Incorporating New Agents into the Treatment Paradigm for Prostate Cancer

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Overview

- Clinical disease states in prostate cancer
  - Description
  - How established
- Treatment paradigm Jan 2010 vs Oct 2011
- New agents by clinical disease state
- How will radium 223 fit into the paradigm now and in the future?
- Concluding remarks
Clinical Disease States

Hormone Sensitive

- Newly diagnosed Localized disease
- Non-metastatic, Biochemical relapse
- Metastatic Hormone-naive

Castration Resistant

- Non-metastatic
- Metastatic, Asymptomatic (chemotherapy naïve)
- Metastatic, Symptomatic (chemotherapy naïve)
- Metastatic, Post docetaxel
How is the clinical disease state established?

- Determine hormonal status
- Evaluate extent of disease
- Evaluate other clinical features
  - Presence of symptoms
  - Prior therapies
Determination of Hormonal Status

On ADT? (testosterone lowering therapy)

Yes

PSA rising?

Yes

Serum testosterone level castrate?

Yes

Castration Resistant

No

Hormone Sensitive

No

Hormone Sensitive

No

Evaluate therapy for timing, compliance, or other issues
Evaluate Extent of Disease

- **Hormone Sensitive** or **Castration Resistant**

  - **Non-metastatic HS**
    - Both negative
    - Imaging Studies: Bone scan, CT (AP+/C)
  
  - **Metastatic HS**
    - Bone scan and/or CT positive
    - Metastatic CRPC
  
  - **Non-metastatic CRPC**
Evaluate other clinical features

Metastatic Castration Resistant

- Symptoms
  - Yes: Symptomatic
  - No: Asymptomatic

 Prior Docetaxel
  - Yes: Post docetaxel
  - No: Docetaxel naive
# Treatment Paradigm by Clinical Disease States

## January 2010

<table>
<thead>
<tr>
<th>Hormone Sensitive</th>
<th>Castration Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Newly diagnosed Localized disease</strong></td>
<td><strong>Non-metastatic, Metastatic</strong>, Asymptomatic (chemotherapy naïve)</td>
</tr>
<tr>
<td>Surgery Radiation</td>
<td>Metastatic, Symptomatic (chemotherapy naïve)</td>
</tr>
<tr>
<td>ADT + radiation</td>
<td>Metastatic, Post docetaxel</td>
</tr>
<tr>
<td>Active surveillance</td>
<td>2nd-line hormones (Docetaxel\textsuperscript{b})</td>
</tr>
<tr>
<td><strong>Non-metastatic, Biocemical relapse</strong></td>
<td><strong>Non-metastatic, Asymptomatic (chemotherapy naïve)</strong></td>
</tr>
<tr>
<td>Observation\textsuperscript{a}</td>
<td>2nd-line hormones other</td>
</tr>
<tr>
<td>ADT\textsuperscript{a}</td>
<td>Docetaxel\textsuperscript{b} Mitoxantrone\textsuperscript{c}</td>
</tr>
<tr>
<td>Salvage radiation\textsuperscript{a}</td>
<td>XRT, \textsuperscript{88}Sr, \textsuperscript{153}Sm</td>
</tr>
<tr>
<td><strong>Metastatic Hormone-naive</strong></td>
<td><strong>Metastatic, Post docetaxel</strong></td>
</tr>
<tr>
<td>ADT</td>
<td>Mitoxantrone Other chemo</td>
</tr>
</tbody>
</table>

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\textsuperscript{a} selected patients  \textsuperscript{b} level 1 evidence for survival  \textsuperscript{c} level 1 evidence for palliation
Metastatic Castration Resistant

Asymptomatic (chemotherapy naïve)
- Sipuleucel-T<sup>b</sup>
- 2<sup>nd</sup>-line hormones
- Abiraterone, off label (Docetaxel<sup>a,b</sup>)

Symptomatic (chemotherapy naïve)
- Docetaxel<sup>b</sup>
- Mitoxantrone<sup>c</sup>
- XRT, <sup>89</sup>Sr<sup>c</sup>, <sup>153</sup>Sm<sup>c</sup>
- Radium 223<sup>b,c,d</sup>

Post Docetaxel
- Abiraterone<sup>b</sup>
- Cabazitaxel<sup>b</sup>
- (Sipuleucel-T<sup>a,b</sup>)
- Radium 223<sup>b,c,d</sup>
- Mitoxantrone

- a. selected patients
- b. level 1 evidence for survival
- c. level 1 evidence for palliation
- d. not yet FDA approved
Asymptomatic Metastatic Castration Resistant

**Asymptomatic (chemotherapy naïve)**

- Sipuleucel-T<sup>b</sup>
- 2<sup>nd</sup>-line hormones
- Abiraterone, off label (Docetaxel<sup>a,b</sup>)

**Symptomatic (chemotherapy naïve)**

- Docetaxel<sup>b</sup>
- Mitoxantrone<sup>c</sup>
- XRT, 89Sr<sup>c</sup>, 153Sm<sup>c</sup>
- Radium 223<sup>b,c,d</sup>

**Post Docetaxel**

- Abiraterone<sup>b</sup>
- Cabazitaxel<sup>b</sup>
- (Sipuleucel-T<sup>a,b</sup>)
- Radium 223<sup>b,c,d</sup>
- Mitoxantrone

---

a. selected patients  
b. level 1 evidence for survival  
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d. not yet FDA approved
Sipuleucel-T Immunotherapy (April 2010)

- Data from IMPACT trial, survival improved but
  - No PSA decline
  - No improvement in imaging studies

- Use early in mCRPC
  - Immune system more robust
  - Lower risk for symptomatic progression

- Slow uptake by clinicians
  - Manufacturing and approved sites ramp up
  - Reimbursement concerns
  - Skepticism about significance of data
  - Confusion about when/how to use sipuleucel-T
Second line hormone manipulation
(not including abiraterone)

- **Options**
  - Add or withdraw anti-androgens
  - Estrogens
  - Ketoconazole
  - Others

- Quality of life usually maintained

- No known survival advantage (but not studied)

- Low cost

- Ketoconazole
  - Reasonable activity even at lower doses
  - Some responses durable > 1 year or more
Abiraterone and prednisone, off label

- More potent inhibitor of CYP17 than ketconazole in preclinical testing
- Phase 2 data and NCCN guidelines
- Considerations for use
  - Phase 3 data (COU-302) likely to be available soon
  - Low dose prednisone required
  - Sequencing with sipuleucel-T
  - High cost
- If FDA approved in this space, abiraterone likely to replace most second line hormone manipulations
Docetaxel and prednisone (2004)

- In TAX 327, docetaxel and prednisone conferred modest survival advantage
  - Asymptomatic and symptomatic patients
  - Deferring chemo until symptoms develop does not negate survival advantage
- Most patients chose to forego chemotherapy if asymptomatic
Metastatic Castration Resistant

Symptomatic Metastatic CRPC

Asymptomatic (chemotherapy naïve)

Sipuleucel-T\textsuperscript{b}
2\textsuperscript{nd}-line hormones
Abiraterone, off label (Docetaxel\textsuperscript{a,b})

Symptomatic (chemotherapy naïve)

Docetaxel\textsuperscript{b}
Mitoxantrone\textsuperscript{c}
XRT, \textsuperscript{89}Sr\textsuperscript{c}, \textsuperscript{153}Sm\textsuperscript{c}
Radium 223\textsuperscript{b,c,d}

Post Docetaxel

Abiraterone\textsuperscript{b}
Cabazitaxel\textsuperscript{b}
(Sipuleucel-T\textsuperscript{a,b})
Radium 223\textsuperscript{b,c,d}
Mitoxantrone

a. selected patients  b. level 1 evidence for survival  c. level 1 evidence for palliation  d. not yet FDA approved
Docetaxel and prednisone (2004)

- Patients more willing to try chemotherapy when symptomatic
- Standard of care first line chemotherapy
- 30-40% of patients with mCRPC die without ever having received docetaxel
  - Medical oncologists
  - Co-morbidities
  - Patient refusal
Mitoxantrone and prednisone (1996)

- Approved for palliative benefit but
- No survival benefit over prednisone
- Option for symptomatic patients with diffuse pain who cannot tolerate docetaxel
External beam radiation therapy

- Suitable for single area(s) of pain
- Preferred treatment for spinal cord compression
- EBRT to multiple sites over time compromises bone marrow function
- Cannot re-irradiate a given site with meaningful dose
Radioisotope therapy options

- Symptomatic patients who
  - Were already treated with chemotherapy
  - Not candidates for chemotherapy
  - Pain in multiple areas

- Beta emitting agents, Strontium 89 or Samarium 153
  - Approved for palliation of pain
  - Main toxicity on bone marrow

- Use very limited
  - Concern about marrow toxicity pre- or post- chemo
  - Logistics of ordering
Radium 223 (Fast Track status, 2012)

- Has both palliative and survival benefit
- Symptomatic patients
  - Not suited for chemotherapy
  - Already received docetaxel
- Simple to administer
- Advantages of alpha emitter
  - Lack of marrow toxicity
  - Double strand DNA breaks
Metastatic Castration Resistant

Asymptomatic (chemotherapy naïve)
- Sipuleucel-T\textsuperscript{b} \\
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- Cabazitaxel\textsuperscript{b} \\
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\textsuperscript{a} selected patients \hspace{1em} \textsuperscript{b} level 1 evidence for survival \hspace{1em} \textsuperscript{c} level 1 evidence for palliation \hspace{1em} \textsuperscript{d} not yet FDA approved
Cabazitaxel and prednisone (June 2010)

- For patients previously treated with docetaxel
- Survival advantage over mitoxantrone and prednisone seen in the TROPIC trial
- Palliation no better than mitoxantrone
- Being studied head to head with docetaxel for first line therapy and at lower dose (20 vs 25)
Abiraterone and prednisone (April 2011)

- Survival and palliative benefit over prednisone and placebo in COU-301 trial
- Approved only in post-docetaxel population at present
- Well tolerated
- Good alternative after docetaxel, before next chemotherapy option
Sipuleucel-T after docetaxel

- Only for very selected patients
  - Asymptomatic
  - Ideally off prednisone for at least 30 days
- Close follow-up after administration
  - Unrealistic expectations of activity by patient and physician
Sites of metastatic disease

- Bone metastases, 90-100%
  - PC autopsy series, 1,589 patients\(^1\)
  - UW rapid autopsy program, 100 patients\(^2\)
- Nodal disease, 40-50%
- Visceral (at autopsy), lung 45%, liver 25%
- Brain, rare to uncommon

Sequelaes of bone metastases

- Skeletal related events, “SREs”
  - Pain
  - Spinal cord compression
  - Pathological fracture
  - Need for surgery or radiation
- Disability
- Decreased quality of life
- Cost
# Zoledronic Acid\(^1\) (2002), Denosumab\(^2\) (Nov 2010)

Bone directed drugs that delay or prevent SREs

<table>
<thead>
<tr>
<th></th>
<th>Zoledronic acid</th>
<th>Denosumab</th>
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<tbody>
<tr>
<td>Route</td>
<td>Intravenous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>MOA</td>
<td>Bisphosphonate</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Acute phase reactions</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Rare</td>
<td>Not rare</td>
</tr>
<tr>
<td>ONJ</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Survival benefit</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cost/month</td>
<td>$ 500-1,000</td>
<td>$ 5-6,000</td>
</tr>
<tr>
<td>FDA approved</td>
<td>CRPC bone mets</td>
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# Treatment Paradigm for Metastatic CRPC

**Oct 2011**

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<td>Abiraterone, off label (Docetaxel&lt;sup&gt;a,b&lt;/sup&gt;)</td>
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<td>Mitoxantrone</td>
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**SRE delay/prevention:** Denosumab<sup>1</sup> or Zoledronic acid<sup>1</sup>

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a. selected patients  
 b. level 1 evidence for survival  
 c. level 1 evidence for palliation  
 d. not yet FDA approved
Radium 223 considerations

- Survival and palliative advantage
- Delays time to first SRE
- Toxicity is very low compared with
  - Docetaxel or cabazitaxel, and prednisone
  - Bone directed drugs
  - Abiraterone and prednisone
Investigational Drugs in Phase 3 Clinical Trials

**Metastatic Castration Resistant**

**Chemotherapy-naïve**
- Asymptomatic
  - MDV3100
  - Abiraterone
  - Ipilimumab
  - TAK-700
  - Prostvac

**Chemotherapy-naïve**
- Symptomatic/Asymptomatic
  - *docetaxel and prednisone plus*
  - Dasatinib
  - Lenalidomide
  - OGX-011

**Post docetaxel**
- MDV3100
- Ipilimumab
- TAK-700
Potential combinations with radium 223

- Lower toxicity drugs with survival advantage
  - Sipuleucel-T
  - Abiraterone and prednisone
  - Others in phase 3 trials

- Chemotherapy with survival advantage
  - Docetaxel and prednisone
  - Cabazitaxel and prednisone
  - Docetaxel combinations in phase 3 trials
Potential combinations with radium 223

- Other bone directed agents
  - Zoledronic acid
  - Denosumab
- Cabozantinib
Case #1

- 77 y/o man with long history of mCRPC
- S/P ADT and 2nd line hormonal therapies
- XRT to spine Dec 1999
- Chemo regimens: docetaxel, carboplatin and taxol, cabazitaxel
- Abiraterone and prednisone
- New bone pain and bone mets on bone scan
Case #2

- 58 y/o diagnosed with PC 2008, RP, ADT for biochemical relapse, no mets
- PSA rising on ADT
- Bone scan shows new metastatic disease
- No bone pain
- Candidate for sipuleucel-T
- What to do next?
Case #3

- 76 yr old man with metastatic CRPC
- COPD and congestive heart failure, wearing oxygen
- Persistent pain in lower back, ribs, left upper arm despite narcotic medication
- Refuses chemotherapy
- Ideal candidate for radium 223
Concluding Remarks

- Exciting and challenging time
- Treatment paradigm is changing
  - Sequencing of drugs
  - Combinations of drugs
- Addition of radium 223
  - Enhances options for patients
  - Opportunity to develop new combinations