Rising PSA after treatment:
How much does it matter, what can I do about it, and who should I ask?

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Agenda

• What is biochemical relapse?
• What are the implications?
  – Does it matter?
• What can be done?
• Who should I ask?
• Where to go from here?
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“Clinical States”

Death from other causes

Clinical Localized Disease → Rising PSA

Rising PSA → Clinical Metastases Non-Castrate

Clinical Metastases Non-Castrate → Castrate Metastatic Disease

Castrate Metastatic Disease → Death from Prostate cancer

50,000 new men per year fall into this category in the U.S. alone
Estimated to be about 700,000 men currently

Adapted from Scher et al.
Why doesn’t surgery and/or radiation cure everyone?
Did my doctor miss something?

• There are 2 possibilities for biochemical “recurrence”
  – Cancer was left behind with surgery or missed with radiation
    • Possible, but uncommon
    • These cases may be cured (“salvage” therapy)
  – At least 1 cancer cell had already spread prior to treatment
    • “Micrometastatic” disease
Agenda

• What is biochemical relapse
• **What are the implications?**
  – Does it matter?
• What can be done?
• Who should I ask?
• Where to go from here?
What is PSA?

• Prostate Specific Antigen (PSA) is a protein produced in prostate and prostate cancer cells
• It is secreted from these cells and can be detected in blood
• The gene which controls PSA production is regulated by the androgen receptor
  – Implications…
Does a rising PSA mean that I have cancer?

• Probably yes (if levels are significant)
• Residual prostate tissue after surgery may produce very low, generally not rising PSA after surgery
• Residual normal prostate tissue following radiation typically produces some level of PSA which may fluctuate
• However, a steadily rising PSA after surgery or radiation essentially signifies the presence of cancer
Will a rising PSA shorten my life?

- **Not necessarily** (usually not)
- The average length of life for the 2/3 of men without biochemical recurrence after local therapy is the same as the average length of life for the 1/3 of men with PSA recurrence
  - Though some choose to receive or require treatment
    - And some unfortunately develop metastatic disease and may die earlier
Agenda

• What is biochemical relapse?
• What are the implications?
  – Does it matter?
• **What can be done?**
  – **Part 1**: testing
• Who should I ask?
• Where to go from here?
Where is my PSA coming from?
Imaging

• Current imaging tools:
  – Xray
  – Ultrasound
  – CT scans
  – MRI
  – Bone scan
    • $^{99m}$Tc-MDP bone scintigraphy
  – Other available/approved nuclear medicine techniques
    • FDG-PET/CT
    • NaF bone PET/CT
    • $^{11}$C choline PET/CT
    • $^{111}$In-capromab penditide (Prostascint®)
Problems with current imaging

- Not sensitive enough
- Not specific
- May not change treatment options
How do we make improvements in medicine?
Percent of patients participating in clinical trials

- Breast: 9.8%
- Colorectal: 11.0%
- Lung: 11.6%
- Prostate: 2.5%

Wassenaar et al, ASCO 2008
# Patient satisfaction with care

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Treated with standard care</th>
<th>Treated on clinical trial</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Cancer</td>
<td>60.1%</td>
<td>69.4%</td>
<td>P=0.03</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>45.5%</td>
<td>58.9%</td>
<td>P=0.009</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>37.7%</td>
<td>63.6%</td>
<td>P=0.001</td>
</tr>
</tbody>
</table>

Wassenaar et al, ASCO 2008
Why don’t more patients participate in clinical trials?
Primary reason for not participating in clinical trial

- Not told trial was an option (60.2%)
- Not eligible for available trial (15.0%)
- Declined participation in available trial (13.9%)
- Did not have insurance coverage for care (2.6%)
Second Generation Anti-PSMA Abs: **J591**

2nd generation mAbs
- Bind extracellular domain
- Bind viable PSMA$^+$ cells
- Rapidly internalized

Liu H *et al.* Cancer Res 1997; 57: 3629
Liu H *et al.* Cancer Res 1998; 58: 4055
J591 PSMA-Targeted PET Scan

Substantial improvement over conventional imaging (bone, CT, MR, FDG)

Confirms ability of J591 to target PC wherever it is in body

Allows quantitative imaging
Pt with no known soft tissue disease until $^{89}$Zr-J591 detected this LN met

Aortocaval node biopsy: Prostatic adenocarcinoma. Positive for PSA and PSAP by IHC.

Patient with rising PSA, suspicious LN on MRI, but CT and FDG negative. $^{89}$Zr-J591 avid; biopsy-proven as the first metastatic site in the patient.

Morris et al, 2013 Genitourinary Cancers Symposium
Agenda

• What is biochemical relapse?
• What are the implications?
  – Does it matter?
• What can be done?
  – Part 2: treatment (if necessary)
• Who should I ask?
• Where to go from here?
Hormones and prostate cancer

• In animal experiments, Huggins and Hodges (1938) demonstrated that castration and estrogen therapy resulted in clinical quiescence of prostate cancer
• This was successfully emulated in humans (1941)
• Translational therapeutics was born
• Charles Huggins - **NOBEL PRIZE 1966**
Results of hormonal therapy for biochemical recurrence

• Universal PSA declines
• No clear improvement in survival across the board
• However, for those with unfavorable PSA kinetics, delay in time to metastatic disease and also death (but no cures currently)
  – “PSA doubling time”
What else can I do if I want (or need) treatment?

• Nutrition
• Exercise
• Pomegranate?
• Other?

• Participate in research
  – Diagnostics
  – Therapeutics
New (prob better) hormonal agents are here (and more on the way)

- Abiraterone acetate (Zytiga)
- Enzalutamide (Xtandi / MDV3100)
- Orteronel (TAK700)
- ARN509
- Galeterone (TOK001)
- …and many others
## Where We Are Now: Positive Phase 3 Trials in Met CRPC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>HR</th>
<th>Endpoint</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian N = 161</td>
<td>Mitoxantrone/prednisone vs prednisone</td>
<td>NR</td>
<td>Palliation in 29% vs 12% (duration 42 vs 18 wks)</td>
<td>Approval of mitoxantrone (also CALGB 9182)</td>
</tr>
<tr>
<td>TAX 327 N = 1006</td>
<td>Docetaxel/prednisone vs mitoxantrone/prednisone</td>
<td>0.76</td>
<td>OS 18.9 vs 16.5 mo</td>
<td>Doce/pred approved as new SOC</td>
</tr>
<tr>
<td>SWOG 9916 N = 770</td>
<td>Docetaxel/estramustine vs mitoxantrone/prednisone</td>
<td>0.80</td>
<td>OS 17.5 vs 15.6 mo</td>
<td>Support doce as new standard</td>
</tr>
<tr>
<td>ZAPCSG N = 643</td>
<td>Zoledronic acid vs placebo</td>
<td>NR</td>
<td>SRE 33.2% vs 44.2%</td>
<td>Zoledronic acid reduces SRE's</td>
</tr>
<tr>
<td>IMPACT N = 512</td>
<td>Sipuleucel-T vs Control</td>
<td>0.78</td>
<td>OS 25.8 vs 21.7 mo</td>
<td>Sip-T approved min sympt metCRPC</td>
</tr>
<tr>
<td>Dmab 103 N = 1904</td>
<td>Denosumab vs zoledronic acid</td>
<td>0.82</td>
<td>SRE-free 20.7 vs 17.1 mo</td>
<td>Denosumab approved</td>
</tr>
<tr>
<td>TROPIC N = 755</td>
<td>Cabazitaxel/prednisone vs mitoxantrone/prednisone</td>
<td>0.70</td>
<td>OS 15.1 vs 12.7 mo</td>
<td>Cabazitaxel approved post-doce</td>
</tr>
<tr>
<td>COU-AA-301 N = 1195</td>
<td>Abiraterone/prednisone vs Placebo/prednisone</td>
<td>0.65</td>
<td>OS 14.8 vs 10.9 mo</td>
<td>Abi/pred approved post-doce</td>
</tr>
<tr>
<td>ALSYMPCA N = 922</td>
<td>Radium-223/BSC vs placebo/BSC</td>
<td>0.70</td>
<td>OS 14.0 vs 11.2 mo</td>
<td>Rad223 approved</td>
</tr>
<tr>
<td>AFFIRM N=1199</td>
<td>Enzalutamide vs Placebo</td>
<td>0.63</td>
<td>OS 18.4 vs 13.6 mo</td>
<td>Enzalutamide approved post-doce</td>
</tr>
<tr>
<td>COU-AA-302 N = 1088</td>
<td>Abiraterone/prednisone vs Placebo/prednisone</td>
<td>0.81</td>
<td>OS 34.7 vs 30.3 mo</td>
<td>rPFS HR 0.43 Led to broad approval</td>
</tr>
<tr>
<td>PREVAIL N=1715</td>
<td>Enzalutamide vs Placebo</td>
<td>0.7</td>
<td>OS 32.4 vs 30.2 mo</td>
<td>rPFS HR 0.18 Led to broad approval</td>
</tr>
<tr>
<td>ELM-PC 4 N=1560</td>
<td>Orteronel/prednisone vs Placebo/prednisone</td>
<td>0.71</td>
<td>rPFS 13.8 vs 8.7 mo</td>
<td>Negative for OS;</td>
</tr>
</tbody>
</table>
Where are we going from here?

• Additional uses for approved drugs
  – Additional (generally earlier) settings
  – Combinations

• New versions of similar drugs

• Treatment optimization
  – Mechanisms of resistance
  – Sequencing

• New targets / drugs

• New disease classifications
  – Precision medicine
If my PSA is rising and old-fashioned hormonal therapy can’t cure me, what about new drugs?

• Example: PCCTC “AbiCure” study
  – Leverage more potent AR-targeted therapy
  – Can this get rid of 100% of leftover cells?
    • Degarelix (Firmagon)
    • Degarelix + Abiraterone/prednisone (Zytiga)
    • Abiraterone/prednisone
  – Treat for 8 months, then monitor closely
\( ^{177} \text{Lu-J591 Salvage RIT} \)

- Biochemical only relapse is common
- Radiotherapy is an effective salvage therapy for selected pts; however most pts suffer distant relapse/progression
- RIT may have greatest effect in setting of minimal disease
- J591 successfully targets known sites of disease and shows efficacy in the advanced setting

Scher JCO 2004
Freedland J Urol 2007
Pazona J Urol 2005
Buskirk J Urol 2006
Stephenson JAMA 2004, JCO 2007

Ward J Urol 2004
Kaminski Blood 2002; JCO 2005; NEJM 2005
Press Blood 2003; JCO 2006
Leonard JCO 2005
Pt with no known soft tissue disease until $^{89}$Zr-J591 detected this LN met

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Morris et al, 2013 Genitourinary Cancers Symposium
A Randomized Phase 2 Trial of $^{177}$Lu Radiolabeled Monoclonal Antibody HuJ591 ($^{177}$Lu-J591) and ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy

High risk castrate biochemically progressive entry criteria:
- PSA DT < 8 months
  and/or
- absolute PSA > 20

2:1 randomization stratified by
- Investigational site
- Type of primary therapy
  (Surgery vs RT)

Tagawa et al, IMPaCT 2011
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• **Where to go from here?**
How can I (we) help?

Two very important elements to make progress:

Awareness / Advocacy

and

Funding
• “Mo” slang for moustache in Australia
• A conversation starter, raises awareness
• Funds raised in the U.S. go towards prostate and testicular cancer and mental health initiatives
MOVEMBER
CHANGING THE FACE OF MEN'S HEALTH

GLOBAL FUNDS RAISED
$299 MILLION USD... SO FAR

GLOBAL REGISTRANTS
1.9 MILLION MO BROS & MO SISTAS... SO FAR
Molecular Classification of Prostate Cancer ➔ Precision Medicine

Tumor traditionally classified by histology, tissue site

Extract tumor biopsy

Extract DNA from tumor to profile for somatic alterations

Define “actionable” mutation profile of tumor

Use genetic alteration profile to choose individualized targeted therapeutic

Inhibitors
Is recurrent prostate cancer curable?

• How can we combat heterogeneity and resistance?

• With combination therapy, what if we could:
  – Ablate AR ligand(s)
  – Inhibit AR (ligand-binding domain and N-term)
  – Inhibit microtubules
  – Inhibit neuroendocrine pathways
  – Deliver lethal DS DNA breaks
  – Then eliminate the rest with immunotherapy following broader antigen exposure
Prostate Cancer Annihilation

- LHRH + CYP17 + AR signaling inhibitor
- Alternating non-cross-resistant therapy
  - Taxane
  - Aurora kinase inhibitor?
  - Platinum?
- Targeted alpha particle
- Other “targeted” (PI3K, MET, PARP, etc)
- Following antigen release, checkpoint inhibitor
"Clinical States"

- Subclinical Disease
- Clinically Localized Disease
- Untreated
- Metastatic Disease
- Treated
- Death from other causes
- Death from Cancer

LIVING YOUR LIFE

Weill Cornell Medical College
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PATIENTS AND THEIR FAMILIES