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

Matthew Rettig, MD
Associate Professor
Department of Medicine
Division of Hematology-Oncology
Department of Urology
Medical Director, Prostate Cancer Program
Institute of Urologic Oncology
David Geffen School of Medicine at UCLA

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, olimersen, etc
• Angiogenesis
  – Avastin, Aflibercept, Thalidomide
• AR targeting agents
  – MDV3100
  – Abiraterone
• Hedgehog inhibitor

Clinical States of Prostate Cancer

Clinically localized → PSA recurrence → Non-metastatic, hormone dependent → Non-metastatic, castration resistant
Non-metastatic, hormone dependent → Metastatic, hormone dependent → Metastatic, castration resistant

Death from prostate cancer

10 – 15+ years

Death from non-prostate cancer illness
What’s New in Advanced Disease (CRPC)?

**Huggins and Hormone Therapy**

Charles Huggins, M.D. (1901-1997)

"We wanted to see if hormone therapy would do for elderly gentlemen what it would do for their best friends, elderly male dogs."

First recognition of CRPC.

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**AR Working Mechanism**

The first series of patients with prostatic cancer treated by orchietomy comprised 21 patients with far advanced metastases; only 4 of them survived for more than 12 years. Despite regressions of great magnitude, it is obvious that there were many failures of endocrine therapy to control the disease but on the whole, the life-span had been extended by the novel treatments and there had been a decrease in main-pain hours.

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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 $\rightarrow$ 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.\textsuperscript{1,2}
  - Well-tolerated and can be given irrespective of age.

\textsuperscript{1} NEJM 351:1502, 2004
\textsuperscript{2} NEJM 351:1513, 2004
Mechanisms of Castration Resistance

1. AR-dependent
2. AR-independent

Mechanisms Giving Rise to CRPC

AR-dependent Pathway: Sustained AR activation

AR-independent Pathway

AR Expression in CRPC

Clin Cancer Res 10:440, 2004
Intracellular Androgen Levels in CRPC

- CRPC = 2.78 nM
- Benign = 3.21 nM

\( p = 0.21 \)


Activation of AR transcriptional activity by androgens


Biosynthesis of Androgens

CRPC cells activate the androgen synthesis enzymatic pathway.

What’s New in Advanced Disease (CRPC)?

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Biosynthesis of Androgens

Inhibition Androgen Production
Abiraterone Phase 2 CRPC: Chemo-Naive
- 27/44 (61%) have durable PSA declines ≥ 50%.
- 11/44 (25%) had ≥ 90% PSA decline.
- 21 patients with measurable disease.
  - 14/21 pts with objective partial response.
  - 7/21 pts with stable disease > 3 months.

Abiraterone Phase 2 CRPC: Post-Docetaxel
- 14/28 patients with ≥ 50% PSA decline.
  - Median time to PSA progression ~ 6 months.
- 4/18 pts with measurable disease had PR.

Phase 3 Study of Abiraterone: (post-chemotherapy metastatic CRPC)
- Multinational, phase 3, placebo-controlled, double-blind study in patients with metastatic CRPC with progression after docetaxel-based chemotherapy.
  - 175 centers, 1158 patients.
- Randomization allocation 2:1 (abiraterone:placebo).
  - All patients receive prednisone 5 mg po bid.
- Primary endpoint = Overall Survival.
- Accrual completed.

Phase 3 Study of Abiraterone: (pre-chemotherapy metastatic CRPC)
- Multinational, phase 3, placebo-controlled, double-blind study in asymptomatic or minimally symptomatic patients with metastatic CRPC who are chemotherapy naive.
- Primary endpoint = Progression-Free Survival.
- First patient enrolled in 2009.
**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.


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**A Cautionary Note**

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Ligand-independent transcriptional activity


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**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.