Chemotherapy in Prostate Cancer: Teaching an Old Dog New Tricks

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Objectives
- Review the basis for use of chemotherapy in castrate resistant prostate cancer
- Understand the new data supporting chemotherapy in hormone sensitive prostate cancer
- Explore emerging data regarding the use of chemotherapy for non-metastatic prostate cancer
- Learn about novel treatment strategies under investigation

CHEMOTHERAPY FOR CASTRATE RESISTANT PROSTATE CANCER

Prostate Cancer Landscape Pre-2010

Hormone Sensitive

Castrate resistant

Hormone Naive

Chemotherapy
(Docetaxel)

Supportive Care

Docetaxel (Taxotere®)
- Mechanism of Action
  - Microtubule inhibitor
- Administration
  - 75mg/m² IV q21 days
  - Central or Peripheral IV
  - Prednisone 5mg PO BID
  - Dexamethasone premeds
- Toxicity
  - Fluid retention* (7%)
  - Low grade nausea
  - Hematologic toxicity (30%) (<5% Febrile Neutropenia)
  - Sensory neuropathy, cumulative (30%)
  - Radiation recall (<5%)
  - Monitor LFTs, CBC

TAX-327 (2004)
- Docetaxel vs Mitoxantrone
- Weekly vs q 3 wks
- GNRH agonist continued
- Results
  - PSA response ~50%
  - Median TTP ~6 mos
  - Median OS ~19 mos (vs 16 mos)
Prostate Cancer Landscape

Pre-2010

- Androgen Deprivation
  - Decreased testicular synthesis
  - AR inhibition
- Chemotherapy (Docetaxel)
- Supportive Care

Evolving

- Hormone "ultrasensitive"

Prostate Cancer Trajectory

- Androgen Deprivation
  - Decreased synthesis
  - AR inhibition
- Chemotherapy
- Supportive Care
- Immunotherapy
- Radiopharmaceuticals

The Renaissance

- In less than 5 years, 5 new therapies approved
  - All evaluated in phase III clinical trials
  - All demonstrate survival benefit
- PLUS: Denosumab for SREs (2010)

Chemotherapy Sequence

- Chemotherapy historically used in men with mCRPC after failure of androgen blockade
  - With novel agents, chemo often delayed even further
- Is there a role for up-front chemotherapy at the time of starting hormonal therapy?
  - Better treatment tolerance
  - Eradicate androgen insensitive clones

CHAARTED STUDY: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer
- Plenary session, ASCO 2014

CHEMOTHERAPY FOR HORMONE SENSITIVE METASTATIC PROSTATE CANCER
**CHAARTED Design**
- ECOG study
  - 790 men
  - 87% received full course
- Primary outcome: Overall Survival
- Secondary outcomes:
  - PSA response, change in PSA over time, time to hormone refractory disease, time to clinical progression, time to PSA progression, toxicity, QOL

**CHAARTED Results**
- Median Age: 63
- range 36-91 yrs
- ECOG 0 or 1: 89%
- Prior therapy
  - No prior therapy: 73%
  - 1st prostatectomy: 20%
  - 1st radiotherapy: 7%
- Started docetaxel
  - <120 days from ADT

**Survival Data**

<table>
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<tr>
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<th>ADT</th>
<th>ADT+D</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)</th>
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<tr>
<td>N=790</td>
<td>42.3</td>
<td>52.7</td>
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<td>High Volume N=520 (66%)</td>
<td>32.2</td>
<td>49.2</td>
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<td>Low Volume N=270 (34%)</td>
<td>NM</td>
<td>NM</td>
<td>0.0838</td>
<td>0.58 (0.31, 1.08)</td>
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**Study Conclusions**
- ADT + D improves survival over ADT alone in metastatic prostate cancer
- Should be considered for men with high volume disease suitable to receive chemotherapy
- Longer follow-up needed for men with low volume prostate cancer
- De-novo disease represents a small subset of patients – do we extrapolate?
Prostate Cancer Trajectory

Androgen Deprivation
• Decreased synthesis
• AR inhibitory

Castrate Resistant

Hormone Sensitive

Chemotherapy

Supportive Care

Chemotherapy in M0 HSPC?

Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localized prostate cancer (SETUG 12): a phase 3 randomised controlled trial


“High Risk” defined as
• Stage T3-T4, Gleason ≥8, PSA >20 ng/mL, node (+)

Randomized to:
• ADT for 3 years
• ADT + docetaxel + estramustine

Chemotherapy in M0 HSPC?

Primary endpoint relapse free survival

Results (median follow up 8.8 years)
• 8 year relapse-free survival
  • ADT Alone: 50%
  • ADT + chemotherapy: 62%

Longer follow up needed
• Metastasis free survival advantage?
• Overall survival advantage?

NRG/RTOG 0521: A Phase III Protocol of Androgen Suppression and Radiotherapy vs. AS and RT Followed by Chemotherapy with Docetaxel and Prednisone for Localized, High Risk Prostate Cancer

RTOG 0521

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NRG
Chemotherapy in M0 HSPC?

- PUNCH Trial (CALGB 90203)
  - Neoadjuvant chemotherapy
  - High risk by Kattan nomogram
- Completed enrollment 12/2015 (~750 pts)

Conclusions

- ADT remains central in the management of high risk prostate cancer
- Risk/benefit ratio needs to be considered
- 2 chemotherapy-related deaths and 4 unknown deaths vs 0 in ADT group
- Chemotherapy likely plays a role in the treatment of carefully selected patients with high risk disease and very long life expectancy

NEW DOGS, NEW TRICKS

New Metastatic Disease

- GNRH agonist + Enzalutamide or Abiraterone (new metastatic disease) (vs monotherapy or CAB)
- TAK-700 (Orteronel): novel androgen synthesis inhibitor (CYP-17)
  - Studied in CRPC (ELM PC4 & ELM PCS) with no differences in OS, but improved rPFS and time to PSA progression
  - Enrolling: role in new metastatic disease (GNRH+TAK700 vs GNRH+Bicalutamide), adjuvant rx with radiotherapy
- Newer agents also under investigation in non-metastatic CRPC

New Metastatic Disease

- STAMPEDE Trial
  - UK enrollment
  - Multi-arm randomization
  - Results anticipated September, 2017

Combination Therapy

- Conceptually attractive
  - Enzalutamide + Abiraterone vs sequential therapy (CRPC)
  - Radium-223 + Enzalutamide or Abiraterone
  - Sipuleucel-T + Enzalutadimide or Abiraterone (potential negative effect of steroids)
- Continuation/maintenance strategies after progression
More Chemo Sequencing

- **FIRSTANA:**
  - Cabazitaxel front line
  - Completion January 2015

- **PROSELICA:**
  - Cabazitaxel 20mg/m² vs 25mg/m²
  - Completion January 2015

- **TAXYNERGY:**
  - Cabazitaxel or docetaxel front-line, early switch if 30% decline in PSA is not achieved
  - Completion July 2015

Targeted Therapy

- **Patel J C. Et al.** *Emerging Molecularly Targeted Therapies in Castration Refractory Prostate Cancer. 2013*

Immunotherapy

- **Vaccines**
  - ProstVac: genetically modified Pox-virus vector
  - GVAX: phase III trials in combo with ADT
  - ProstAtak: adenovirus vector with Herpes gene integration; in phase III study in combo with RT

- **Immune checkpoint inhibitors**
  - Ipilimumab, Nivolumab
    - 1st clinical use in melanoma
    - Variety of phase II and phase III investigations in metastatic prostate cancer

Parallel Landscapes?

- **Conclusions**
  - Current standards
    - Chemotherapy
      - Offer early for fit patients with high volume disease
      - Consider use after definitive radiation/ADT for men with high risk disease who have very long life expectancy
    - Abiraterone – approved pre AND post docetaxel
    - Enzalutamide – approved pre AND post docetaxel
    - Immunotherapy and Radiopharmaceuticals should be considered at some point for men with metastatic disease
  - Use sequentially – combinations still under investigation

- **Conclusions**
  - For now, practical treatment decisions based on
    - Patient preference
    - Functional status/comorbidities
    - Disease trajectory
    - Economic considerations
  - Most patients will ultimately be exposed to several, if not all, agents in succession
Questions?

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