Initial Hormone Therapy

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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.... eg Abiraterone
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
Diabetes and cardiovascular disease during androgen deprivation for prostate cancer

Keating  JNCI 2010
VA Study

N=37443 diagnosis 2001-4 ; 14,597 had ADT. Mean observation 2.6 yrs.
Rate of event/1000 patient years and adjusted Hazard Ratio

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

Fig 1. Time to cardiovascular mortality by treatment arm for all eligible patients.

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
## 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>Duration of hormone therapy</td>
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<tr>
<td>Incidence of osteoporosis</td>
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<tr>
<td>Relative risk of hip fracture</td>
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Loss of bone mineral density particularly in first 6–12m (Daniell 2000, Mittan 2002)
Osteoporotic fracture rate increased. 4% 5yr, 20% 10yr (Oefelein 2001)
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?

④ Role with RT to the primary?
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)

![Graph showing survival rates for M1 patients treated with bicalutamide 150 mg monotherapy or castration. The bicalutamide group has a higher death rate compared to the castration group.]

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.

Median survivals:
Early-7.8 yrs
Delayed 6.2 yrs
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

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

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
Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial

Gravis G, Fizazi K et al 2013.
Lancet Oncol

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

PSA- PFS

Median 23 v 13 months p=0.005

OS
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
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

Zol

Doc

FFS

OS

HR 0.76

P<0.005
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].
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.
6. STAMPEDE FROM 2014
PEACE-1: European Phase III Trial of Abiraterone Acetate in patients with newly diagnosed (hormone-naïve) metastatic prostate cancer

Androgen deprivation therapy (ADT)

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

Co-primary endpoints:
OS and PFS (HR: 0.75)

Patients with newly diagnosed metastatic prostate cancer

n= 916 planned patients

2x2 design
Study sponsor: Unicancer
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 in combination with Docetaxel is the standard of care for initial Rx of M1 disease.

• Variations such as deferred or intermittent treatment are options to consider with your patients.