Initial Hormone Therapy

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Conflicts of Interest Disclosure

Alan Horwich

I have no personal conflicts of interest relating to prostate cancer.
MANAGEMENT OF PROSTATE CANCER

Treatment “windows”

Subclinical

- Localised
  - PSA only recurrence
  - Asymptomatic metastases
  - Symptomatic metastases
- Castration resistant
- Post docetaxel
- Palliative care

20 years
Hormone Therapies for Prostate Cancer

- LHRH agonists
  - eg Zoladex, Prostap
- LHRH antagonists
  - eg Degarelix
- Androgen Receptor targeted
  - eg Casodex, Flutamide, Enzalutamide
- Steroids
  - eg Prednisone, Dexamethasone
- Oestrogens
  - eg Stilboestrol
- Cyp 17 inhibitors
Androgen Deprivation in M1 Disease

- 917 men with M1 disease treated 2005-2014 in the control arm of STAMPEDE
- Median FFS 11.2 months (IQR 5.1-28.8 months)
- Median overall survival 42.1 months (IQR 22.7-90.7 months)
Androgen Ablation in Prostate Cancer

- Loss of libido
- Erectile dysfunction
- Hot flushes
- Fatigue
- Loss of muscle mass
- Insulin resistance
- Cardiovascular effects
- Decreased bone mineral density
N=37443 diagnosis 2001-4 ; 14,597 had ADT. Mean observation 2.6 yrs.

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>Incident CHD</th>
<th>MI</th>
<th>Sudden Cardiac Death</th>
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<tbody>
<tr>
<td>No ADT</td>
<td>87</td>
<td>81</td>
<td>7.3</td>
<td>12</td>
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<tr>
<td>LHRHa</td>
<td>160</td>
<td>144</td>
<td>12.8</td>
<td>22</td>
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<tr>
<td>Orchidectomy</td>
<td>190</td>
<td>210</td>
<td>24.3</td>
<td>23</td>
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<tr>
<td>Antiandrogen</td>
<td>130</td>
<td>143</td>
<td>11.2</td>
<td>19</td>
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Cardiovascular Mortality After Androgen Deprivation Therapy for Locally Advanced Prostate Cancer: RTOG 85-31

Efstathiou JCO 2009 2792-99

No. = 945 FU 8.1 yrs
CVD = 117

At 9 yrs CVD 8% vs 11%
In favour of LHRHa group

Fig 1. Time to cardiovascular mortality by treatment arm for all eligible patients.
Osteoporosis and duration of LHRHa therapy Stage I-II Ca Prostate with PSA control

Morote  Eur Urol  2003  44  661

Prostatectomy controls == “None” for duration

<table>
<thead>
<tr>
<th>Femoral neck bone densitometry</th>
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<tr>
<td><strong>Duration of hormone therapy</strong></td>
</tr>
<tr>
<td>Incidence of osteoporosis</td>
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<td>Relative risk of hip fracture</td>
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Issues for Hormone Therapy in Metastatic Prostate Cancer

① Type of hormone therapy

① Immediate vs Deferred in asymptomatic patients?

② Intermittent or continuous?

③ Combine with other treatment eg chemotherapy, bone targeting agents, newer AR targeted drugs, radiotherapy to the primary site, steroids?
Issue 1-drug choice
A randomised comparison of 'Casodex' (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer.

- 1453 patients with locally advanced or metastatic prostate cancer.

- Less hot flushes and improved physical activity and sexual health on bicalutamide.

- In M1 disease bicalutamide was less effective (HR for mortality 1.3)
- No difference in the 480 men with locally-advanced disease

Figure 1  Kaplan-Meier analysis of overall survival in M1 patients treated with bicalutamide 150 mg monotherapy or castration (n = 805). Reproduced with kind permission.

Tyrrell et al 1998
Systematic Review of 13 studies (Kunath et al 2015 BMJ Open)
“Insufficient evidence to draw conclusions about efficacy compared to LHRH agonists”

• Role
  • in emergencies eg impending SCC
  • ? in intermittent therapy
  • BUT only monthly prep. And more injection site reactions
Issue 2. Immediate versus deferred treatment for advanced prostatic cancer:


- 948 men with locally-advanced or metastatic prostate cancer
- Randomised to immediate or deferred treatment (orchx or LHRH)

- Deferred patients had more prostate cancer deaths (257 vs 203 (p=0.001)
- Also more TURPs, pathological fractures, spinal cord compressions.

- BUT Pre PSA and 29 deferred patients died from prostate cancer without having started hormone treatment!

- Conclusion: Deferred treatment remains an option for selected indolent cases
Issue 2. EARLY VERSUS DELAYED ENDOCRINE TREATMENT OF pN1-3 M0 PROSTATE CANCER---Schroeder et al 2004 for EORTC

234 node positive patients having no local prostate treatment were randomised to immediate or deferred hormones

Underpowered.
Trend to improved survival with early treatment-HR 1.23 (95%ci 0.88-1.71)
but Delayed Treatment remains an option.
Issue 2. Immediate vs deferred hormone therapy in 985 men with M0 prostate cancer who had refused or were unsuitable for radical treatment. RESULT HR 1.25 for OS favours immediate treatment.

BUT Prostate cancer deaths deaths-no difference

Other cause

Conclusion: Deferred treatment an option in selected cases.

EORTC 30891 Studer et al 2006 JCO 24; 1868-76
Issue 3. Intermittent Androgen Suppression vs Continuous Androgen Deprivation
– PSA progression after local Rx; Crook et al NEJM 2012

Equivalent efficacy and Intermittent Hormones had improved Quality of Life

European Trial in M0 & M1 (de Silva et al 2009) - no significant difference in S
Issue 3. BUT Intermittent versus Continuous Androgen Deprivation in M1 Prostate Cancer. Hussain et al 2013 NEJM

Randomised after 7 months combined androgen blockade IF PSA≤4

Hazard Ratio 1.1 (95% CI 0.99-1.23)
“As CI exceeded 20% detriment, it CANNOT be concluded that Intermittent therapy is not inferior”.
Therefore Intermittent Hormones NOT standard in M1 disease.
Issue 4. Adding treatments to androgen deprivation.

COMBINED ANDROGEN BLOCKADE
= adding anti-androgen to hormone ablation

Systematic Review and Meta-Analysis of Monotherapy Compared with Combined Androgen Blockade for Patients with Advanced Prostate Carcinoma

Samson et al 2002

Modest benefit at 5 years probable outweighed by increased side-effects
Issue 4. Adding treatments to androgen deprivation.

STAMPEDE trial of celecoxib, Lancet Oncology 2012
Management of advanced/metastatic disease

• Continuous ADT is recommended as first-line treatment of metastatic, hormone-naïve disease [I, A].

• Men starting ADT should be informed that regular exercise reduces fatigue and improves quality of life [I, A].

• ADT plus docetaxel is recommended as first-line treatment of metastatic, hormone-naïve disease in men fit enough for chemotherapy [I, A].
6. STAMPEDE FROM 2014
STAMPEDE comparison of Standard of Care (ADT) versus ADT plus Abiraterone
James et al 2017 NEJM

2011-2014, n=1002 M1  median FU  40 months

HR 0.61
Latitude Trial
Fizazi et al 2017
ADT + Abiraterone vs ADT + Placebo

1199 M1 patients median FU 30.4 months

At 3 years, survival 66% for Abi vs 49% for placebo
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E-Update 2017

ADT plus abiraterone/prednisone may be considered as first-line treatment for metastatic, hormone-naïve disease. [I, A]
Role of radiotherapy to the primary in patients with metastases?

Mouse models of metastasis. Factors secreted by the primary tumors (e.g., VEGF-A, PIGF, PSAP) are thought to mobilize bone marrow–derived cells that are subsequently attracted to premetastatic sites. The cells of this “premetastatic niche” then release factors that can attract disseminating tumor cells...
Retrospective study in M1 Ca Prostate starting ADT

Local RT associated with longer survival on Uni and on Multi variate analysis

Bianchini et al 2017
PEACE-1: European Phase III Trial of Abiraterone Acetate in patients with newly diagnosed (hormone-naïve) metastatic prostate cancer

- Patients with newly diagnosed metastatic prostate cancer

Randomized

Androgen deprivation therapy (ADT)

ADT + Abiraterone 1000mg Prednisone 5mg BID

ADT + Local radiotherapy

ADT + Local radiotherapy + Abiraterone 1000 mg Prednisone 5mg BID

Co-primary endpoints:
OS and PFS (HR: 075)

n= 916 planned patients

2x2 design
Study sponsor: Unicancer

Courtesy of K Fizazi
Conclusions

• Hormone therapy is a highly effective initial systemic treatment for prostate cancer.

• It is a low toxicity treatment but there are impacts on quality of life.

• Single modality androgen deprivation with Docetaxel is the standard of care for initial Rx of M1 disease. ADT with Abiraterone has now been shown to be more effective than ADT alone.

• Variations such as deferred or intermittent hormone treatment are options to consider with selected patients.
Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial

- 385 M1 hormone-naïve: randomised 2004-2008 (median FU 50 months).
- No difference in overall survival (59 vs 54 months)

Gravis G, Fizazi K et al 2013. Lancet Oncol
Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer  
Sweeney et al 2015  NEJM 373: 737-46

790 M1 patients, 2006-2012
6x Docetaxel at 75mg/m2

Median OS 57 vs 44 months

HR similar over all subgroups
In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months. We projected 33 months in ADT alone arm with collaboration of SWOG9346 team.
Meta-analysis of trials of ADT + or – Docetaxel
Vale 2016 Lancet Oncology

In M0 disease there is no clear evidence of benefit
Though Confidence intervals still wide
And Benefit on FFS
Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

James et al Lancet 2015
2962 men randomised in 4 groups

1184 men Standard of Care (SOC)
593 men SOC plus zoledronic acid (2 years)
592 men SOC plus docetaxel x6
593 men SOC plus zoledronic acid plus docetaxel

PATIENTS
M1  1817  61%
N+/X  448  15%
N0M0  697  24%
Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

James et al. Lancet 2015 Open access

FFS

OS

HR 0.76
P<0.005
5. Adding steroid to androgen ablation -

Dexamethasone versus Prednisone Venkitaramen et al 2015
Eur Urol 67:673-679

Phase 2 RCT in 82 men with CRPC on ADT

Dex 1mg may be more effective than Pred 10mg as daily oral dose in CRPC
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PSA- PFS

OS

Median 23 v 13 months p=0.005
Docetaxel in hormone-naive metastatic prostate cancer. CHAARTED Trial: Sweeney et al ASCO 2014

Improved Overall Survival by 13 months!! Significant in High Volume subgroup.
And improved time to develop CRPC by 6.7 months and TTP (imaging) by 13 months.
GETUG-15 update

Median OS
ADT alone: 35.1 [29.9-44.2]
ADT + D: 39 [28-52.6]
HR: 0.8 [0.6-1.2]
p=0.35

Fizazi  GU ASCO 2015—median FU 83 months
Subgroup analysis of those with “High-Volume” metastases.