New Treatment Modalities and Clinical Trials for HRPC

계명의대
김천일
Castrate-Resistant Prostate Cancer (CRPC)

- Current standard therapy
- Androgen receptor (AR) in CRPC
- New systemic therapies
  - Hormonal therapy: Abiraterone, MDV3100
  - Chemotherapy: Cabazitaxel
  - Immunotherapy: Sipuleucel-T
  - Targeted therapies
1. Hormone therapy-naïve

2. Hormone therapy-responsive

3. Castration-resistant
   - The recent work replace AIPC and HRPC
   - AR is still active in CRPC cells
   - Adequate levels of androgens to activate AR persist despite low levels of serum testosterone
Classical ADT

- Resistance occurs typically after ~18-24 months
- Contemporary treatment options reduce but do not eliminate androgens at target tissue
- Intraprostatic DHT ↓ by 50-70% only
- Intraprostatic T-concentration in CRPC similar to BPH
- AR expression and signaling remains intact after ADT even in CRPC

→ Drugs that more effectively abrogate AR pathway are required
Patients who “fail” first-line hormone therapy

- Confirm castration levels of testosterone
  - 20% of pts. do not have castration levels
  - if testosterone level is above 20ng/ml
    - LH > 1 : inadequate androgen suppression
      - dose interval, body habitus, orchiectomy
    - LH < 1 : excessive adrenal androgen production
      - antiandrogen, ketoconazole
- AAW if CAB initially
Second line hormone therapy

1. Secondary antiandrogen therapy
   - use different antiandrogen (different activity)

2. Adrenal androgen targeted therapy
   - ketoconazole, aminoglutethimide
   - corticosteroid

3. Estrogens or progestins
   - low-dose DES 1mg po q day + ASA
   - megestrol acetate
# Second Line Hormonal Therapy

## The role of antiandrogens in CRPC

<table>
<thead>
<tr>
<th>Action</th>
<th>Response rate (%)</th>
<th>Duration of response</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AA}_{\text{mono}} \rightarrow \text{Castration}$</td>
<td>55 - 65</td>
<td>?</td>
</tr>
<tr>
<td>$\text{Castration} \rightarrow \text{MAB}$</td>
<td>15 - 80</td>
<td>$\varnothing$ 6 months</td>
</tr>
<tr>
<td>$\text{AA Withdrawal}$</td>
<td>15 - 50</td>
<td>$\varnothing$ 3 - 6 months</td>
</tr>
<tr>
<td>$\text{AA1} \rightarrow \text{AA2}$ (switch)</td>
<td>22 - 38</td>
<td>$\varnothing$ 3 - 6 months</td>
</tr>
</tbody>
</table>

Wirth et al., 2007
Fowler et al., 1995; Scher et al., 1997
Scher et al., 1995; Small et al., 1995; Figg et al., 1995; Herrada et al., 1996 Schellhammer et al., 1997; Nieh et al., 1995
Scher et al., 1997; Joyce et al., 1997; Eastham et al., 1998
Postdocetaxel therapies showed no significant improvement in Overall Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Setting</th>
<th>Patients (n)</th>
<th>Response and overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixabepilone (epothilone)</td>
<td>Docetaxel-refractory mCRPC</td>
<td>82</td>
<td>↓PSA≥50%: 17% Median OS: 10.4 months</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Docetaxel-refractory mCRPC</td>
<td>82</td>
<td>↓PSA≥50%: 20% Median OS: 9.8 months</td>
</tr>
<tr>
<td>Docetaxel → mitoxantrone</td>
<td>TAX 327 cross over to mitoxantrone after docetaxel</td>
<td>71</td>
<td>↓PSA≥50%: 15% DP→MP Median OS after crossover: 10 months</td>
</tr>
<tr>
<td>Doxorubicin/ ketoconazole</td>
<td>Docetaxel-refractory mCRPC</td>
<td>32</td>
<td>↓PSA≥50%: 44% Median OS: 13 months</td>
</tr>
<tr>
<td>Satraplatin/ prednisolone</td>
<td>mCRPC progression after 1 prior chemotherapy regimen</td>
<td>950</td>
<td>PSA response: 2.4% (median duration: 44.1 weeks)</td>
</tr>
</tbody>
</table>
Re-induction of hormone sensitivity following failure of chemotherapy

- No hormonal therapy during chemotherapy
  
  ; DES and corticosteroid: PSA reduction (57%)
  
  ; May be due to the growth of androgen-dependent clones

- Previous orchiectomy, LHRH agonist during chemotherapy
  
  ; Rechallenge with DES (estramustine) is a worthwhile option
  
  ; May have an androgen independent mechanism of action

*Br J Cancer* 92: 36-40

*Br J Cancer* 98: 238-239
Androgen receptor (AR) – Structure and function

- Xq11-12
- Member of steroid hormone receptor family of ligand activated nuclear transcription factors
- Unligated AR → cytoplasm bound to HSP90, 70, 56, 23
- Stabilisation of AR tertiary protein structure permitting androgen binding
Androgen receptor (AR) – Structure and function

- Androgen binding
  - Dissociation from HSP90
  - Dimerisation and TK-phosphorylation
  - Translocation of AR to the nucleus

- Inside the nucleus
  - Binding to androgen response elements of target genes
  - Concomittant recruitment of coregulatory proteins → formation of active transcription complex
Old Theories for CaP Recurrence

- Ligand specificity broadened by AR mutations
- AR overexpressed by amplification
- Ligand-independent AR activation
- AR-independent androgen-regulated gene expression
But... AR Gene Amplification Unrelated To Duration of CaP Survival

Androgen Receptor (AR) responds to castration with molecular and biochemical alterations that cause hypersensitivity to low levels of ligand.

CaP responds to castration by synthesizing DHT from weaker androgens and/or cholesterol.
Tissue Androgen Levels using RIA in Benign Prostate (n=32; gray) vs Castration–Recurrent CaP (n=23; white)
AR mutations that broaden ligand specificity
- an *in vitro* mistake

- DHT from weak adrenal androgens
- DHT from cholesterol
Testicular Androgen Production from Cholesterol

- $^{14}$C-cholesterol appears as $^{14}$C-DHT in LNCaP cells thru up-regulation of StAR, the rate-limiting enzyme in steroid synthesis (Locke, *Prostate*, 2010)

AR 10,000 times more sensitive in androgen-independent than androgen-sensitive CaP cell lines

AR coactivators change from SRC-1 to TIF-2 cell lines, xenografts, and clinical specimens

AR phosphorylated by SRC or Ack1 tyrosine kinases
Targeting the Hypersensitive Pathway

- Decrease of tissue DHT by 5a reductase inhibitor
- Decrease of adrenal and intratumoral androgen synthesis by aromatase inhibitor (abiraterone acetate)
- Decrease of tissue cholesterol by statins
- Selective AR modulators (SARM’s): MDV-3100 and RD 162
Secondary Hormonal Therapies Target the AR Directly or Target Ligand Production

Ligand Production
Abiraterone
Ketoconazole
Tak-700
Tok-001

AR Antagonists
Bicalutamide
Nilutamide
MDV-3100
ARN-509
Adrenal Androgen Synthesis

Pituitary

ACTH

Cholesterol

desmolase

Pregnenolone

3-BHSD-I

17α-hydroxylase

170H-pregnenolone

3-BHSD-I

C17-20 lyase

DHEA

3-BHSD-I

Progesterone

DOC

11β-hydroxylase

180H-Corticosterone

18-hydroxylase

Aldosterone

18-oxidase

Ketoconazole

11-DOC

Cortisol

Peripheral Tissues

Androstenedione

Testosterone

DHT

17-keto-reductase

5α-reductase
Abiraterone—4 years on, what do we know?

- **Phase I Questions**
  - Toxicity and PSA effects
  - Fasted vs Fed
  - Adrenal insufficiency?
  - Corticosteroids necessary?

- **Phase II Questions**
  - Efficacy/Durability
    - pre-chemotherapy with prednisone (02)
    - post-chemotherapy without prednisone (03)
    - post-chemotherapy with prednisone (04)

- **Phase III Questions**
  - Efficacy/Durability
    - survival vs prednisone
    - pre vs post docetaxel
<table>
<thead>
<tr>
<th>Patient #</th>
<th>Doc</th>
<th>Keto</th>
<th>≥50% PSA Decline</th>
<th>RECIST Partial Stable</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Bono Cou-AA-00</td>
<td>54</td>
<td>Pre</td>
<td>N/A</td>
<td>38/54 (70%)</td>
<td>15/29 (52%) 8/29 (28%)</td>
</tr>
<tr>
<td>Ryan Cou-AA-002</td>
<td>Ph I: 30 &amp; Ph II: 33</td>
<td>Pre</td>
<td>15/30 (63%) Excluded</td>
<td>16/30 (53%) 16/21 (76%)</td>
<td>N/A N//A</td>
</tr>
<tr>
<td>Reid Cou-AA-003 pred allowable</td>
<td>47</td>
<td>Post</td>
<td>6</td>
<td>24/57 (51%)</td>
<td>6/35 (17%) 23/35 (66%)</td>
</tr>
<tr>
<td>Danila Cou-AA-004 (+ pred)</td>
<td>56</td>
<td>Post</td>
<td>24/56 25/56 (43%) (45%) 33 vs no keto keto vs no keto</td>
<td>2/26 (8%) 16/26 (62%)</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Logothetis Cou-AA-BMA</td>
<td>44</td>
<td>37/44 (86%) 24/44 (56%) 21/41 (51%)</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
NCT00638690: Schematic of Phase III Trial Design (Trial 301)

Progressive prostate cancer after docetaxel-based chemotherapy

2:1 Randomization
Primary Endpoint - Overall Survival
MDV–3100; A Second–Generation Antiandrogen

- Small molecule AR antagonist; retain activity in increased AR expression
- Binds the AR more potently than bicalutamide
- Unlike bicalutamide, MDV-3100 inhibits nuclear translocation of the AR and its binding to DNA
- No AR agonistic activity
**AR Antagonism with MDV-3100**

Possibly Related Grade 2/3 Adverse Events in > 2 Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Doses (N = 140)</th>
<th></th>
<th>&lt; 240 mg/day (N = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G2</td>
<td>G3</td>
<td>G2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29 (21%)</td>
<td>12 (9%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (8%)</td>
<td></td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td></td>
<td>3 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

1. Only one subject discontinued treatment due to fatigue that coincided with disease progression.
2. There were 2 witnessed seizures (1 each at 600 and 360 mg/day) and a possible unwitnessed seizure (at 480 mg/day).
   - Both patients with witnessed seizures were taking concomitant medications that can cause seizure.
3. MTD determined to be 240 mg/day; patients at higher doses were lowered to 240 mg/day.
MDV 3100 Phase I-II Study
PSA response

No previous chemotherapy

PSA Change from Baseline

-100%
-75%
-50%
-25%
0%
25%

62% (40/65) >50% Decline

Previous chemotherapy

51% (38/75) >50% Decline
NCT00974311: Schematic of Phase III Trial Design

- Progressive prostate cancer after docetaxel-based chemotherapy
- No prior abiraterone or ketoconazole

2:1 Randomization
Primary Endpoint - Overall Survival
Secondary aims – PFS and Pain control

Arm A
MDV-3100

Arm B
Placebo
Conclusions

- Therapeutic efficacy of standard ADT is limited, due to:
  - Reduction, but not elimination, of androgen at target tissues

- Clinical trial data with abiraterone and MDV-3100 confirm continued AR addiction in patients with CRPC
  - target the fundamental mechanisms of development of CRPC

- Given the safety and efficacy of these agents, they may replace or delay the need for other therapies
  (eg, chemotherapy)
Cabazitaxel: A Next-Generation Taxane

- New semi-synthetic taxane
  - Microtubule stabilizer selected to overcome the emergence of taxane resistance in model systems
  - As potent as docetaxel against sensitive cell lines and tumor models$^{1,2}$
  - Activity against tumor cells and tumor models that are resistant to, or are not sensitive to, currently available taxanes$^{1,2}$

- In Phase I trials:$^3$
  - Dose-limiting toxicity (DLT) was neutropenia
  - Antitumor activity included responses in docetaxel-resistant mCRPC

Cabazitaxel in Second-line mCRPC: TROPIC Phase III Study

mCRPC Progression on Docetaxel-containing Regimen

- Stratification factor:
  - Disease measurability
  - ECOG PS
- Primary Endpoint:
  - Overall survival (OS)
- Secondary Endpoints:
  - Progression-free survival (PFS)
  - Response rate and safety
- Interim analysis:
  - PFS after 225 events

RANDOMIZE

Cabazitaxel 25 mg/m² q3w + Prednisone 10 mg qd

755 Patients Accrued

Mitoxantrone 12 mg/m² q3w + Prednisone 10 mg qd

- The Plan:
  - 146 investigator sites in 26 countries
  - Maximum treatment duration of 10 cycles
  - 511 events needed to detect 25% reduction in hazard ratio (HR)
  - 90% power; 2-sided, 5% alpha level

Primary Endpoint: Overall Survival Intent to Treat Analysis

- Median OS (months): MP 12.7, CBZP 15.1
- HR (95% CI): 0.70 (0.59-0.83)
- P value: <.0001

Number at risk:
- MP: 377, 300, 188, 67, 11, 1
- CBZP: 378, 321, 231, 90, 28, 4
### Secondary Endpoints: Response Rates and Time to Progression (TTP)

<table>
<thead>
<tr>
<th></th>
<th>MP (n = 377)</th>
<th>CBZP (n = 378)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate*, %</td>
<td>4.4</td>
<td>14.4</td>
<td>–</td>
<td>.0005</td>
</tr>
<tr>
<td>Median TTP, months</td>
<td>5.4</td>
<td>8.8</td>
<td>0.61 (0.49–0.76)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PSA assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate*, %</td>
<td>17.8</td>
<td>39.2</td>
<td>–</td>
<td>.0002</td>
</tr>
<tr>
<td>Median TTP, months</td>
<td>3.1</td>
<td>6.4</td>
<td>0.75 (0.63–0.90)</td>
<td>.0010</td>
</tr>
<tr>
<td>Pain assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate*, %</td>
<td>7.7</td>
<td>9.2</td>
<td>–</td>
<td>.6286</td>
</tr>
<tr>
<td>Median TTP, months</td>
<td>NR</td>
<td>11.1</td>
<td>0.91 (0.69–1.19)</td>
<td>.5192</td>
</tr>
</tbody>
</table>

*Determined only for subjects with pain or PSA ≥20 or measurable disease at baseline, respectively. NR, not reached.
**Most Frequent Treatment-Emergent AEs* in Safety Population**

<table>
<thead>
<tr>
<th>Event</th>
<th>MP (n = 371)</th>
<th>CBZP (n = 371)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades, %</td>
<td>Grade ≥3, %</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>88.4</td>
<td>39.4</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27.5</td>
<td>3</td>
</tr>
<tr>
<td>Asthenia</td>
<td>12.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Back pain</td>
<td>12.1</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>22.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.2</td>
<td>0</td>
</tr>
<tr>
<td>Hematuria</td>
<td>3.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3.5</td>
<td>0</td>
</tr>
</tbody>
</table>

*Sorted by decreasing frequency of events grade ≥3 in the CBZP arm
### Total Deaths During Study

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>CBZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 371)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total deaths during study</td>
<td>275</td>
<td>227</td>
</tr>
<tr>
<td></td>
<td>(74.1%)</td>
<td>(61.2%)</td>
</tr>
<tr>
<td>Deaths due to progression</td>
<td>253</td>
<td>197</td>
</tr>
<tr>
<td></td>
<td>(68.2%)</td>
<td>(53.1%)</td>
</tr>
<tr>
<td>Deaths due to AEs</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>(1.9%)</td>
<td>(4.9%)</td>
</tr>
<tr>
<td>Deaths due to other reasons</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>(4.0%)</td>
<td>(3.2%)</td>
</tr>
</tbody>
</table>
Conclusions from TROPIC

- Cabazitaxel demonstrated a statistically and clinically significant OS improvement compared with mitoxantrone in study population
  - 30% risk reduction of death (HR = 0.70, \( P<.0001 \))
  - OS benefit was consistent across subgroups
- Secondary endpoints support the OS benefit
- Safety profile was predictable and manageable
  - Neutropenia, diarrhea, fatigue/asthenia were the most common adverse events

**Cabazitaxel is the first therapy shown to prolong survival after docetaxel treatment in mCRPC**
Targeting angiogenesis

- Bevacizumab
- Afibercept (VEGF-TRAP)
- Sunitinib
- Lenalidomide
VEGF Trap – aflibercept
A unique anti-angiogenic agent

A recombinantly-produced fusion protein: Human VEGF receptor extracellular domains fused to the Fc portion of human Immunoglobulin G1 (IgG1)

- Innovative concept
  - Increased affinity for VEGF compared to mAbs
  - Binds to VEGF-A, but also VEGF-B and PIGF

- Potential for broader/better spectrum of activity

mAb - monoclonal Antibody
VEGF - Vascular Endothelial Growth Factor
PIGF - Placental Growth Factor
Sunitinib in mCRPC – SUN study design

mCRPC docetaxel up to one prior chemotherapy regimen

Randomize 2:1 N = 819

Sunitinib 37.5 mg daily + prednisone 5 mg po bid (n = 546)

Placebo + prednisone 5 mg po bid (n = 273)

Primary endpoints: OS
Secondary endpoints: PFS, RR, QoL

35% increase in OS (12 months vs 16.2 months)
Bone Targeted Agents

- CRPC: develop bone metastases and related symptoms; prevent or delay bone metastasis

- RANK-Ligand inhibitor of osteoclasts: denosumab

- Endothelin-A receptor antagonist: atrasentan and zibotentan (ZD4054)

- Inhibition of SRC (steroid receptor coactivator): dasatinib
Receptor Activator of Nuclear Factor–kB ligand (RANKL) Mononuclear Antibody Denosumab (AMG 162)

- RANKL-RANK is essential for osteoclast differentiation & survival

- Randomized phase III study in men on hormone therapy for prostate cancer
  - Increased lumbar spine bone density vs. placebo
  - Decreased incidence of vertebral fractures (1.5% vs 3.9% placebo)

- Phase III trial evaluating effect on prolonging metastasis free survival completed

- Head-to-head comparison with bisphosphonates in ongoing trials
Targeting Osteoblastic Bone Metastases: Endothelin-1 Antagonists

- Tumor produces endothelin-1 (ET-1)
- ET-1 stimulates new bone formation via endothelin-A (ET_A) receptor
- Endothelin receptor antagonists
  - Atrasentan
  - Zibotentan
Phase III Randomized Trial of Atrasentan in CRPC

**Progression**

- Placebo: 267/474 (56.3%)
- Atrasentan: 227/467 (48.6%)

**Survival**

- Placebo: 250/474 (52.7%)
- Atrasentan: 237/467 (50.3%)
Phase II Placebo Trial of Zibotentan in CRPC Patients

- No difference in time to progression between groups
- Overall survival

**Median overall survival months (updated)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>17.3</td>
</tr>
<tr>
<td>ZD4054 10 mg</td>
<td>24.5</td>
</tr>
<tr>
<td>ZD4054 15 mg</td>
<td>23.5</td>
</tr>
</tbody>
</table>

ZD4054 10 mg versus placebo: HR 0.38; 80% CI 0.22, 0.64; p = 0.019
ZD4054 15 mg versus placebo: HR 0.61; 80% CI 0.38, 0.99; p = 0.190
Phase II study of oral dasatinib in patients with mCRPC

- Inhibition of SRC (steroid receptor coactivator, also an androgen receptor transcriptional cofactor)
- Reduces osteoclast activity and inhibits osteolysis
- Biologic activity, via bone turnover markers and disease stabilization
  - Lack of progression in 43%
  - 51% reduction in urinary N-telopeptide
  - 60% reduction in bone alkaline phosphatase
Immunotherapy

- Sipuleucel-T
- PROSTVAC
- Targeting CTLA-4: Ipilimumab
- G-VAX
Sipuleucel-T (Provenge) – Therapy with pulsed dendritic cells

Dendritic-cell (APC) precursors are harvested by leukapheresis (day 1)

Purified dendritic cells (APC) with prostate-specific peptides (days 2–3)

Pulse with PAP-GM-CSF fusion protein for 40 hrs

MHC

Inject back into prostate cancer patient (day 3–4)

Complete course of therapy: Weeks 0, 2, 4
IMPACT trial: a phase III trial to assess the efficacy of Sipuleucel-T in the treatment of CRPC patients

Final Analysis (349 events)

36.5 mo median f/u
HR = 0.759 (95% CI: 0.606, 0.951)
p = 0.017 (Cox model)
Median Survival Benefit = 4.1 months

CRPC: castration resistant prostate cancer; HR: hazard ratio; CI: confidence interval
Kantoff P et al. ASCO-GU 2010 (abstract no. 8); http://www/dana-farber.org/; date last accessed 04-10
PROSTVAC (PSA Expressing Vaccina Virus Vaccine) is a recombinant vaccinia virus-encoding transgenes for PSA and multiple T-cell costimulatory molecules.

A phase I trial of PROSTVAC (SQ injection) showed safety and PSA stabilization in 40%.

Phase II trial did not achieve its primary end point of PFS. Updated result showed a 44% reduction in the death rate and an 8.5-month improvement in median OS.

Vaccine extends life of metastatic Pca patients.
Never be surprised by the course of disease
CRPC is a very predictable disease
Convince the patients that you are expert
being in control of every respective situation

Intermediate endpoints of overall survival such as CTC counts are fundamental

Right treatment for the right patient
Concerns all therapies including biologics and chemotherapy