NEW TREATMENTS FOR PROSTATE CANCER
Initial Management to Metastatic Disease
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Disclosures
- Consultant, Jansen Pharmaceuticals, MDB Holdings, Cougar
- Past consultant: TAPP, Bayer, Novartis
- Stockholder: Gonex, PreTecSure Scientific, Aurora Oncology

Outline
- Biology
- Screening technologies
- Initial Treatment
- New Pharmaceuticals
- Future Directions
BIOLOGY

Prostate cancer is unlikely to be amenable to single targeted treatment strategies, except in the non-metastatic setting.

The evolutionary history of lethal metastatic prostate cancer
Gundem et al.
Nature 520, 353–357 (16 April 2015)

Subclonal structure within 10 metastatic lethal prostate cancers.

Whole Genome Sequencing of multiple metastatic sites at autopsy.

Monoclonal Seeding Example

<table>
<thead>
<tr>
<th>Trunk</th>
<th>Branches</th>
<th>Leaves</th>
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How the cancer spread over time in a single patient.

Biology Conclusions

- Few targetable “trunk” mutations
  - Unlike EGFR, ALK mutations in lung cancer or BRAF in melanoma.
- Exception might be TMPRSS-ERG found in >50% of patients
  - Androgen receptor remains targetable
- Hypermethylation of some genes has led to new diagnostics

EARLY PROSTATE CANCER

Management Dilemmas and Challenges
Case Presentation

- 54 year old software engineer; married with 3 children; healthy; no family history of cancer
  - Sexually active with no ED
  - Nocturia x 1
- PSA values:
  - 2014 1.8
  - 2015 2.4
  - 2016 3.7
- Digital rectal exam: 40 gram prostate, smooth, no nodules.

Do you recommend a prostate biopsy?

- YES
- NO
- Maybe – shared decision
- I don’t know

Risk Calculator

12% Risk for positive biopsy
2% Risk for high grade or >T2B

12 Core Transrectal Ultrasound Directed Biopsy

Our patient’s results are negative. Mild inflammation. 2 cores show PIN

Improved (?) ways to determine whether Pca present if initial biopsy negative

- Multiparametric MRI
- PCA3 test
- TMPRSS-ERG Fusion gene
- Confirm Dx
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Biopsy Results:

- 2/12 cores positive
- 5-10% of the linear specimens
  - Both from the lateral base
- Gleason Score 3+3

What are his options and the results of his choice?

Focal Therapy – the male lumpectomy

- HIFU - High intensity focused ultrasound
- PDT - photodynamic therapy
- Cryotherapy
- LITT – laser interstitial thermotherapy
- Brachytherapy - “seeds”
- IRE – irreversible electroporation
- RFA – radiofrequency ablation

Things to consider
- About 1/3 of patients with radical prostatectomy will have either MORE or WORSE cancer than the biopsy indicated.
- No long term oncology efficacy studies
- Mapping biopsies can rule out more or worse cancer

Focal therapy is safe – meta analysis of 3200 patients
- Pad free/leak free 83-100%
- Potency preserved 81-100%

Randomized Trial

*Active Monitoring vs Surgery vs Radiation*

ProtecT Study Group, UK. Sept, 2016

1999-2009. 82,429 men aged 50-69 who had PSA testing

2664 diagnosed with localized prostate cancer

1643 agreed to randomization

Median PSA Level 4.6 ng/ml

77% Gleason 6

76% T1c (no palpable tumor)

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**Treatment Protocols**

- **Monitoring**
  - PSA level q3 months x 1 yr, then q6-12 months
  - Intervention, further testing, treatment for PSA increase >50% over 12 mo.

- **Radiotherapy**
  - ADT for 3-6 months before and during RT
  - 74 Gy in 37 fractions

- **Radical Prostatectomy**
  - Adjunct or salvage RT for positive surgical margins, EC disease or PSA >0.2

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Randomization, Treatment, and Follow-up.
Conclusion

- Very few men diagnosed with localized, small volume, low grade prostate cancer die from their disease
- Disease progresses over time
- 44% of the men in the trial avoided the side effects of treatment for 10 years
  - >50% went on to treatment

Randomized Trial

Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

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Outcomes for Urinary Function and Effect on Quality of Life.

Outcomes for Sexual Function and Effect on Quality of Life.

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ADVANCED DISEASE

Extraordinary Progress in the past 6 years
New challenges
Hypothalamic-Pituitary-Gonadal-Target Axis

Hypothalamus

Anterior Pituitary

Adrenal Cortex

Testis Leydig Cells

Dehydroepiandrosterone

Androstenedione

Testosterone

Dihydrotestosterone

Abiraterone

LHRH agents

Phase III study of abiraterone after docetaxel

- mCRPC with progression after docetaxel
Abiraterone Acetate phase III trial

147 sites in North America, Europe and Australia

- Primary endpoint was Overall Survival (25% improvement)
- Secondary endpoints included time to PSA progression, radiographic progression-free survival, PSA responses

COU-AA-301: AA Improves Overall Survival in mCRPC in Comparison to Placebo

- Placebo: 10.9 months (95% CI: 10.2-12.0)
- Abiraterone acetate: 14.8 months (95% CI: 14.1-15.4)

HR = 0.646 (0.54-0.77) P < 0.0001

Cougar 302 Trial. Abiraterone before chemotherapy

B Overall Survival

No. of Events
Abiraterone-prednisone: 147
Prednisone alone: 138

No. at Risk
Abiraterone-prednisone: 146
146 146 146 146 146 146 146 146 146 146 146 146 146 146 146 146 146 146 146 146
Ryan et al. NEJM Jan 10, 2013

GU ASCO 2011
Final overall survival analysis
34 months in the Abiraterone arm

• From 30 to 34 months on final analysis
  This is despite the use of Abiraterone in the post-docetaxel setting

Time to opiate use

• From 23 to 33 months
  10 months delay in the development of significant cancer pain requiring narcotic pain medication.

The activity of AR
Phase 3, double blinded trial of 1199 men with mCRPC after docetaxel chemotherapy.
- 2:1 randomization
- 280 mg of Enzalutamide versus placebo

A brief review of medical therapy for prostate cancer

- Sipuleucel – T in April, 2010
- Cabazitaxel in June, 2010
- Denosumab in November, 2010
- Enzalutamide in January, 2011
- Radium-223 in May 2013
Challenges in the new era of Prostate Cancer Management

- Use of molecular markers
  - >10 gene expression profiles that have predictive value
  - No prospective validation of their use in clinical decisions
  - AR-V7 as a screen for androgen axis sensitivity
- New hormonal agents
  - When to use them?
  - Sequential vs combination?
  - How can we afford their use? (> $6k/month for Abiraterone or Enzalutamide)

E3805 – CHAARTED

Hypothesis:
Docetaxel added at the time of starting androgen deprivation therapy (ADT) for hormone naïve metastatic prostate cancer will prolong overall survival

HR=0.61 (0.47-0.80) p=0.0003
Median OS:
ADT + D: 57.6 months
ADT alone: 44.0 months


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  - Immunotherapy, genetics, prevention
Prostvac Immunotherapy

Kantoff et al. JCO September 2016

Thanks

Questions?