Castration resistant prostate cancer—what is it?

...and what do we do about it?

Urology Postgraduate Course
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Localized Disease
Rising PSA (non-castrate)
Metastatic Disease
Castration Resistant Prostate Cancer
Death

Treatment Population = Incidence of 30,000 pts/yr X 4 years Natural History = 120,000 pt prevalence

The Hypothalamic-Pituitary-Gonadal Axis and Therapeutic Interventions

HYPOTHALMUS
LHRH agonists
(Lupron, Zoladex)

PITUITARY
FSH, LH
Ketoconazole / aminoglutethimide
Antiandrogens:
steroidal (Megace) and non-steroidal (Casodex, Flutamide, Nilutamide)

TESTIS
Kispeptin
Testosterone

PROSTATE CANCER CELLS
500 ng/mL
Testosterone

Hypothesis: Low androgen levels + Hypersensitive AR drives Resistance

Schematic Model of Castration Resistance

50 ng/mL
PSA
Castration Therapy
Castration Resistance
The Reality of CRPC Treatment

Primary Hormonal Therapy  
Secondary Hormonal Therapy  
Chemotherapy

...why truly “Androgen Independent” Prostate cancer may not exist...

- Persistent AR signaling may be an early event associated with recurrence
- AR copy number increases with disease progression.
- Persistent Serum Androgens may stimulate tumor growth despite “castration” therapy
- Intratumoral androgens may stimulate tumor growth
- Novel therapies are in development that exploit these axes.

Mechanism 1

AR Amplification

Higher AR levels in HRPC tumors
**Mechanism 2: Persistent Serum Androgens**

- **Androgens**
  - Cholesterol
  - Cholesterol Side Chain Cleavage
  - 3-BHSD-I
  - C17-20 lyase
  - 17-hydroxylase
- **Glucocorticoids**
  - Cortisol
  - Androstenedione
  - Testosterone
  - DHT
  - 5-reductase
- **Mineralocorticoids**
  - Aldosterone
  - DOC
  - Corticosterone
- **Peripheral Tissues**
  - ACTH
  - Pituitary
  - Glucocorticoids
  - Mineralocorticoids

**Randomized Phase III Study of Ketoconazole vs AAWD->Keto**

- **AAWD**
- **AAWD + Ketoconazole 400 tid plus HC 20/10**

**Are Serum Androgens Important in Castration Resistant Disease?**

- **AAWD**
- **AAWD + Ketoconazole 400 tid plus HC 20/10**

Tail of Curve Effect - 20-30: prolonged PFS / Survival -

Are pretreatment androgen levels a treatment predictive factor for patients receiving secondary hormonal therapy?

Small et al, *Journal of Clinical Oncology* 2004
CALGB 9583: Adrenal Androgens During Ketoconazole Therapy

Androstenedione 0.63 (0.5, 1.1) 0.31 (0.2, 0.4) 0.33 (0.2, 0.6) 0.45 (0.3, 0.6)
DHEAS 317 (144, 696) 30 (1, 86) 53 (1, 173) 119 (30, 258)
DHEA 2.1 (1.6, 3.3) 1.0 (0.8, 1.3) 1.0 (0.7, 1.5) 1.2 (0.8, 2.0)
Testosterone 13 (1, 19) 11 (1, 17) 10 (1, 15) 10 (1, 17)

Ketoconazole Therapy

AAWD

Androgen Resurgence at Progression on Keto

Do Androgen levels predict outcome?

Androgens as Treatment Predictive Factors: Conclusions

- Presence of androgens modestly associates with likelihood of response to ketoconazole.
- Low levels of androstenedione associates with shortened survival.
  - Truly “hormone refractory”
- Do these androgens represent the only available “supply” for the AR?

Mechanism 3

Intratumoral Androgen (production and sequestration)
Male volunteers N=13 (4 per group)
ages 35-55 yr (prostate-specific antigen < 2.0 ng/ml; normal transrectal ultrasound)
randomly assigned to:
1) a long-acting GnRH-antagonist, acyline, every 2 wk;
2) acyline plus testosterone (T) gel (10 mg/d);
3) placebo for 28 d.
Serum hormones were assessed weekly.
Prostate biopsies were obtained on d 28.
Extracted androgens were measured by RIA, and immunohistochemistry for androgen-regulated proteins was performed.

Persistent Intraprostatic Androgen Concentrations after Medical Castration in Healthy Men

Prostate sequesters DHT, T to a lesser extent

5 Alpha Reductase in Recurrent prostate Cancer
•5 alpha reductase converts:
  • T to DHT in Tumor
  •Androstenedione to Androstanediene

Results:
•Type 1 5 alpha reductase increases relative to Type 2 in recurrent CaP

Intraprostatic Androgens in Recurrent PC = Androgen Stimulated Prostate

Genes Expressed at Higher Levels in AIPC BM Biopsies
(Compared to primaries - among others)

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Fold (AIPC/Primary)</th>
<th>Gene Name</th>
<th>Significance</th>
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<tbody>
<tr>
<td>ARC1</td>
<td>5.84</td>
<td>Androgen Receptor</td>
<td>Androstenedione to Androstenedione</td>
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<tr>
<td>ARK1C3</td>
<td>5.27</td>
<td>Aldo-keto reductase family 1, member C3</td>
<td>Converts androstenedione to Androstenedione</td>
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<tr>
<td>SRT5M1</td>
<td>3.2</td>
<td>5 alpha reductase type 2</td>
<td>Converts T to DHT</td>
</tr>
<tr>
<td>HSD11B2</td>
<td>3.4</td>
<td>11 beta-hydroxysteroid dehydrogenase type 2</td>
<td>Converts DHEA to Androstanediene</td>
</tr>
<tr>
<td>ARK1C2</td>
<td>3.4</td>
<td>Aldo-keto reductase 1</td>
<td>Converts Androstenedione to Androstenedione</td>
</tr>
<tr>
<td>ARK1C1</td>
<td>3.1</td>
<td>Aldo-keto reductase 1</td>
<td>Carboxyl Dioxygenase</td>
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Stanbrough et al Cancer Research March 1, 2006
Net Increase in Androgen Synthesis Enzymes

Figure 3. Increased expression of enzymes mediating androgen synthesis and catabolism in androgen-independent prostate cancer. Androgen synthesis (from adrenal DHEA and androstenedione) and catabolism are outlined, and fold increase for each enzyme is indicated. The indicated metabolites are 5-androstane-3,17α-diol (3α-diol), and 5-androstane-3α,17β-diol (3β-diol).

Secondary Hormonal Therapy:

“Adrenal” Androgen Inhibition – Does it Validate Mechanism?
Activity of Abiraterone in Patients Previously Treated with Ketoconazole

- Response to abiraterone in patients with prior ketoconazole therapy: 10/19 (53%)
- Response to abiraterone in patients with no prior ketoconazole therapy: 6/11 (55%)
- Time to Progression in post-ketoconazole patients: 21 weeks

Ryan et al. Proc ASCO GU Symposium 2008

Conclusions

Androgen/AR interactions persist in Castration Resistant Prostate Cancer.

Intratumor steroid production suggests these effects are not "endocrine" or even "hormonal" at all.

Abiraterone acetate demonstrates considerable activity.

Responses in prior ketoconazole responders suggest "Pathway addiction" can be identified by these therapies.