Prostate Cancer Therapy: New Drugs and Vaccines
Kaiser Permanente, 2010

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Clinical States Describe the Disease Continuum
For Untreated and Treated Patients

Urology 55:323, 2000

AUA panel: No consensus on best Tx for localized PCa
Randomized trials show that higher-dose radiation may lower risk of PSA recurrence
AUA prostate cancer guidelines highlights
Charles Bolden
Local Therapy for Prostate Cancer

Overall lack of quality Level I randomized data with single modality therapy

- Outcomes for Radical Prostatectomy (RP) and Radiation Therapy (RT) for similar disease stage and grade are EQUIVALENT (Level 1)
  - Open and Minimally invasive techniques are likely EQUIVALENT – minimally invasive currently more expensive
  - Newer modalities of radiation therapy such as 3D conformal and high dose rate brachytherapy do provide more effective RT than four field EBRT (Level 2)
  - However, seed implants, Proton beam and Brachytherapy have not been demonstrated in randomized trials to be superior and are more expensive than standard techniques
  - IMRT and IMRT+seed implantation produced less rectal & bladder toxicity in 2 recent studies (Level 2)

- RP reduces overall and prostate cancer specific mortality compared to watchful waiting (Level 1)
  - The effect is most pronounced in:
    - Men less than 67 years at time of diagnosis
    - Men with high grade prostate cancer

- Adjuvant androgen deprivation therapy reduces overall and prostate cancer specific mortality in patients with LN+ at RP (Level 1)
  - Adjuvant pelvic radiation reduces prostate cancer specific mortality in patients with extracapsular (T3+) or margin positive disease at RP (Level 1)

In locally advanced prostate cancer:
- Adding ADT to RT improves prostate cancer specific and overall survival (Level 1)
- Adding BT to androgen blockade decreases prostate cancer specific and overall mortality (Level 1)
Systemic Therapy in Advanced Prostate Cancer

- Androgen deprivation therapy is a standard (Level 1)
- Impact of current second line hormonal manipulations limited
  - Bicalutamide, Flutamide, Nilutamide, Ketoxazole
- Cytotoxic chemotherapy (docetaxel) palliates and improves survival in castrate resistant prostate cancer (Level 1)
- Zoledronic acid reduces BMD loss and reduces skeletal event rate (Level 1). Pamidronate (Aredia) has no effect on SRE.

New hormonal agents in clinical trials
- "Lyase" inhibitors in hydrolyses responsible for steroid production adrenal, testis and prostate cancer cells
  - Abiraterone, TAK 700 and drug
- Non-reversible androgen receptor antagonists
  - MDV3100, BMS compounds: oral drugs

Immunotherapies in clinical trials
- 1 Antigen (PAP, PSA), Polyvalent or Non-specific immunotherapies
  - Sipuleucel-T, Provenge, PSA TRICOM, CTLA4 therapies

New targeted therapy in clinical trials
- Bone targeting
  - Osteoclast inhibition: bisphosphonates, Rank ligand
  - Osteoblast inhibition: Endothelin pathway
- Antiangiogenesis
  - VEGF ligand / VEGF R2 inhibition

History of Androgen Therapy: Charles B. Huggins

- In 1940 Huggins reported that testosterone removal (castration) resulted in rapid shrinkage of the enlarged prostate of older dogs.
- In 1941 Huggins and Hodges reported that androgen removal greatly aided patients with advanced prostate cancer.
  - "Prostatic cancer is influenced by androgenic activity in the body."
- Later that year, Huggins reported that oral estrogens had the same effect as castration for prostate cancer patients.
Androgen Deprivation Therapy

Evolution of Hormone Blockade

We were wrong!!

CAB = Complete androgen blockade is a misnomer

Meta-Analysis: 27 Randomized Trials of CAB vs Androgen Suppression Alone

Physiologic Effects of Testosterone Withdrawal

- Decrease in libido
- Decrease in erections
- Hot flashes
- Breast swelling
- Breast tenderness


Fracture-free Survival Diminishes with Cumulative ADT Exposure


Androgen-deprivation related bone loss: potential strategies

- Limit therapeutic loss of testosterone
  - Later therapy when benefit limited
  - Risk strata - rising PSA group
  - Intermittent deprivation
  - Ongoing trials: SWOG 9346, NCIC JPR7
- Impacting the process of bone loss
  - "Bone health"
  - Exercise, Dietary calcium, Vitamin D
  - Osteoclast inhibition
    - Bisphosphonates
    - Denosumab: monoclonal antibody
  -Raloxifene: SERM
  - Denosumab: rank ligand inhibitor
  - Other therapies: monoclonal antibodies, small molecules etc.
Intermittent Androgen Deprivation in Advanced Prostate Cancer

- Most proposed regimens require zero PSA for 6 - 12 months
- Preset re-introduction level
  - PSA 4, 10, 20 ng/ml or new symptoms
- Duration off therapy may be Gleason score dependent
- Some men given LHRH agonists from >12 months will remain hypogonadal off therapy
  - Mean return to normal testosterone: 7 months
  - Dependent upon patient age and duration of therapy

Intermittent Androgen Deprivation: Trial data and Further trials

- Phase II trials demonstrate:
  - Times off AD of 37 - 58%
  - Improved sexual function
  - Better QOL
- Phase III trials: randomized
  - SWOG 9346, NCIC (SWOG) JPR7 and others accruing
- Experimental
  - Appears not to be significantly detrimental (phase II and animal model data)

SWOG 9346 - PSA response data

<table>
<thead>
<tr>
<th>PSA ≤ 0.2 ng/ml</th>
<th>0.2 ≤ PSA ≤ 4.0</th>
<th>PSA &gt; 4.0</th>
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</thead>
<tbody>
<tr>
<td>140</td>
<td>210</td>
<td>60</td>
</tr>
<tr>
<td>210</td>
<td>77</td>
<td>20</td>
</tr>
<tr>
<td>92</td>
<td>17</td>
<td>7</td>
</tr>
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</table>
Prostate cancer cell-osteoblast-osteoclast interaction within the bone microenvironment

Bone markers as predictors of skeletal events in prostate cancer

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone-specific alkaline phosphate &gt; 246 IU/L</td>
<td>Baseline: 1.82 (1.15 – 2.90), 0.012</td>
<td></td>
</tr>
<tr>
<td></td>
<td>On study: 3.03 (1.67 – 5.51), 0.001</td>
<td></td>
</tr>
<tr>
<td>N-telopeptide &gt; 100 nmol/mmol creatinine</td>
<td>Baseline: 1.57 (1.09 – 2.26), 0.015</td>
<td></td>
</tr>
<tr>
<td></td>
<td>On study: 3.25 (2.26 – 4.68), &lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Both resorption and absorption markers are predictive.

Lipton A. Semin Oncol. 2001;28:54-59.

Bisphosphonate Pharmacology

Proposed mode of action

Aminobisphosphonates

Bisphosphonates

Precursor cells

Mature osteoclasts

Prostaglandins and other factors

Bone complications

Bone

Tumour cells

Accession

Bisphosphonates

Pamidronate in Prostate Cancer

No Effect on Proportion of Patients With SRE and Mean SMR

(-HCM) at 6 months—Protocols 032 and INT05

Total N = 378

24% 24%

P=1.0

Proportion with SRE (-HCM)

SRE SMR

Mean SMR (-HCM)

P=0.942

0.30 0.29


A randomized, placebo-controlled trial of zolodronic acid in patients with hormone-refractory metastatic prostate carcinoma


J Natl Cancer Inst 2002 94: 1458-68

• 422 patients with HRPC and bone metastases
• Randomized to ZA or placebo
Time to first skeletal complication: Zoledronic acid vs. placebo (24 month data)

Saad et al, J Natl Cancer Inst 2004; 96: 879

HR: 0.677 (0.505-0.908)*
*p=0.009

Time to First Skeletal Event by Treatment

Median time, days
Zolodronic Acid 4 mg NR
Placebo 321
P = .011

Mean Change From Baseline of the Composite Pain Score by Treatment (Intent-to-Treat Patients)

Higher score means more pain.
Time to Death by Treatment Group (Safety-Evaluable Patients)

Mechanism of Action for Rank-Ligand directed monoclonal antibody Denosumab

Osteoclast modulator side effects: the first 4 weeks
Denosumab may be better tolerated than ZA early
HALT Study: Denosumab Increases Bone Mineral Density in Men With Prostate Cancer on ADT

Smith MR et al. Denosumab in men receiving...

HALT Study: Denosumab decreases Verterbral Fracture Risk in Men With Prostate Cancer on ADT

DAHRT Rationale: Target three critical processes in the bone millieu

Prostate cancer cell

Docetaxel

Atrasentan

Bisphosphonates
**Table 1: Effect of Prior Ketoconazole**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>PSA Decline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>21/33</td>
<td>63%</td>
</tr>
<tr>
<td>Prior Ketoconazole</td>
<td>10/19</td>
<td>52%</td>
</tr>
<tr>
<td>No Prior Ketoconazole</td>
<td>11/14</td>
<td>79%</td>
</tr>
</tbody>
</table>

**Graph:**

- **Y-axis:** PSA Decline (IU/mL)
- **X-axis:** Prior Ketoconazole (n = 19) vs. No Prior Ketoconazole (n = 14)
- **Legend:**
  - Prior Ketoconazole
  - No Prior Ketoconazole

**Notes:**
- **Baseline vs. Post Cycle 6**
- **Imaging:**
  - Baseline: Normal prostate gland
  - Post Cycle 6: Decreased prostate size

**Reference:**
Ryan et al. Submitted, 2009
**Abiraterone Acetate and Reversal of Resistance in CRPC**

**De Bono, ASCO 2008, Abstract 5005**

Efficacy

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Docetaxel Naive (n=54)</th>
<th>After 1st Progression (n=30)</th>
<th>Prior Docetaxel (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50% PSA Decline</td>
<td>70%</td>
<td>30%</td>
<td>47%</td>
</tr>
<tr>
<td>≥30% PSA Decline</td>
<td>80%</td>
<td>NR</td>
<td>65%</td>
</tr>
<tr>
<td>Radiologic Response: PR</td>
<td>52%</td>
<td>NR</td>
<td>26%</td>
</tr>
<tr>
<td>Median Time to (PSA) Progression</td>
<td>231 days</td>
<td>339 days (n=54)</td>
<td>161 days</td>
</tr>
</tbody>
</table>

**Phase I**
- Abiraterone acetate 250 mg-2000 mg daily with mineralocorticoid antagonist
- Patients with CRPC
- Docetaxel naive

**Phase II**
- Abiraterone acetate 1000 mg daily with mineralocorticoid antagonist
- Docetaxel naive

**Radiologic Response**
- PR 52%
- NR 26%

**Median Time to (PSA) Progression**
- 231 days
- 339 days (n=54)
- 161 days

**Cougar Biotechnology: Schematic of Phase III Trial Design (Trial 301)**

- 2:1 Randomization
- Primary Endpoint - Overall Survival

**Antitumor Activity of MDV3100 in a Phase 1-2 Study of Castration-Resistant Prostate Cancer**


Memorial Sloan-Kettering Cancer Center, New York, NY; Oregon Health and Science University, Portland, OR; University of Washington, Seattle, WA; Dana Farber Cancer Institute, Boston, MA; M.D. Anderson Cancer Center, Houston, TX; Medivation, San Francisco, CA; and the Prostate Cancer Clinical Trials Consortium
MDV3100
A Second-Generation Antiandrogen

Why are MDV3100 and similar compounds better than bicalutamide?

1. greater binding affinity for AR
2. different mechanism of AR inhibition
   - reduced nuclear localization
   - impaired DNA binding at AR target genes
   - induces an AR conformation that cannot bind co-activators
   - associated with resistance acquisition

Waterfall Plot of Best Percent PSA Change from Baseline

Radiographic Changes in Soft Tissue (N=59) and in Bone (N=109)

*59 patients with evaluable soft tissue disease as defined by PCWG2 consensus 7 Clin Oncol 2008.
Summary and Conclusions

1. MDV3100 is a second-generation antiandrogen engineered for activity in cells that overexpress AR, unique from bicalutamide.

2. The drug is active in CRPC both before and after chemotherapy as shown by:
   - declines in PSA, imaging, CTC conversion rates, and PET

3. MDV3100 is generally well-tolerated

4. A Phase 3 placebo-controlled survival trial in post-docetaxel CRPC patients is beginning 2009

5. Dose selected to be 240 mg/day based upon:
   - Significant anti-tumor effects plateau at this dose
   - Few side effects
   - Benefit:risk ratio

AFFIRM Phase 3 Registration Trial of MDV3100 in Post-Chemotherapy CRPC Patients

Primary Endpoint: 25% survival increase (12 to 15 months)
Sample size: ~1170 (780 and 390)
Statistics: 85% Power; p=0.05, two-sided
Biomarkers: CTC enumeration and profiling with outcome

Scher, H. (North America) and De Bono, J. Co-PI, Medivation
Immunotherapy in HRPC: Single antigen vs Polyvalent vs Non-specific

- Single-antigen immunotherapies (sipuleucel-T: PAP, PSA-TRICOM vaccines)
  - Target antigen may be absent
  - if present, may no longer be expressed in metastasis
  - Target antigen may be a weak antigen

- Polyvalent cellular immunotherapies (GVAX)
  - More potential tumor antigens = higher potential for control of antigenically distinct lesions
  - Potential for more "hits"
  - Less selective with more potential for adverse effects
  - GVAX studies have been terminated - futile and/or negative

- Non-specific immune stimulation (GM-CSF, CTLA-4 antibody)
  - Lower efficacy if immune system doesn't choose to target prostate cancer antigens
  - Higher toxicity

Active Cellular Immunotherapy with Sipuleucel-T

The precise mechanism of sipuleucel-T in prostate cancer has not been established.

Sipuleucel-T Immunotherapy for Advanced Prostate Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial

IMPACT STUDY

David Penson, MD, MPH

For the IMPACT Study Investigators

American Urological Association Annual Meeting
Abstract 1408, April 28, 2009
Sipuleucel-T: Patient-Specific Therapy

Day 1
Leukapheresis

Day 2-3
sipuleucel-T is manufactured

Day 3-4
Patient is infused

Apheresis Center
Dendreon
Doctor's Office

COMPLETE COURSE OF THERAPY:
Weeks 0, 2, 4

Randomized Phase 3 IMPACT Trial
(IMmunotherapy Prostate AdenoCarcinoma Treatment)

Asymptomatic or Minimally Symptomatic Metastatic Castrate Resistant Prostate Cancer
(N=512)

Primary endpoint: Overall Survival
Secondary endpoint: Time to Objective Disease Progression

Placebo
Q 2 weeks x 3

Sipuleucel-T
Q 2 weeks x 3

P R O G R E S S I O N
Treated at Physician discretion
and/or Salvage Protocol

S U V I L
Treated at Physician discretion
and/or Salvage Protocol

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and/or Salvage Protocol

IMPACT Overall Survival: Primary Endpoint Intent-to-Treat Population

P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]
Median Survival Benefit = 4.1 Mos.
Sipuleucel-T (n = 341)
Median Survival: 25.8 Mos.
Placebo (n = 171)
Median Survival: 21.7 Mos.
Time to Objective Disease Progression

- Secondary endpoint: PSA dependent
- Result
  - Independent radiologic review
  - HR=0.951 (95% CI: 0.77, 1.17); P=0.628 (log rank)
- Consistent with other trials in advanced prostate cancer
- Difficult endpoint to measure reliably and doesn't correlate with overall survival

Summary

- First active immunotherapy to demonstrate improvement in overall survival for advanced prostate cancer
- Highly favorable benefit to risk profile
- Short duration of therapy
- Potential to create new treatment paradigm in oncology

PSA-TRICOM

- Pox virus expressing PSA and 3 co-stimulatory moieties (B7.1, ICAM-1, LFA-3)
- Phase II presented ASCO 2009
  - 129 patients, placebo controlled
  - Median overall survival 8.5 months longer in vaccine group (expected HR 0.56)
- Fatigue, fevers, chills in 10-30%
Androgen deprivation therapy is a standard (Level 1).

Impact of current second line hormonal manipulations limited:
- Bicalutamide, Flutamide, Nilutamide, Ketoconazole

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  - Abiraterone, TAK 700: oral drugs
- Non-reversible androgen receptor antagonists
  - MDV3100, BMS compounds: oral drugs

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Castrate-resistant Prostate Cancer

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Summary:
- La segunda línea actualmente autorizada agentes hormonales es de valor limitado y ninguna ha demostrado supervivencia mejorada.
- La quimioterapia es activa.
  - Resultados de Docetaxel en una ventaja de la supervivencia.
- Mitoxantrone es un agente selectivo LH
- La inhibición de la diferenciación y de la función osteoclastas por el ácido zoledronico disminuye tanta esquelética del afección.
- Denosumab, un inhibidor del rank-ligand, puede ser útil en este ajuste.
- El progreso reciente se ha hecho en más bajo la supresión de la testosterona y de DHT en el cuerpo y dentro de la célula cancerosa de la próstata - inhibidores de la lisa tales como abiraterone, TAK-700.
- Un ataque más eficaz del receptor de andrógeno por ejemplo por MDV3100 tiene potencial terapéutico importante.
- Cytohistat que agota, especialmente con el camino del endotelio, tiene el potencial para rendir varias nuevas drogas futuro próximo: ZE1454.
Castrate-resistant Prostate Cancer

Summary

- Currently licensed second line hormonal agents are of limited value and none have demonstrated improved survival.
- Chemotherapy is active.
  - Docetaxel results in a survival advantage.
  - Mitoxantrone is a useful palliative agent.
- Inhibition of osteoclast differentiation and function by zolendronic acid decreases skeletal event rate.
  - Denosumab, a rank-ligand inhibitor, may be useful in this setting.
- Recent progress has been made in further suppressing testosterone and DHT in the body and within the prostate cancer cell. Lyase inhibitors such as abiraterone, TAK-700.
- More effective binding of the androgen receptor such as by MDV3100 has major therapeutic potential.
- Osteoblast targeting, especially through the endothelin pathway, has the potential to yield several new drugs near future: atrasentan, ZD4054.