Hormone therapy in prostate cancer - overview

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Prostate cancer and treatment options

- High-grade PIN
- Localised prostate cancer
- Locally advanced disease
- Metastatic disease
- Hormone insensitive

Treatment options:
- Radical prostatectomy
- Radiotherapy
- ‘Active Surveillance’
- Hormonal therapy (Orchidectomy/LHRHa; CAB)
- Radiotherapy
- ‘Active Surveillance’
- Hormonal therapy
- Chemotherapy

Time (years)

PIN, prostatic intraepithelial neoplasia
Hormonal Therapy Options
Prostate cancer is hormone-dependent

LHRH, luteinising hormone-releasing hormone
LH, luteinising hormone
ACTH, adrenocorticotropic hormone

Testosterone

Hypothalamus

Pituitary

LHRH

Prolactin

Adrenal

Cortisol

Testes

Prostate

LH

Oestrogen

Adrenal androgens
Hormonal Therapy

- Bilateral orchiectomy
- LHRH analogs
- Antiandrogens
- Combined Androgen Blockade (CAB)
Bilateral Orchiectomy

- In 1941, Huggins and Hodges made original discovery of hormonal effect on prostate cancer

- Same studies also showed that bilateral orchiectomy improved pain or neurological symptoms in 71% of patients with metastatic disease

- Advantages:
  - Immediate castration without testosterone surge
  - Outpatient procedure, general anesthesia not required
  - No compliance issues

- Disadvantages:
  - Irreversible

Hormonal Therapy in Metastatic Disease

- HT has been most widely used in metastatic disease
- When to initiate HT is often debated
- MRC (UK) Study
  - 938 patients with locally advanced and asymptomatic, metastatic prostate cancer
  - Early HT (89% orchiectomy; within 6 weeks of entry) vs Deferred HT (71.5% orchiectomy)
- Survival, local and distant progression, major complications evaluated

934 evaluable patients results

<table>
<thead>
<tr>
<th></th>
<th>Deferred ARM (# of patients)</th>
<th>Immediate ARM (# of patients)</th>
<th>P values</th>
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</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td>361</td>
<td>328</td>
<td>P=0.02 Two-tailed</td>
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<td><strong>Cause Specific Death</strong></td>
<td>257</td>
<td>203</td>
<td>P=0.001 Two-tailed</td>
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<td><strong>TUR</strong></td>
<td>141</td>
<td>65</td>
<td>P&lt;0.001 Two-tailed</td>
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Castration alone in advanced disease

- Of all hormone-sensitive cancers, prostate cancer is the most sensitive to endocrine therapy
- Castration has been the ‘gold standard’ for treatment of advanced disease
- Surgical orchiectomy vs medical castration
Similar mean serum testosterone concentrations achieved with Zoladex (goserelin) 3.6 mg vs orchiectomy

Mean serum testosterone (nmol/L)

- Goserelin 3.6 mg (n=148)
- Orchiectomy (n=144)

Adapted from Peeling 1987
Zoladex 3.6 mg is as effective as orchiectomy in terms of overall survival in metastatic disease.

Kaisary et al 1991
Castration: Summary

- Patients prefer LHRH agonists vs surgical castration
  - LHRH agonist therapy can be reversed
- With 20 years' clinical experience, LHRH agonist therapy with goserelin has proven equivalent efficacy to surgical castration
- Goserelin is as effective as castration in terms of overall survival
- Compared with castration, goserelin offers¹
  - higher QoL scores (p=0.0001)
  - improved psychosocial status (p=0.01)

¹ Cassileth et al 1992
Mechanism of Action of Antiandrogens

GnRH = gonadotropin-releasing hormone
Rationale for Bicalutamide 150 mg monotherapy

- Bicalutamide 150 mg has shown equivalent efficacy to castration in M0 patients\(^1\)
- Bicalutamide 150 mg may offer additional significant QoL advantages over castration

1. Iversen et al 2000
Bicalutamide 150 mg in M0 disease

Studies 306 / 307

- Two open-label, multicentre studies that were pooled according to protocol
- 480 M0 patients with stage T3/4 prostate cancer were randomised 2:1 to receive
  - 150 mg bicalutamide daily
  - castration (patients chose either orchiectomy or goserelin 3.6 mg every 28 days)

Iversen et al 2000
Overall survival in M0 patients:
Median 6.3 years’ follow-up

HR 1.05; 95% CI 0.81, 1.31; p=0.70

Iversen et al 2000
CI, confidence interval; HR, hazard ratio
Bicalutamide 150 mg vs Castration
Quality of Life: M0 Patients

Favours castration Favours bicalutamide 150 mg

- Physical capacity
- Emotional well being
- Sexual interest
- Vitality
- Social function
- Pain
- Activity limitation
- Bed disability
- Overall health

Treatment effect and 95% 2-sided CI

Iversen et al, Urology 1998
Anti-androgen Monotherapy: Summary

- Bicalutamide 150 mg is as effective as castration in patients with non-metastatic disease
- Bicalutamide 150 mg may offer QoL benefits over castration
- Bicalutamide 150 mg is a viable treatment option
Combined androgen blockade (CAB)

- Bilateral orchiectomy or LHRH agonist
- Suppression of serum testosterone

- Antiandrogen
- Blockade of androgen action

LHRH, luteinsing hormone-releasing hormone
The biological Rationale for CAB

- Addition of antiandrogen to castration further suppresses activity of androgens and the AR
- There is a strong biological rationale for CAB in the treatment of prostate cancer
More recently, PCTCG meta-analysis of combination therapy versus monotherapy
- 27 trials: 8275 men
- 5-year overall survival favoured combination therapy (25.4% versus 23.6%)
- overall 1.8% improvement in survival at 5 years
CAB: findings from the PCTCG meta-analysis (n=8275)

5-year survival favoured CAB (25.4% vs 23.6%)

Outcome dependent on choice of antiandrogen

With NON-STEROIDAL antiandrogens*, there was a significant 8% reduction in the risk of death (p=0.005)

With STEROIDAL antiandrogens, there was a significant 13% increase in the risk of death (p=0.04)

*Flutamide or nilutamide

Klotz 2001; PCTCG 2000
PCTCG, Prostate Cancer Trialists' Collaborative Group
Adding Bicalutamide 50 mg to castration reduces the risk of death by 20%\textsuperscript{1}

\[ \text{HR (A vs C)} = \text{HR (A vs B)} \times \text{HR (B' vs C)} \]
\[ 0.80 = 0.87 \times 0.92 \]
\[ 20\% = \text{reduction in risk of death} \]

CAB with Bicalutamide vs castration: phase III study

- LHRHa plus bicalutamide 80 mg vs LHRHa alone in advanced disease (n=205)
- At 15 months follow-up, PFS longer for CAB ($p=0.016$)

Akaza et al 2005
Is there a role for hormonal therapy in localised disease?
RP as primary treatment with adjuvant HT
Locally advanced patients have an increased risk of prostate cancer death after RP.


*Localised disease was defined as T1-2, M0 patients, >64% had GS <7
**Locally advanced disease was defined as pN+, M0 patients, >88% had GS >6
Immediate castration* adjuvant to RP significantly improves OS in N+ patients
ECOG 7887 at 11.9 years’ median follow-up

Goserelin adjuvant to RP significantly reduced the risk of death by 46%
compared with RP alone

Messing et al 2006

*70% of patients received goserelin (Zoladex),
28% received orchietomy and 2% refused treatment
Bicalutamide 150 mg adjuvant to RP provides progression benefits
EPC programme at 7.6 years’ median follow-up

Bicalutamide adjuvant to RP significantly reduced the risk of progression by 25% compared with RP alone. There was no OS difference.

HR 0.75 (95% CI 0.61, 0.81; p=0.004)

- Bicalutamide 150 mg + RP (n=870)
- Placebo + RP (n=849)

McLeod et al 2006
T3-4, any N, M0 or any T, N+, M0 patients
RT as primary treatment with adjuvant HT
Goserelin adjuvant to RT significantly improves OS
EORTC 22863 at 5.5 years’ median follow-up

Patients surviving (%)

HR 0.51 (95% CI 0.36, 0.73; p=0.001)

Goserelin adjuvant to RT significantly reduced the risk of death by 49% compared with RT alone

Bolla et al 2002
T1-2 of WHO grade 3 or T3-4 N0-1, M0 disease
Bicalutamide 150 mg adjuvant to RT significantly improves OS EPC programme at 7.2 years’ median follow-up

- Bicalutamide 150 mg adjuvant to RT significantly reduced the risk of death by 35% compared with RT alone.

McLeod et al 2006
T3-4, any N; or any N, T, N+ patients
Summary: advantages of HT for patients with locally advanced disease

- HT adjuvant to RT and RP and as an alternative to WW offers clinical benefits\(^1\)
- Bicalutamide 150 mg and goserelin have similar OS benefits as monotherapy and as adjuvant to RT\(^1-3\)
- Bicalutamide 150 mg has additional quality-of-life benefits compared with castration; it maintains
  - sexual interest (\(p=0.029\))\(^3\)
  - physical capacity (\(p=0.046\))\(^3\)
  - BMD (\(p<0.0001\) at 48, 72 and 96 weeks)\(^4\)

The choice of therapy can be tailored to patients’ individual needs

Intermittent hormonal therapy in advanced disease

- CAB is effective
- It has been suggested that intermittent therapy could potentially
  - prolong the response to hormonal therapy
  - improve QoL
- EAU 2005 guidelines\(^1\) define intermittent therapy as ‘investigational’
- Phase III survival are now coming, data from ongoing studies are anticipated

1. Aus et al 2005
IAD: ongoing phase III studies

Portuguese trial

- 766 patients on HT, including CAB
- 626 randomised for continuous vs intermittent
  - 50% patients off therapy for ≥52 weeks
  - 20% patients off therapy for ≥36 months
- Responses linked to PSA at randomisation (<1 ng/mL)
- No difference in overall survival
  - HR for IAD 1.03 (95% CI, 0.83-1.28); p=0.79

Da Silva et al 2006
IAD: ongoing phase III studies

Portuguese trial: overall survival

Proportion surviving vs Time (months)

Da Silva et al, 2006
IAD: Summary

- Phase II trials have confirmed the feasibility of IAD in metastatic or biochemically recurrent disease
- PSA-response rates and improvements in symptoms are comparable to CAB
- Phase III prospective, randomised controlled trials are ongoing
  - survival and QoL data not yet mature
- IAD is currently offered to many patients in various clinical settings
- Until survival data mature, IAD should be regarded as an investigational approach

EAU guidelines 2005
Median response at approximately 6 months

Antiandrogen withdrawal and second-line hormonal therapy in CAB

Antiandrogen withdrawal

Progression generally occurs at approximately 5 months

Restart CAB with alternative antiandrogen

Median response at approximately 6 months
Antiandrogen withdrawal can reduce PSA levels: overview\textsuperscript{1,2,3}

- Response criteria: $\geq 50\%$ PSA decrease from baseline PSA level before antiandrogen withdrawal
- Response rate approx $25\%$ (range $10$-$80\%$)
- Responses occurred within $2$-$6$ weeks with flutamide and $4$-$8$ weeks with bicalutamide
- Median response duration approx $5$ months (range $2$-$25$)
- Objective clinical response: $2$-$15\%$ with antiandrogen withdrawal alone

Antiandrogen switching can prolong response to CAB: overview

- **CAB with bicalutamide switched to flutamide:**
  - 45% biochemical response rate
  - 22% durable response rate
  - Median response time 6 (1-13) months\(^1\)

- **CAB with flutamide switched to bicalutamide:**
  - 38-42% of biochemical response rates\(^2,3\)

- **CAB with flutamide switched to bicalutamide or bicalutamide switched to flutamide:**\(^4\)
  - Second-line flutamide response rate = 38%
  - Second-line bicalutamide response rate = 44%
  - Switching to a third-line antiandrogen was less effective

\(^{1}\) Miyake 2004; \(^{2}\) Scher 1997; \(^{3}\) Joyce 1998; \(^{4}\) Kojima 2004
PROSTATE CANCER

Overview of Hormone responsive Prostate Cancer

- Neo adjuvant AAT is shown to prolong survival in high risk patients treated with RT & RP
- Earlier AAT is better than delayed AAT as it delays appearance of symptoms and metastases in recurrent disease.
- LHRH agonists and bilateral orchiectomy is equally effective
- MAB limited benefit over castration
PROSTATE CANCER

Overview of Hormone responsive Prostate Cancer

- Anti androgens should precede LHRH agonists in patient with overt metastases.
- Anti androgen monotherapy is less effective than castration.
- Intermittent androgen ablation to reduce side effects – long efficacy remains unproven.
- Androgen receptors active in HRPC. Thus testosterone suppression to continue.
THANK YOU