The FDA, New Drugs for Prostate Cancer & Surrogate Markers: Who Cares?

Derek Raghavan MD PhD FACP
Cleveland Clinic Taussig Cancer Center
Cleveland, OH.

Prostate Cancer: Agenda

- Relevant biology of prostate cancer
- Initial studies of chemotherapy
- How new drugs reach clinical practice
  - FDA rules
  - Surrogate markers
- Innovations in systemic therapy
Importance of Research
Why Do Women Live Longer than Men?

Biology of Hormone Regulation
Hormone-refractory Prostate CA

<table>
<thead>
<tr>
<th>ENTITY</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>True hormone resistance</td>
<td>Receptor expression</td>
</tr>
<tr>
<td></td>
<td>Resistant clones</td>
</tr>
<tr>
<td></td>
<td>Neuro-endocrine cells</td>
</tr>
<tr>
<td>Compliance</td>
<td>Sub-capsular orchiectomy</td>
</tr>
<tr>
<td></td>
<td>Patient compliance</td>
</tr>
<tr>
<td>Other histologies</td>
<td>Transitional cell cancer</td>
</tr>
<tr>
<td></td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Other tumors - rectal</td>
</tr>
</tbody>
</table>

Hormone Refractory Prostate Cancer

- Median survival of ~6 months for patients with established clinical bone metastases
- Generally an elderly population
- Common problems:
  - Pain
  - Decreasing function
- Compromised bone marrow
Presentation of Advanced Prostate Cancer: Syndromes

- Bone pain
- Constitutional symptoms – the great mimic
- Urinary obstruction
  - Slow stream, nocturia, frequency, hematuria
  - Acute/chronic renal failure
- Bone marrow failure
- Unusual sites – liver, lungs, nodes, skin
- New pattern – stage migration – SCANS!!

Oral Cyclophosphamide for Advanced Prostate Cancer

- N=30 patients
- Median age 67 (54-79)
- ECOG 0-1: 19
- ECOG 2-3: 10
- Bone dominant disease
- All hormone-refractory

Outcome:
- 60% reduced symptoms
- CR 0/30
- PR 6/30 (20%)
- SD 13/30 (43%)

Survival:
- Median 33 mos from presentation
- Median 13 mos from Rx
Mitoxantrone for Prostate CA
(Raghavan et al, 1989)

- N = 50 patients
- Prior hormone Rx
- Sites:
  - mainly bone metastases
  - prostate
  - nodes
  - liver
  - skin
- Outcome:
  - 60% with less tumor-related symptoms
  - Objective response of 0-35%, depending on criteria of response
  - Survival:
    - Median 10 mos from Rx

Mitoxantrone vs Prostate CA: Results

- Subjective Response:
  - Decreased pain 18/46 (38%)
  - Decreased symptoms 21/46 (46%)
  - Weight gain (>2kg) 19/46 (41%)
  - Improved ECOG status 13/50 (26%)
Mitoxantrone Phase III Canadian Trial: Study Design

Symptomatic HRPC

Randomize

Mitoxantrone + Prednisone

N = 80

Primary Endpoint: Palliation

Prednisone*

N = 81

*Crossover on progression (N = 50)


Mitoxantrone for Advanced Prostate Cancer: Overall Survival

Mitoxantrone for Advanced Prostate Cancer: Quality of Life


Mitoxantrone-Tesmilifene (n=29)

- Tesmilifene modulates cytochrome p450 & of multidrug resistance pump
- 75% with pain response (narcotic-dependent)
  - Reduction of 2 on PPI (McGill-Melzack)
  - EORTC QLQ 30 & Prostate Specific Module
  - Discrepancies between pain reduction & QOL
- 66% with reduced analgesia
- 48% with PSA reduction >75%
- 2 year survival 21% (BUT median 11 months)

(Raghavan et al, J Urol, 2005)
**TAX 327**

Randomize

- **Mitoxantrone** 12 mg/m²
- **Prednisone** 10 mg q day
- Q 21 days up to 10 cycles

- **Docetaxel** 30 mg/m²/wk
- **Prednisone** 10 mg q day
- 5 on; 1 off x 6 cycles

- **Docetaxel** 75 mg/m²
- **Prednisone** 10 mg q day
- Q 21 days up to 10 cycles

**N=1006**

---

**SWOG 9916**

Randomize

- **Mitoxantrone** 12 mg/m²
- **Prednisone** 5 mg bid
- Q 21 days

- **Docetaxel** 60 mg/m² d 2
- **Estramustine** 280 mg d1-5*
- **Dexamethasone** 20 mg, tid d 1 & 2

**N=770**

*Warfarin and aspirin


---

**Docetaxel vs. Mitoxantrone**

- Median survival 18 mos vs. 16 mos.
- Greater toxicity for estramustine
- Two studies:
  - Southwest Oncology Group: TE vs MP
  - Aventis Pharmaceuticals: TP vs MP
**SWOG 9916 (MP vs DE)**

![Graph showing overall survival comparison between Docetaxel + Estramustine and Mitoxantrone + Prednisone.](image)

- **No. at Risk**
  - Docetaxel + Estramustine: 338
  - Mitoxantrone + Prednisone: 336

- **Hazard ratio**
  - Docetaxel + Estramustine: 0.89 (0.82-0.97)
  - Mitoxantrone + Prednisone: 0.94 (0.87-1.03)

- **Median survival**
  - Docetaxel + Estramustine: 19.3 months
  - Mitoxantrone + Prednisone: 17.8 months

- **3 yr Survival**
  - Docetaxel + Estramustine: 17.9%
  - Mitoxantrone + Prednisone: 16.7%

---

**TAX 327: Another Update** (Berthold et al, abst. 5005)

- Docetaxel + Prednisone vs. Mitoxantrone + Prednisone
- Original analysis August 2003 (557 deaths)
- Current analysis December 2006 (833 deaths)

<table>
<thead>
<tr>
<th></th>
<th>D q3week</th>
<th>D q1week</th>
<th>M q3week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>335</td>
<td>334</td>
<td>337</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.89 (0.82-0.97)</td>
<td>0.94 (0.87-1.03)</td>
<td>1.0</td>
</tr>
<tr>
<td>Median surv.</td>
<td>19.3 m</td>
<td>17.8 m</td>
<td>16.3 m</td>
</tr>
<tr>
<td>3 yr Survival</td>
<td>17.9%</td>
<td>16.7%</td>
<td>13.7%</td>
</tr>
</tbody>
</table>
TAX 327: Multivariate Analysis
(ASCO, 2007, Armstrong et al)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver metastases</td>
<td>1.64</td>
<td>1.07–2.50</td>
<td>0.023</td>
</tr>
<tr>
<td>Number of metastatic sites (&gt;2 vs ≤2)</td>
<td>1.58</td>
<td>1.19–2.09</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain at baseline</td>
<td>1.46</td>
<td>1.21–1.76</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Performance status (≤70 vs ≥80)</td>
<td>1.42</td>
<td>1.08–1.85</td>
<td>0.011</td>
</tr>
<tr>
<td>Progression type:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measurable disease</td>
<td>1.40</td>
<td>1.13–1.76</td>
<td>0.002</td>
</tr>
<tr>
<td>Bone scan progression</td>
<td>1.28</td>
<td>1.05–1.55</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Criterion 1c: Survival by Treatment and Surrogate

D + E, no 50% dec
D + E, 50% dec
M + P, no 50% dec
M + P, 50% dec

P < .0001
Hormone Refractory Disease: Stage Migration

- **20th century:**
  - Used to be predominantly narcotic-dependent with bone metastases
  - Stage migration from PSA, CT scan, PET and newer scans (1995-2000)

- **21st century:**
  - Rising PSA
  - Earlier diagnosis
  - Urologists more optimistic re. chemotherapy → refer for treatment earlier and more often

---

Median Time from Progression to Death

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA increase</td>
<td>52</td>
</tr>
<tr>
<td>Bone scan change</td>
<td>41</td>
</tr>
<tr>
<td>Alkaline phos increase</td>
<td>35</td>
</tr>
<tr>
<td>Pain increase</td>
<td>32</td>
</tr>
<tr>
<td>Performance status decline</td>
<td>24</td>
</tr>
<tr>
<td>Hemoglobin decline</td>
<td>22</td>
</tr>
<tr>
<td>Weight loss</td>
<td>12</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>10</td>
</tr>
</tbody>
</table>

Changing Endpoints in Prostate Cancer Therapy

- Impact of stage migration
  - PSA only disease
    - Rising after radiotherapy or surgery
    - Asymptomatic disease
  - Earlier intervention for +ve bone scans
- Measurement of quality of life
- Measurement of time to progression
- Adjuvant trials

Why Do Women Live Longer than Men?
How Does this Impact on New Drugs?

- Stage migration makes new drugs look good
  - Improved innate survival with PSA-only cancer
  - Smaller volumes = better results?
  - Perhaps fewer mutations?
- FDA has responsibility to community
  - Allow access to new drugs
  - New drugs have to be safe
  - Therefore need phase III trials & good endpoints

To Market, To Market!

- Phase I
  - Safe dose?
  - Pattern and scope of toxicity?
- Phase II
  - Any activity in a specific tumor?
  - More information on toxicity
- Phase III – compare old vs. new – better????
- Presentation to FDA – Oncology Drug Advisory Committee (ODAC)
- Phase IV – post-marketing surveillance & trials
What Does FDA Require?

- Survival benefit
- Better quality of life – must be REAL
- Surrogate endpoints?
  - ? Survival at (say) 3 years?
  - ? Early endpoints
    - PSA?
    - Circulating tumor cells?
    - Other?

To Market, To Market!

- Phase I
  - safe dose?
  - Pattern and scope of toxicity?
- Phase II
  - Any activity in a specific tumor?
  - More information on toxicity
- Phase III – compare old vs. new – better?????
- **Presentation to FDA – Oncology Drug Advisory Committee (ODAC)**
- Phase IV – post-marketing surveillance & trials
Biochemical modulation of docetaxel: A failure!!!!

- **Calcitriol**
  - Natural ligand for vitamin D receptor
  - Exerts anti-cancer effect in preclinical models
  - Enhances activity of docetaxel in models

- **Phase I trial of docetaxel-calcitriol**
  - 75% PSA reduction in 60% of cases
  - Measurable objective response in ~50% studied
  - Median survival of about 19 months
  - Case selection bias? (median SAP 127 IU/l)


(BUT: Randomized Phase III trial – failed at FDA)
Sternberg et al (abst. 5019): Satraplatin vs. Prednisone

- SPARC trial – Satraplatin, oral platinum compound
- Regimen: (patients failed prior chemotherapy)
  - Satraplatin 80 mg/m2/day x 5 q 5 weeks + Prednisone
  - Placebo + Prednisone
- Satraplatin wins?
  - PSA response: 25% vs. 12%
  - Pain response 24% vs. 14%
  - Progression-free survival p< 0.00000003
  - Time to pain progression
  - No overall survival benefit – fails at FDA

To Market, To Market!

- Phase I
  - safe dose?
  - Pattern and scope of toxicity?
- Phase II
  - Any activity in a specific tumor?
  - More information on toxicity
- Phase III – compare old vs. new – better????
- Presentation to FDA – Oncology Drug Advisory Committee (ODAC)
- Phase IV – post-marketing surveillance & trials
Why Do Women Live Longer than Men?

Surrogate Endpoints in CAP

- Quality of life
- PSA?
  - Absolute decline?
  - Percentage decline?
  - Decline at a time point – 3 months?
- Progression free survival – not robust
- Circulating tumor cells?
**Criterion 1c: Survival by Treatment and Surrogate**

![Survival Curve Graph](image)

**TAX 327 – Prognostic Factors**

*(Armstrong et al, ASCO, 2007, abst 5009)*

- Surrogacy examined for
  - PSA decline $0 \rightarrow 90\%$
  - PSA normalization
  - Altered PSA kinetics
- Prentice criteria for surrogacy using Cox prop. hazards
- 30% PSA decline @ 3 months with best surrogacy
  - Associated with HR 0.43 (95% CI 0.36-0.51)
  - Treatment effect *per se* lost significance = surrogacy
Standardized Enumeration of CTC

Blood Collection

Sample Processing

Fluorescent Image Analysis

CIRCULATING TUMOR CELLS: ADVANCED PROSTATE CANCER
(2-5 week measurements)

CTC (n=210)  PSA (N=214)

≥5 CTCs (41%)  ≥50% PSA ↓ (18%)
<5 CTCs (59%)  <50% PSA ↓ (82%)

Time from 2-5 Week Blood Draw (Months)
CTC & PSA at 13-20 weeks vs. Survival

CTC (n=145)

PSA (n=144)

Circulating Tumor Cells

- Cleared for further use by FDA
- Utility demonstrated
  - Breast cancer (Cristanofilli, Budd, NEJM)
  - Prostate cancer (DeBono, Raghavan, CCR)
  - Colon cancer (Meropol, Proc. ASCO)
- Requires phase III validation
  - SWOG trial in progress for breast cancer
Investigational Agents

- Biphosphonates
- Signal transduction inhibitors
- Differentiating agents
- Vitamin D analogs
- Dietary agents
- Gene therapy – bcl-2 modulation?
- Angiogenesis inhibitors
- Metalloproteinase inhibitors
- Vaccines?

Summary of Phase II First-Line Chemotherapy Trials in HRPC

(Regimens reported with PSA reduction ≥ 50% among 30%-80% of HRPC patients in phase I-II clinical trials)

- Docetaxel/estramustine
- Docetaxel/mitoxantrone/prednisone
- Docetaxel/estramustine/bevacizumab
- Docetaxel/thalidomide
- Mitoxantrone/prednisone/thalidomide
- Docetaxel/oblimersen
- Docetaxel/enzastaurin (PKC inhibitor)
- Docetaxel/calcitriol (ASCENT trial)

Anti-angiogenics
Apoptosis inducers
Anti-sense agent
Adjuvant Cytotoxics?

**NEO-ADJUVANT:**
- Dreicer et al
- Oh et al
- No major impact of docetaxel on survival
- No major impact on stage
- Abraxane also failed
- Appropriate endpoints?

**CLASSICAL ADJUVANT:**
- SWOG 9921
  - Flaig et al, JCO, 2008
  - Leukemias
  - Early closure
- Adjuvant docetaxel study – closed early
- Other trials

Important Ancillary Therapy for Advanced Prostate Cancer

- **Effective** analgesia is of critical importance
- Additional medications
  - Biphosphonates
  - NSAID’s or COX-2 inhibitors
- Optimal use of radiation modalities
  - External Beam
  - Hemi-body
  - Short course, range of fraction sizes & schedules
  - Systemic irradiation – beware marrow toxicity
    - Strontium
    - Samarium
Advanced Prostate Cancer: Summary

- Hormonal therapy still dominant factor
- Emerging role for cytotoxic chemotherapy
- Stage and response migration
- Newer entities – e.g. small cell prostate cancer
- Work-in-progress: genes and prostate CA
- Novel approaches