

What's New in Advanced Disease (CRPC)?

~ *Matthew Rettig, MD*

What's New in Advanced Disease (castration resistant prostate cancer = CRPC)?

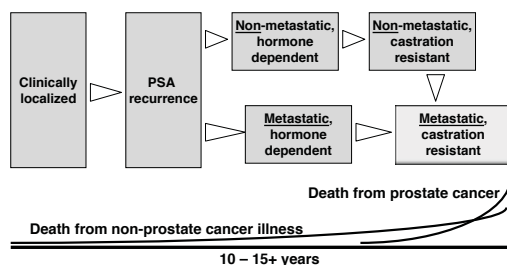
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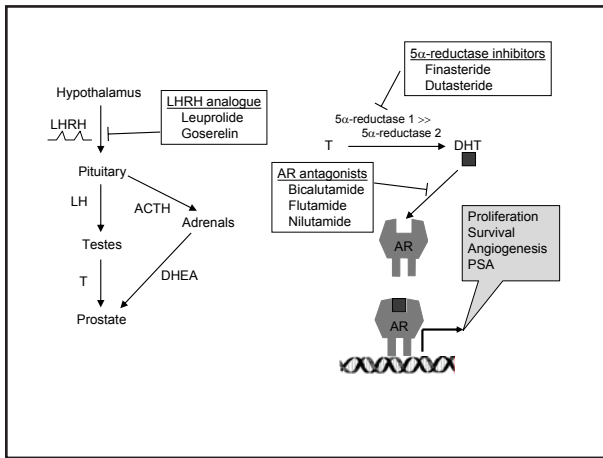
Novel/Emerging Therapies

- Differentiating Agents
 - HDAC inhibitors (vorinostat)
- Immunotherapies
 - Sipuleucel (Provenge), ipilimumab (anti-CTLA4)
- Gene Therapy—Virus Based
 - Induce death, Enzyme/Prodrug, replace defective genes
- Targeting Aberrant Cell Signaling
 - ZD4054, oblimersen, etc
- Angiogenesis
 - Avastin, Aflibercept, Thalidomide
- AR targeting agents
 - MDV3100
 - Abiraterone
- Hedgehog inhibitor



Clinical States of Prostate Cancer





CRPC as the Preferred Terminology

- The terms androgen-independent prostate cancer (AIPC) and hormone refractory prostate cancer (HRPC) imply that additional hormonal manipulations will be ineffective, yet secondary and tertiary hormonal therapies may be effective.
- CRPC indicates some measure of progression of disease (i.e. biochemical, clinical or radiographic) despite castrate levels of circulating androgens.

Current Management of Metastatic CRPC

- Median survival is 12-18 months.
- Secondary and tertiary hormonal manipulations are reasonable options:
 - Stop AR antagonist and observe for AR "withdrawal response."
 - Switch AR antagonist. (e.g. flutamide => bicalutamide).
 - Initiate ketoconazole.
 - Estrogens: high CV risk.
 - PSA response rates from 20-60%. No established survival benefit.
- Palliative management:
 - Spot radiation
 - radionuclide therapy
 - samarium 153
 - strontium 89
 - Bisphosphonates (zoledronate)

Current Management of Metastatic CRPC

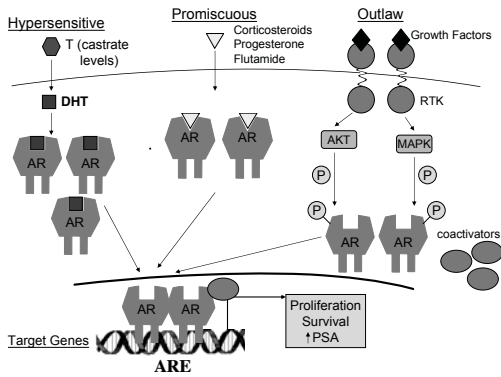
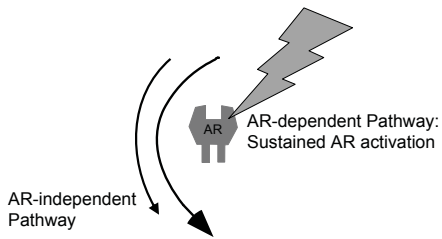
- Docetaxel-based chemotherapy is the only treatment that has been established to extend life expectancy in patients with *metastatic* CRPC.
 - extends median survival by 2-3 months.^{1,2}
 - Well-tolerated and can be given irrespective of age.

¹ NEJM 351:1502, 2004
² NEJM 351:1513, 2004

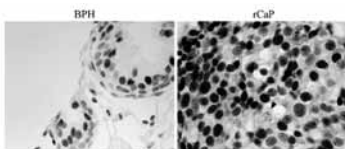
Mechanisms of Castration Resistance

- 1. AR-dependent
- 2. AR-independent

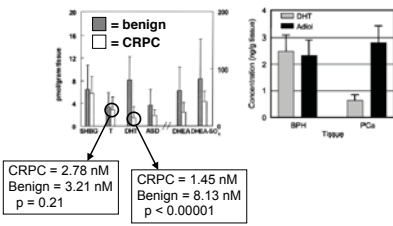
Mechanisms Giving Rise to CRPC



AR Expression in CRPC

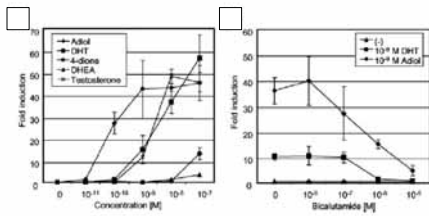


Intracellular Androgen Levels in CRPC



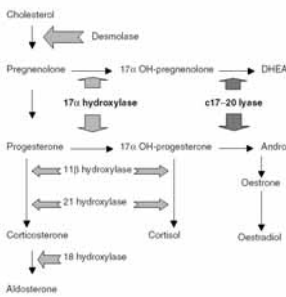
Clin Can Res 10:440, 2004.
Can Res 64:765, 2004.

Activation of AR transcriptional activity by androgens

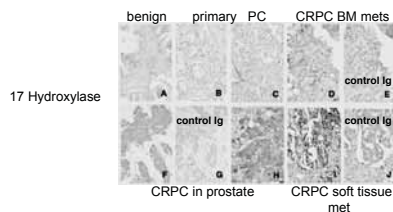


Can Res 64:765, 2004.

Biosynthesis of Androgens



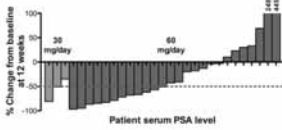
CRPC cells activate the androgen synthesis enzymatic pathway.



Cancer Res 66:2815, 2006.

MDV3100: Phase 1-2 results

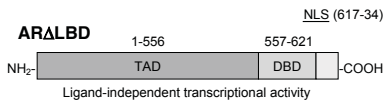
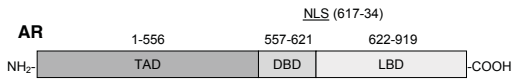
- 22/30 have PSA response, 12 of which were > 50% decline.



- Phase 3 has enrolled first patient in 9/09.

Science 324:787, 2009.

A Cautionary Note



J. Steroid Biochem Mol Biol. 41: 671-675, 1992.
 Cancer Res. 67:2007, 2007.
 Cancer Res. 68:5469, 2008.
 Cancer Res. 69:16, 2009.

Conclusions, Take Home Messages, and Other Comments

- CRPC is a lethal event.
- The AR represents a viable molecular target in at least a subset of CRPCs.
 - However, the biochemical and molecular events that lead to castration resistance are extremely complex and a simple therapeutic agent is not apt to be effective in all or perhaps even most cases.
- Innumerable drugs are in various stages of pre-clinical and clinical development, and incremental advances are anticipated. Major advances will require the identification and targeting of sentinel growth promoting molecular events.