Prostate Cancer in the Elderly: Role for New Agents

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Disclosure

Honoraria from AMGEN
Outline

• Epidemiology
• Castration-resistant Prostate Cancer (CRPC)
  – Prognosis
  – New therapies
• Bone disease
  – New therapies
5-Year Survival by Stage

- Stage of PC at diagnosis is a primary factor controlling patient survival

Therapeutic Options for CRPC Today

- Secondary hormonal manipulations
  - Antiandrogen administration
  - Antiandrogen withdrawal
  - Adrenal suppressives (ketoconazole)
  - Corticosteroids (prednisone, dexamethasone, etc)
  - Estrogens (DES, etc)

- External beam radiation therapy

- Intravenous bone-seeking radioisotopes
  - Samarium-153 EDTMP
  - Strontium-89

- Chemotherapy
  - Docetaxel
  - Cabazitaxel
  - Mitoxantrone

- Immunotherapy
  - Sipuleucel-T

- Androgen biosynthesis inhibitor
  - Abiraterone

- Bone metastases
  - Zoledronate
  - Denosumab

- Experimental therapies
  - Many
Sipuleucel-T (Provenge®)

• Sipuleucel-T is an autologous active cellular immunotherapy that activates the immune system against prostate cancer
  – Stimulates T-cell immunity to prostatic acid phosphatase (PAP), an antigen expressed in most prostate cancers
• Sipuleucel-T is composed of autologous antigen-presenting cells from the patient cultured with a fusion protein PA2024
  – PA2024 consists of PAP linked to granulocyte/macrophage colony-stimulating factor

Asymptomatic or minimally symptomatic metastatic androgen independent prostate cancer

Randomize

(n=341) Sipuleucel-T q 2 wk × 3 cycles

(n=171) Placebo q 2 wk × 3 cycles

Treatment at physician discretion

Salvage protocol or treatment at physician discretion

Overall Survival

- **Sipuleucel-T (n=341)**
- **Placebo (n=171)**

**Median OS Benefit**: 4.1 mo

**HR**: 0.775 (95% CI: 0.614-0.979)

**P-value**: 0.032

Sipuleucel-T Summary

- Sipuleucel-T is the first active immunotherapy to improve overall survival in patients with advanced prostate cancer.

- Sipuleucel-T has:
  - Favorable benefit-to-risk profile
    - Infusion reaction
    - CVA
  - Short duration of therapy (3 doses at 2 week intervals)

- Sipuleucel-T is indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer
  - No visceral disease, Any Gleason score, Before or after chemotherapy
  - A significant proportion of patients were aged 65 and over

*Cost is significant-- ~$31,000 per infusion

Cabazitaxel (Jevtana®)

• Cabazitaxel is the first agent to be approved against an active control (mitoxantrone) in the post docetaxel setting

  – Mitoxantrone is used in patients who progress after first-line docetaxel-based therapy, but its activity in this setting is modest and it has not demonstrated an OS benefit\(^1\)

TROPIC: Phase III Registration Study

mCRPC patients who progressed during and after treatment with a docetaxel-based regimen (N=755)

- Stratification factors
  - ECOG PS (0, 1 vs 2)
  - Measurable vs non-measurable disease

- cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles (n=378)
- mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles (n=377)

*Oral prednisone/prednisolone: 10 mg daily.

Primary end point: OS
Secondary end points: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression

### Summary of Demographics and Patient Characteristics (N=755)

<table>
<thead>
<tr>
<th></th>
<th>MP (n=377)</th>
<th>CBZP (n=378)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>67.0</td>
<td>68.0</td>
</tr>
<tr>
<td>≥65 (%)</td>
<td>57.0</td>
<td>64.9</td>
</tr>
<tr>
<td><strong>ECOG PS (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 1</td>
<td>91.2</td>
<td>92.6</td>
</tr>
<tr>
<td>2</td>
<td>8.8</td>
<td>7.4</td>
</tr>
<tr>
<td><strong>PSA (ng/mL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>127.5</td>
<td>143.9</td>
</tr>
<tr>
<td><strong>Measurability of disease (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurable</td>
<td>54.1</td>
<td>53.2</td>
</tr>
<tr>
<td>Non-measurable</td>
<td>45.9</td>
<td>46.8</td>
</tr>
<tr>
<td><strong>Disease Site (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>87.0</td>
<td>80.2</td>
</tr>
<tr>
<td>Lymph node</td>
<td>44.8</td>
<td>45.0</td>
</tr>
<tr>
<td>Visceral</td>
<td>24.9</td>
<td>24.9</td>
</tr>
</tbody>
</table>

PSA = prostate specific antigen.

Primary End Point: Overall Survival (ITT Analysis)

<table>
<thead>
<tr>
<th></th>
<th>CBZP</th>
<th>MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>15.1</td>
<td>12.7</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.59-0.83</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; .0001</td>
<td></td>
</tr>
</tbody>
</table>

Proportion of OS (%)

Cabazitaxel Summary

• Cabazitaxel was approved for use in patients with mCRPC previously treated with a docetaxel-containing regimen on June 17, 2010
• Most common (>5%) grade 3/4 AEs were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia
• Cabazitaxel demonstrated a significant OS improvement compared with mitoxantrone
  – 15.1 months vs 12.7 months
  – 30% Reduced risk of death (HR=0.70, \( P < .0001 \))
  – OS benefit was consistent across subgroups
  – Febrile neutropenia and diarrhea are concerns in the elderly and consideration for dose reduction is recommended

Abiraterone acetate (Zytiga®)

• FDA approved abiraterone acetate for treatment of castration-resistant prostate cancer as a combination therapy with prednisone
• Abiraterone decreases the production of the protein cytochrome P450 17A1 -- which the body uses in the production of testosterone
### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Abiraterone Acetate (N=797)</th>
<th>Placebo (N=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>69 (42–95)</td>
<td>69 (39–90)</td>
</tr>
<tr>
<td>≥75 yr — no. of patients/total no. (%)</td>
<td>220/797 (28)</td>
<td>111/397 (28)</td>
</tr>
<tr>
<td>Disease location — no. of patients/total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>709/797 (89)</td>
<td>357/397 (90)</td>
</tr>
<tr>
<td>Node</td>
<td>361/797 (45)</td>
<td>164/397 (41)</td>
</tr>
<tr>
<td>Liver</td>
<td>90/797 (11)</td>
<td>30/397 (8)</td>
</tr>
<tr>
<td>BPI-SF score for pain† — No. of patients</td>
<td>792</td>
<td>394</td>
</tr>
<tr>
<td>BPI-SF score for pain† — Median score (range)</td>
<td>3.0 (0–10)</td>
<td>3.0 (0–10)</td>
</tr>
<tr>
<td>No. of patients — No. of previous cytotoxic chemotherapy regimens —</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>558/797 (70)</td>
<td>275/398 (69)</td>
</tr>
<tr>
<td>2</td>
<td>239/797 (30)</td>
<td>123/398 (31)</td>
</tr>
<tr>
<td>ECOG performance status — No. of patients/total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>715/797 (90)</td>
<td>353/398 (89)</td>
</tr>
<tr>
<td>2</td>
<td>82/797 (10)</td>
<td>45/398 (11)</td>
</tr>
</tbody>
</table>

De Bono et al.  NEJM, 2011
Survival

De Bono et al. NEJM, 2011
Abiraterone Summary

- FDA approval was based on a clinical trial of 1,195 castration-resistant prostate cancer. Patients were randomized to abiraterone (1 gm/day) and prednisone twice daily, or to both placebo and prednisone twice daily.
- Those in the active treatment group had a median overall survival of 14.8 months, versus 10.9 months for those in the placebo group.
- Adverse events were overall similar in both groups except for events related to CYP17 blockade (hypokalemia, fluid retention, hypertension: 55% vs 43%)
- Should monitor liver transaminases
Spectrum of bone disease in prostate cancer.

Hazard: Treatment-related fractures → Hazard: Disease-related skeletal events

Castrate-sensitive nonmetastatic → Castrate-resistant nonmetastatic → Castrate-resistant metastatic

Saylor P J et al. JCO 2011;29:3705-3714
Denosumab (XGEVA®)

- Indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors
- Does not require dose adjustments, regardless of renal function
- Administered once every 4 weeks as a single 120 mg subcutaneous injection
- Binds to RANK Ligand, the key mediator of bone resorption, to inhibit osteoclast activity
- Can cause hypocalcemia and osteonecrosis of the jaw
The role of the receptor activator of nuclear factor kappa B (RANK) and RANK ligand (RANKL) in normal bone physiology.

Saylor P J et al. JCO 2011;29:3705-3714
Primary analysis of the Denosumab 103 trial.

- HR = 0.82 (95% CI: 0.71 to 0.95)
- P < .001 (Noninferiority)
- P = .008 (Superiority)

No. at risk:
- Zoledronic: 951, 733, 544, 407, 299, 207, 140, 93, 64, 47
- Denosumab: 950, 758, 582, 472, 361, 259, 168, 115, 70, 39

Saylor P J et al. JCO 2011;29:3705-3714
Denosumab (XGEVA®)

- FDA recently approved Denosumab at 60 mg every 6 months to improve bone mineral density and lower risk for vertebral fractures in men on ADT based on a Phase III study (versus placebo (n=1468))
- Another Phase III study (n=1432) showed that denosumab can delay onset of bone metastases in men with CRPC at 120 mg monthly
  - Increased median bone-metastasis-free survival: 29.5 months with denosumab and 25.2 months with placebo (P = .03).
Therapies available and in development based on mechanism of action: Tak-700 (Millenium Pharmaceuticals, Cambridge, MA), Abiraterone (Johnson & Johnson, New Brunswick, NJ), Tok-001 (Tokai Pharmaceuticals, Cambridge, MA), MDV-3100 (Medivation, San Francisco, ...
Prostate cancer clinical states model; framework for patient management and drug development.

OBJECTIVES: Control/relieve/eliminate disease manifestations that are present. Prevent/delay new manifestations from occurring in the future: Symptoms/death from disease.

1. Rising PSA: castrate; denosumab
2. Clinical Metastases: castrate; predocetaxel sipuleucel-T, abiraterone
3. Clinical metastases: castrate; 1st line chemotherapy docetaxel
4. Clinical Metastases: castrate; postdocetaxel cabazitaxel, abiraterone


Scher H I et al. JCO 2011;29:3695-3704