>Teillac 2005</td>
<td>Review</td>
</tr>
</tbody>
</table>

References for excluded publications


