Contemporary Management of Advanced Prostate Cancer

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MGH Prostate Cancer Support Group
14 May 2014
Outline

A recap of FDA-approved therapies

- Chemotherapy
- Hormonal agents
- Immunotherapy
- Radiotherapy

A selection of treatments under investigation
Defining the disease: advanced prostate cancer has multiple disease states

Treatment of metastatic prostate cancer 2009

- **Castration (ADT)**
  - **Castration-sensitive**
  - **Hormone-sensitive**
  - **Androgen-independent**
  - **Castration-resistant**

- **Secondary Hormone Rx**
  - **Docetaxel**

- **Highly variable**
Castration stops testosterone stimulation of prostate cancer via the androgen receptor (AR)

Nobel Prize in Physiology or Medicine, 1966

“for his discoveries concerning hormonal treatment of prostatic cancer”

Charles Huggins, M.D. (1901 – 1997)

1. Huggins C, Hodges CV. Cancer Res. 1:293-297, 1941

Source: www.Nobelprize.org
Hormone manipulations

- Castration (surgical or medical)
- Anti-androgens
- Ketoconazole

Chemotherapy

- Docetaxel (FDA-approved: 5/19/2004)
- Mitoxantrone
FDA-approved drugs for mCRPC, 2010-2013

**Improved Overall Survival**
- 4/29/10: sipuleucel-T
- 6/17/10: cabazitaxel (post-docetaxel)
- 4/28/11: abiraterone (post-docetaxel)
- 8/31/12: enzalutamide (post-docetaxel)
- 12/10/12: abiraterone (pre-docetaxel)
- 5/15/13: radium-223 dichloride

**Supportive Care**
- 11/18/10: denosumab (for prevention of skeletal problems)
- 9/19/11: denosumab (for fracture prevention)
FDA-approved treatment of metastatic prostate cancer 2014

Tumor Burden

- Castration (ADT)
- Hormone-sensitive
- Castration-sensitive
- Androgen-independent
- Castration-resistant
- Highly variable

Secondary Hormone Rx

- Docetaxel
- Sipuleucel-T
- Abiraterone
- Enzalutamide
- Cabazitaxel
- Radium-223 Cl

Time
# Treatment of metastatic prostate cancer 2014

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**Chemotherapy**
- Docetaxel*      
- Mitoxantrone    
- Cabazitaxel*    

**Bone health**
- Zoledronic acid 
- Denosumab        
- Toremifene

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*survival benefit
Understanding the data: Things we care about in clinical trials

Number of patients

What is the “treatment arm” compared against (“control arm”)?

Was there adequate follow-up?

Were any findings statistically significant?
Understanding the data: “Survival curves” (Also called the Kaplan-Meier curve)
Docetaxel (Taxotere)

Intravenous chemotherapy, every 3 weeks

Mechanism of action: interferes with cell division

FDA approved, 5/19/04

Still effective despite the emergence of new drugs!
Docetaxel: TAX 327 Study

Docetaxel: SWOG Intergroup 99-16

FDA-approved drugs for mCRPC, 2010-2013

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Supportive Care

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Sipuleucel-T (Provenge)

A vaccine delivered via intravenous infusion

Mechanism / logistics:

- “Autologous active cell immunotherapy”: a patient’s own blood cells are removed, “activated” with a protein (PA2024, prostatic acid phosphatase fused to GM-CSF), and re-infused
- Requires 3 rounds of pheresis and re-infusion 3 days later
Sipuleucel-T: Overall survival

Sipuleucel-T: considerations

How do you know if it’s working?

- PSA does not change

How is sipuleucel-T optimally sequenced with other therapies that include immunosuppressants?

- An ongoing question in the face of emerging therapies.

Cost: is a 4 month improvement “worth it”? 

- $93,000 for all 3 infusions
FDA-approved drugs for mCRPC, 2010-2013

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An intravenous chemotherapy like docetaxel

Mechanism: interferes with cell division, but may be less likely to be pumped out of cancer cells than docetaxel

Phase III trial design

- Patients who have progressed on docetaxel therapy
Cabazitaxel: TROPIC Overall survival

Cabazitaxel: notes and considerations

The *first* drug to show a survival benefit after docetaxel

**Adverse events**

- More grade 3+ neutropenia (82% vs. 58%) led to more fevers, infections, and deaths (5% vs. 2%)
FDA-approved drugs for mCRPC, 2010-2013

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Looking back at the androgen receptor (AR) to move forward

- Testosterone
- DHT
- AR
- PSA
↑ growth, survival, PSA
Why bother with hormone therapies if the disease is castration resistant?

**Mechanisms of resistance to hormone therapy**

- Androgen production from non-testicular sources
  - Adrenal glands
  - Tumor cells themselves
- AR gene mutations (18-50%)
- AR gene amplification (up to 30%)
- Other ways to activate the AR without testosterone (ligand-independent)
Abiraterone acetate (Zytiga)

Oral medication, taken daily, with prednisone (steroid)

**Mechanism:**

- A steroidogenesis inhibitor
- Irreversible inhibitor of 17α-hydroxylase and C17,20-lyase CYP17 activity, two enzymes that are important for testosterone production in the adrenal glands
Abiraterone (Zytiga) in patients previously treated with docetaxel (Cougar 301 trial): Overall survival

Abiraterone: considerations

The *second* drug to show a survival benefit after docetaxel

- Longer progression free survival: 5.6 mos vs. 3.6 mos.

Might there be a benefit when given before docetaxel chemotherapy?

- The Cougar 302 study (Phase 3, randomized controlled trial in chemo-naïve patients)...

[The image contains a footer with the logo of Massachusetts General Hospital Cancer Center.]
Abiraterone (Zytiga) in patients *without prior docetaxel* (Cougar 302 trial): Overall survival

Hazard ratio, 0.75 (95% CI, 0.61–0.93)  
P=0.01

Abiraterone–prednisone, not reached

Prednisone alone, 27.2 mo

**Overall Survival**

No. of Events  
Abiraterone–prednisone: 147  
Prednisone alone: 186  

**Months**

FDA-approved drugs for mCRPC, 2010-2013

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Enzalutamide (Xtandi)

Oral medication, taken daily

Mechanism of action

- An anti-androgen
- Competes for androgen binding to AR
- Inhibits AR translocation to the nucleus
- Inhibits binding to DNA
Enzalutamide (Xtandi) in patients *previously treated* with docetaxel (AFFIRM trial): Overall survival

Another option that extends survival after docetaxel chemotherapy

Might there be a benefit when given before docetaxel chemotherapy?

- PREVAIL (Phase 3, randomized controlled trial in chemo-naïve patients)…
- … presented in Feb 2014 with positive results
- … not yet published
- … not yet FDA-approved for this population of patients
FDA-approved drugs for mCRPC, 2010-2013

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Radium-223 dichloride (Xofigo)

An intravenous radiation treatment

Mechanism

- A radioisotope containing an $\alpha$-emitting nuclide
- Targets bone metastases with high-energy $\alpha$ radiation of extremely short range that spares bone marrow, limiting toxic effects
- For patients with bone-only or bone-dominant disease

Logistics: monthly infusions x 6 months
Radium-223 (Xofigo) in patients with symptomatic bone metastases (ALSYMPCA): Overall survival

Radium-223: ALSYMPCA – first symptomatic SRE (skeletal related event)

Improved Overall Survival

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# mCRPC and overall survival

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<tr>
<th>Agent(s)</th>
<th>N</th>
<th>OS</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td><strong>Docetaxel-Naive</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mitoxantrone + hydrocortisone</td>
<td>119</td>
<td>12.3mo</td>
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<td>Hydrocortisone</td>
<td>123</td>
<td>12.6mo</td>
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<tr>
<td>Docetaxel/estramustine</td>
<td>338</td>
<td>17.5mo</td>
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<td>336</td>
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<td>Docetaxel/prednisone q3wk</td>
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<td>18.9mo</td>
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<td>Docetaxel/prednisone q1wk</td>
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<tr>
<td>Mitoxantrone/prednisone q3wk</td>
<td>337</td>
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<td>Abiraterone acetate/prednisone</td>
<td>546</td>
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<tr>
<td>Placebo/prednisone</td>
<td>542</td>
<td>27.2mo</td>
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<tr>
<td><strong>+/- Docetaxel</strong></td>
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<tr>
<td>Sipuleucel-T</td>
<td>341</td>
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<tr>
<td>Placebo</td>
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<td>Radium-223 chloride</td>
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<td>Placebo</td>
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<td><strong>Docetaxel-pretreated</strong></td>
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<td>Cabazitaxel/prednisone</td>
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<td>Prednisone</td>
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<td>800</td>
<td>18.4mo</td>
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Treatment of metastatic prostate cancer 2014

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  - Castration-sensitive
  - Highly variable
  - Castration-resistant

  **Secondary Hormone Rx**
  - Docetaxel
  - Abiraterone
  - Cabazitaxel

  **Androgen-independent**
  - Sipuleucel-T
  - Enzalutamide
  - Enzalutamide
  - Radium-223 Cl
Looking to the future…

**Outstanding questions**

- With so many drugs, what is the optimal sequence?
- Is there a role for these therapies in earlier or even localized disease?
- Are specific genetic alterations associated with treatment response?

**Outstanding needs**

- Predictive biomarkers for heterogeneous disease
- New imaging techniques
- Intermediate end-point biomarkers
# Treatment of metastatic prostate cancer 2014

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<td>Zoledronic acid</td>
<td>PROSTVAC</td>
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<tr>
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*survival benefit

**Radiopharmaceutical**
- Radium-223 Chloride*

**Bone health**
- Zoledronic acid
- Denosumab
- Toremifene
Investigational therapies

Old drugs, new packaging
BIND-014

Targeted therapies
Cabozantinib
Dasatinib
Tasquinimod

Immune manipulations
PROSTVAC
Ipilimumab
PD-1 inhibition
PD-L1 inhibition

Hormonal manipulations
TAK700
ARN509
Galeterone
Old drugs, new packaging: Targeted polymeric nanoparticles

Potential to deliver more drug
Potential to target tumor

Now in phase 2 for mCRPC

Investigational therapies

Old drugs, new packaging

BIND-014

Targeted therapies

Cabozantinib
Dasatinib
Tasquinimod

Immune manipulations

PROSTVAC
Ipilimumab
PD-1 inhibition
PD-L1 inhibition

Hormonal manipulations

TAK700
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Galeterone
Cabozantinib inhibits MET and VEGFR pathways

- **MET:**
  - Important for cell growth, metastasis
  - Important in bone biology
  - Expression on prostate cancer cells increases with prostate cancer progression; highest in bone metastasis

- **VEGF/VEGFR:**
  - Important for forming new blood vessels for growing tumors
  - Plasma or urine VEGF levels are independent predictors of overall survival in men with metastatic CRPC
Cabozantinib: An unexpected response in prostate cancer patients in an early phase clinical trial

- 19 of the first 20 subjects had profound change in bone scans
- Randomization was stopped early, more patients enrolled

Cabozantinib: Phase 2 study, 12 weeks

- RECIST: 5% improvement; 75% stability
- Bone scans: 68% improvement; 12% complete response
- Bone pain: 67% improvement; 56% decrease in narcotic use
- PSA change was *discordant* with other evidence of treatment effect (symptoms or scans) in 40% of subjects.

- Safety/Tolerability of cabozantinib 100mg daily:
  - 51% had ≥1 dose reduction by Week 12
  - 12% discontinued treatment due to adverse events by Week 12
  - Fatigue (16%), HTN (12%), hand/foot syndrome (8%)

Ongoing Phase III studies: COMET-1, COMET-2

mCRPC
Bone mets
prior docetaxel
prior abiraterone
or enzalutamide
(Target n=960)

Randomize

Cabozantinib 60mg daily
Prednisone 5mg BID

Overall Survival

mCRPC
Bone mets
Pain requiring opioids
prior docetaxel
prior abiraterone
or enzalutamide
(Target n=264)

Randomize

Cabozantinib 60mg daily
Mitoxantrone+Prednisone

Confirmed Pain Response
An oral medication

Mechanism of action (proposed):

- SRC is a protein that can stimulate cell growth
- SRC may operate via the AR but without androgen
- Inhibiting SRC may inhibit cell growth in mCRPC

Phase 3 clinical trial dasatinib (or placebo) given with docetaxel
Dasatinib in patients with mCRPC without prior docetaxel chemotherapy: READY phase 3 trial

Investigational therapies

Old drugs, new packaging
BIND-014

Targeted therapies
Cabozantinib
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Immune manipulations
PROSTVAC
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PD-1 inhibition
PD-L1 inhibition

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Blockade of PD-1 or CTLA-4 signaling in tumor immunotherapy

CTLA: cytotoxic T-lymphocyte-associated antigen
PD-1: programmed death-1
PD-L1: programmed death ligand-1

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Coming soon?
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- ARN509
- Galeterone
- PROSTVAC

*survival benefit