PROSTATE CANCER

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Learning Objectives

□ Discuss the cancer diagnosis and screening, including the role of Prostate Specific Antigen (PSA).
□ Review the basics of treatment of prostate cancer.
□ Explain the benefits and risks of the latest oral therapies for prostate cancer.

Question

□ Which of the following has NOT been shown to increase the risk of prostate cancer?
  A) Male Gender
  B) African-American Race
  C) 5-alpha-reductase polymorphism (SRD5A2)
  D) Benign Prostatic Hyperplasia (BPH)
  E) Age
Background of Prostate Cancer

- Most common (non-dermatologic) cancer among men
- 2nd leading cause of cancer-related death in men
- Hormone-dependent

Risk Factors for Prostate Ca

- Race/Ethnicity Effects on Risk Factor
  - Scandinavian countries & US = highest reported rates
  - African American = highest overall incidence & death rates
    - Testosterone levels are 15% higher
    - More activation of testosterone receptor
  - Japan & Asian countries report lowest rates
    - May be due to low activity of 5-alpha-reductase
    - Converts testosterone to more active dihydrotestosterone (DHT)
    - Also have a diet relatively high in phytoestrogens which may be chemoprotectants

- Family history
  - Can increase risk 2 – 3x

- Genetic Links
  - Lower number of CAG repeats in the androgen receptor
  - Higher activation of the receptor & thus cancer
  - Variant SRD5A2 of the 5-alpha-reductase enzyme
  - Increases risk of prostate cancer by increasing activity of that enzyme
Risk Factors for Prostate Ca

- Environmental Factors
  - Smoking & Alcohol
    - NOT associated!
  - UV exposure
    - More cases further away from the equator?
  - Obesity
  - Diet
    - May be associated
      - Increased fat and/or meat intake
    - Supplementation does not decrease risk
      - Vitamin E/Selenium (SELECT Trial)

Mythbustin' in Prostate Cancer

- No link between prostate cancer and:
  - BPH
    - Can complicate diagnosis
  - Sexual activity
  - Vasectomy

- Serum testosterone or DHT not always correlated with Prostate CA
  - Indicates Multifactorial Cause

Prevention of Prostate Cancer

- Prostate Cancer Prevention Trial (PCPT)
  - Over 18,000 men with PSA <3 ng/dL
  - Finasteride 5mg po daily x7 years
  - Treatment group:
    - 30% reduction in prostate Ca (NNT=41)
    - Higher Gleason Score in those that developed cancer
  - Unknown survival benefit
Question

- What class of medications has been recently suggested to decrease risk of prostate cancer?
  - A) Calcium-channel Blockers
  - B) Beta-Blockers
  - C) Quinolone antibiotics
  - D) Statins
  - E) Prostablationers

Prostate Physiology

- Aids in seminal fluid production and control of urination
- Prostate Specific Antigen (PSA)
  - Produced by prostate cells
  - Role in prostate growth
  - Increased in:
    - Damage to the prostate
    - Prostatitis
    - Benign Prostatic Hyperplasia (BPH)
    - Ejaculation

Prostate Cancer Detection

- Prostate Specific Antigen (PSA)
  - Cut-off is approximately 4ng/ml
  - Positive Predictive Value = 30%
- Digital Rectal Exam (DRE)
  - Detects nodules, induration & asymmetry
  - High interrater variability
  - Value of the Test
  - Positive Predictive Value = 5-30%

Brawer et al. 1999 & Meigs et al. 1996
### Screening Controversy

- **Observational Studies**
  - **PLCO Study**
    - Showed no mortality benefit in PSA screening
    - May not have enough power
  - **ERSPC Study**
    - 20% relative risk reduction in death rate
    - More variability in screening methods
    - 1410 screenings & 48 treatments needed to prevent one death in 10 years
- **Meta-analyses**
  - 2010 & 2011
    - Screening does NOT reduce death, but does increase cancer diagnosis

### Screening Controversy

- **American Cancer Society**
  - Age >50
- **American Urologic Society**
  - Ages 55 – 69
- **US Preventative Services Task Force**
  - No routine screening
- **March 2014** – “Radical Prostatectomy is better than watchful waiting”

### Diagnosing Prostate Cancer

- **Biopsy Recommendations**
  - Highly recommended in PSA >10ng/mL
  - Greater than 50% will have positive biopsies
  - Recommended in PSA 4-10ng/mL
    - About 20% will have positive biopsies
  - 20-40% will have cancer despite PSA <4ng/mL
- **Transrectal prostate biopsy** is the gold standard of diagnosis
  - 6-12 samples taken, give 90% detection

*Presti et al. 2000*
Prostate Cancer Staging

- Stage I – Stage II
  - Confined to prostate
- Stage III
  - Extending outside the capsule
- Stage IV
  - Metastatic disease
  - Lymph nodes → blood stream → bones → liver & lungs

Gleason Score

- Reports primary & secondary
- Helps account for inherent heterogeneity of the prostate
- Summate scores to get total Gleason Score

<table>
<thead>
<tr>
<th>Histologic Grade</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>Gx</td>
<td>Cannot be assessed</td>
</tr>
<tr>
<td>G1</td>
<td>Well differentiated (Gleason 2-4)</td>
</tr>
<tr>
<td>G2</td>
<td>Most differentiated (Gleason 5-6)</td>
</tr>
<tr>
<td>G3-4</td>
<td>Poorly or Undiff (Gleason 7-10)</td>
</tr>
</tbody>
</table>

Treatment Goals

- Overall goal is to minimize overall morbidity & mortality
- Stage I – III (Stage A – C)
  - Active surveillance is appropriate tx
    - <10% death over 20 years from low-risk, low-grade tumors
  - Goal = Symptom Relief (low risk) vs Cure (high risk)
- Stage IV (Stage D)
  - Not curable
  - Goal = symptom relief, extend life
Prostate Cancer Treatment, Stage I - III

- **Surgery**
  - Radical Prostatectomy
    - 85% cure rate
    - Impotence 37%, Incontinence 17%, Mortality 0.3%
  - **Radiation Therapy**
    - Brachytherapy
      - Insertion of radioactive beads into prostate
      - Fast, outpatient procedure
    - External Beam Radiation Therapy (EBRT)
      - 7 – 8 weeks of treatment
      - 50% incontinence, 30% ED
      - Combined with hormones in high risk patients

Prostate Cancer Treatment, Stage IV

- **Goal:** Shut off testosterone
  - Bilateral orchiectomy
  - vs
  - **Medical castration**
    - LHRH Agonists
    - Non-steroidal Antiandrogens

LHRH Agonists

- Leuprolide Depot (Lupron®)
  - 7.5mg IM QMonth
  - 22.5mg IM Q3Months
  - 30mg IM Q4Months
- Leuprolide Suspension (Eligard®)
  - 7.5mg SQ QMonth
  - 22.5mg SQ Q3Months
  - 30mg SQ Q4Months
  - 45mg SQ Q6Months
- Goserelin implant (Zoladex®)
  - 3.6mg SQ qmonth
  - 10.8mg SQ q3months
  - Given in upper abdominal wall
LHRH Agonists

- Reversible method of androgen ablation as effective as orchiectomy
- Agents:
  - Leuprolide
  - Goserelin
- Response rate of up to 80%
- AE: disease flare at first week of therapy (bone pain or LUTS) that usually resolves after 2 weeks

LHRH Flare

- Can be fatal in patients with extensive mets
- Antiandrogens used for prevention
- NCCN guidelines recommend use in those patients who are at risk of metastatic symptomatic flare
- Antiandrogens should be used for at least two weeks surrounding LHRH Dose

Non-steroidal Antiandrogens

- Monotherapy shown to be less effective than LH-RH alone
- Response rate 50-87% reported
- Objective responses seen as decreased bone pain, decreased prostate size, decreased PSA and/or improved functional status
- Agents:
  - Bicalutamide
  - Flutamide
  - Nilutamide
Complete Androgen Blockade

- Combination of Antiandrogen & LHRH agonist
  - Good for creating a state of maximal androgen deprivation to avoid other mechanisms of hormonal stimulation of the prostate
  - Response rate >90% in untreated patients (<35% in previous tx)
  - Improved survival, but may have more AE

Efficacy of ADT

- Early vs Deferred Therapy
  - 17% decrease in relative risk for prostate cancer specific mortality
  - No decrease in overall mortality
- Intermittent ADT
  - Shown to be better tolerated
  - Insufficient data- need more clinical trials


Benefits of ADT

<table>
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<tr>
<th>Decrease In:</th>
<th>Control</th>
<th>ADT</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Cord Compression</td>
<td>4.9</td>
<td>1.9</td>
<td>&lt;0.025</td>
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<tr>
<td>Ureteral Obstruction</td>
<td>11.8</td>
<td>7.0</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Metastases</td>
<td>11.8</td>
<td>7.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pathologic Fracture</td>
<td>7.9</td>
<td>2.3</td>
<td>NS</td>
</tr>
</tbody>
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Question

- What are the potential adverse effects of complete androgen blockade?
  - A) Fatigue
  - B) Bone Loss
  - C) Breast Changes
  - D) Hot Flashes
  - E) All of the above

Other ADT ADRs


Castrate-Resistant Prostate Cancer (CRPC)

- Criteria:
  - Testosterone <30ng/dL
  - Prostate cancer growing, spreading despite this

- Treatment Options:
  - Prior to 2004
    - Docetaxel + Prednisone
    - Androgen withdrawal - no survival benefit
    - Ketoconazole + Hydrocortisone - no survival benefit
  - Today
    - Docetaxel + Prednisone
    - Abiraterone + Prednisone
    - Sipuleucel-T

10
**Docetaxel**
- Classical chemotherapeutic agent
- 75mg/m² given every 21 days
- Significant ADRs
  - Full-body hair loss
  - Neuropathy
  - Hypersensitivity Reaction
    - Manifests acutely during treatment
    - 2/2 Diluent

**Abiraterone (Zytiga)**
- CYP 17 Inhibitor (17 alpha-hydroxylase)
- Blocks formation of testosterone within tumor cells
- Oral agent
  - 4 tabs (1000mg) q day
- Used in combination with prednisone 5mg po bid
- 4 month survival benefit vs placebo

**Abiraterone ADRs**
Sipuleucel-T

- Autologous cells fused with PA2024 gene
  - (PAP linked to GMCSF)
- 4 month increase in median survival (vs active controls)
- ADR: COSTI, Rigors, tremors, fever, cold sensation

Post-Docetaxel Treatment

- Enzalutamide (Xtandi)
  - Small molecule inhibiting overexpression of androgen receptor
  - Blocks translocation of the receptor to cell surface
  - Binds DNA
  - Oral agent
  - 4 tabs q day (160mg)
  - 5 month survival benefit (vs placebo)

Bone Health in Prostate Cancer

- Preventative
  - Androgen Deprivation Therapy
    - Annual BMD loss of ~5%/year
    - Greatest loss in the first year
  - Other risk factors: white, BMI <25, length of ADT
- Treatment:
  - Calcium + Vitamin D
  - Exercise
  - Smoking Cessation
  - IV or PO bisphosphonates
Bone Health in Prostate Cancer

- Palliative
  - Metastatic/Lytic bone disease common in CRPC
- Treatment
  - Zoledronic Acid 4mg q3 – 4 weeks
  - Denosumab 120mg SQ q4 weeks
  - Pamidronate and PO bisphosphonates NOT shown to have benefit in this population
    - Except clodronate, not FDA approved

Investigational Therapies

- Prostate Cancer Vaccines
- Cabozantinib

Conclusions

- PSA Screening no longer recommended for all
- Hormonal Therapies:
  - LHRH Agonists
  - Antiandrogens
- Medications for CRPC:
  - Abiraterone
  - Enzalutamide
  - Docetaxel
- Coming Soon:
  - Vaccines??!!