Prostate Cancer Treatment in men with germline DNA repair deficiency

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## Disclosures

<table>
<thead>
<tr>
<th>Company</th>
<th>Relationship</th>
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<tbody>
<tr>
<td>Tokai, ESSA, Janssen, Medivation, Astellas, AstraZeneca</td>
<td>Research funding</td>
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</table>
Prostate Cancer

- Prostate cancer – general facts and approach
- Outcomes for carrier men diagnosed with prostate cancer
- Homologous recombination deficiency in advanced prostate cancer
  - Frequency of inherited germline variants
  - Frequency in advanced prostate cancer
  - Implications for therapy
- Clinical studies for screening and therapy
Prostate Cancer

- The most common cancer in men – 1 in 6 men, 28,000-30,000 deaths per year. The lethality rate is significantly lower than many other malignancies (10%)
- Controversies about prostate cancer
  - Who needs screening?
    - PSA screening leads to many biopsies of men without cancer
  - Who needs treatment?
    - PSA screening leads to diagnosis of men who do not need treatment and overtreatment causes significant morbidity
- This has led to a perception that prostate cancer is not lethal, and that men die with but not because of prostate cancer. PSA screening is grade C by USPSTF
Prostate Cancer – Treatment of localized disease

- Active surveillance
- Androgen-deprivation therapy alone
- Cryotherapy
- High-intensity focused ultrasound
- Radiation
  - External beam radiotherapy (EBRT)
  - Intensity-modulated RT
  - 3D-conformal RT
  - Hypofractionated RT
  - Brachytherapy (± EBRT)
  - Proton beam
- Prostatectomy
  - Radical retropubic
  - Laparoscopic/da Vinci®-assisted
  - Perineal
- Combination
  - Androgen deprivation + RT

A bewildering array of options
No specific therapy is definitely better than any other
Insights into lethal prostate cancer

• What is significant prostate cancer?
  – Cancer that carries risk of relapse despite local therapy and development of metastatic disease
  – High risk cancer
    • Metastatic
    • Localized – Gleason 8-10, PSA over 20, T3 (getting out of the prostate) – men with these cancers have a greater than 50% chance that the cancer will not be cured with surgery or radiation
Prostate Cancer - Time Trends in Risk Stratification

Cooperberg et al. J Urol 2007; 178:S14
Prostate Cancer in BRCA2 carrier men

- Men who are BRCA2 carriers carry 2.5-4 fold higher risk of prostate cancer
  
  van Asperen, J Med Genet 2005;42:711
  JNCI 1999; 91: 1310

- Men who are BRCA2 carriers who develop prostate cancer are 8 fold more likely to die of the disease
  
  Castro, J Clin Onc 2013; 31: 1748
  Akbari, Br Journal of Cancer 2014; 111, 1238

BRCA2 carrier men are more likely to be diagnosed with prostate cancer and that disease is more biologically aggressive
Resource

Integrative Clinical Genomics of Advanced Prostate Cancer

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Himisha Beltran,7,8,13,38 Wassim Abida,14,20 Robert K. Bradley,9 Jake Vinson,16 Xuhong Cao,1,42 Pankaj Vats,1
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Elisabeth I. Heath,33,34 Howard I. Scher,13,29 Kenneth J. Pienta,35 Philip Kantoff,3,44 Johann S. de Bono,11,12,44
Mark A. Rubin,5,6,7,3,44 Peter S. Nelson,10,35,37,36,44 Levi A. Garraway,3,44 Charles L. Sawyers,14,41,44,*
and Arul M. Chinnaiyan1,2,17,18,42,44,*
Precision Oncology: Prostate Cancer
Men with metastatic cancer are more likely to be carriers

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

- 12% of men with metastatic prostate cancer inherited their risk through BRCA/ATM/other variants

Pritchard, NEJM July 2016
Figure 2. Distribution of Presumed Pathogenic Germline Mutations.
Shown are mutations involving 16 DNA-repair genes. Four genes did not have any pathogenic mutations identified and are not included in the distribution.

Pritchard, NEJM July 2016
Why does knowing carrier status make a difference?

- Implications for family
- Prostate cancer with BRCA2 inactivation is much more sensitive to drugs that we currently don’t use to treat prostate cancer with potential for “exceptional response”
- Response rates to platinum agents and PARP inhibitors is 80-90%
Olaparib in metastatic prostate cancer with DNA repair deficiency

Prostate cancer
Olaparib in metastatic CRPC with DNA repair deficiency

DNA repair defect neg. vs. positive
rPFS 3 vs. 10 months with olaparib
OS 7.5 vs. 14 months with olaparib

DNA repair deficient cancer is sensitive to platinum

Prior therapy (outside)
- Docetaxel
- Cabazitaxel
- Thalidomide
- abiraterone
- enzalutamide

Gene Mutation(s)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation(s)</th>
<th>Status</th>
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<tbody>
<tr>
<td>PALB2</td>
<td>c.1032 1033 dup FS</td>
<td>Germline</td>
</tr>
<tr>
<td>PALB2</td>
<td>COPY LOSS</td>
<td></td>
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</table>
DNA repair deficient cancer is sensitive to platinum

BRCA2

Liver
Bx

30 months

PSA (ng/mL)

Prostate Ca. Dx 70

Esophageal Ca. Dx 58


docetaxel+ carboplatin
abiraterone
docetaxel+ carboplatin
maintenance
carboplatin
cisplatin etoposide
weekly paclitaxel

DNA repair deficient cancer is sensitive to platinum

BRCA2

Prostate Ca. Dx 66
Colon Ca. Dx 70

DNA repair deficient cancer is sensitive to platinum
Implications

Men with advanced prostate cancer and DNA repair deficiency (BRCA2 or other) can have exceptional responses to;
• Platinum based chemotherapy – off label or on study
• PARP inhibitors – off label or on study
Germline testing in advanced prostate cancer

Germline testing is recommended for all men with metastatic prostate cancer (NCCN Genetic/Familial High risk Assessment and Prostate cancer)
Screening for prostate cancer in carrier men

Men who are germline BRCA2 carriers have increased risk of prostate cancer and those with cancer are at significantly increased risk of that cancer being life threatening (Castro et al, Na et al)

How has this influenced screening guidelines?
• PSA is screening is recommended for BRCA2 carrier men by one national guidelines panel and not recommended by another
• However the PSA screening frequency and decisions about biopsy are no different than for “high risk” men

IMPACT shows that biopsy at PSA of 3 demonstrates intermediate/high risk disease in 50% of those men biopsied
Prostate Cancer Risk in Genetic Syndromes

NCCN Guidelines for “Genetic/Familial High-Risk Assessment: Breast and Ovarian” recommend men with BRCA2 mutations start PC screening at age 45 and those with BRCA1 consider the same.

The NCCN Prostate Cancer Early Detection panel “…believes that data supporting a change in the PSA screening and biopsy recommendations for men with germline BRCA1/2 mutations relative to men without mutations are insufficient. Referral to a cancer-genetics professional is recommended.”
PSA screening in carrier men

IMPACT shows that biopsy at PSA of 3 demonstrates intermediate/high risk disease in 50% of those men biopsied

IS THIS ADEQUATE?

Consider age specific PSA thresholds for biopsy or abnormality on imaging

<table>
<thead>
<tr>
<th>Suggested PSA (ng/mL) Thresholds for Action</th>
<th>Age (years)</th>
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<tr>
<td>Consider biopsy and/or MRI</td>
<td>≤44</td>
</tr>
<tr>
<td>0.45 - 1.0</td>
<td></td>
</tr>
<tr>
<td>0.6 - 1.5</td>
<td></td>
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<tr>
<td>0.8 - 2.0</td>
<td></td>
</tr>
<tr>
<td>1.25 - 2.5</td>
<td></td>
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<tr>
<td>Suggest biopsy with/without MRI</td>
<td>&gt;1.0</td>
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How is this relevant for carrier men?

MOST PRIMARY CARE PROVIDERS AND UROLOGISTS DO NOT KNOW THAT CARRIER STATUS INCREASES RISK OF PROSTATE CANCER

CARRIER MEN HAVE TO KNOW THEIR STATUS AND ADVOCATE FOR SCREENING GIVEN THE CURRENT ATTITUDE TOWARDS SCREENING FOR PROSTATE CANCER AMONGST PRIMARY CARE PROVIDERS

EARLY DETECTION AND TREATMENT ARE CRITICAL (we think)

CARRIER MEN WITH METASTATIC PROSTATE CANCER SHOULD BE CONSIDERED FOR TARGETED THERAPY
Prostate Cancer

- DNA repair deficiency is present in 25-30% of advanced prostate cancers with BRCA2 being the most common mutation.
- Half of the tumors with DNA repair deficiency have germline mutations as part of the deficiency.
- The enrichment in men with metastatic prostate cancer is consistent with those cancers being more biologically aggressive.
- Prostate cancers containing DNA repair deficiency can be exquisitely sensitive to platinum chemotherapy and PARP inhibitors.
- Screening for prostate cancer in carrier men is in its early stages but consideration should be given to biopsy at the first sign of abnormality on exam or imaging or if PSA is out of range for age.
Prostate Cancer
Ongoing research

Screening of men with metastatic prostate cancer for germline variants

- Veterans Affairs (PCF/VA Precision Oncology Consortium)
- “GENTLEMEN” Univ WA/Fred Hutch based free screening of men with metastatic prostate cancer

Early treatment of men with localized prostate cancer

- Neoadjuvant PARP inhibitor prior to prostatectomy

Treatment of men with advanced prostate cancer with

- Platinum chemotherapy (Univ of Washington/Fred Hutchinson/VA Puget Sound and West LA VAMC)
- Induction chemotherapy with PARP maintenance (“Plati-PARP” – Univ of Washington/Fred Hutchinson)
- Randomized studies of PARP inhibitor in advanced prostate cancer - GALAHAD, PROFOUND, TRITON
Thank you!