Clinical Trials in Prostate Cancer: To do or not To Do?

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Disclosures

• None.
Racial Differences in Cancer:

A Comparison of Black and White Adults in the United States

Robin Hertz, Ph.D
Edith Mitchell, MD, FACP
Trends in Death Rates Among Males for Selected Cancers: 1930-2009

Causes of Health Disparities

- Poverty / low economic status
- Social injustice
- Culture

Possible influence on gene environment interaction

Prevention, Early detection, Diagnosis/ incidence, Treatment, Post treatment/ quality of life, Survival and mortality

Freeman H. Adapted from Cancer Epidemiology Biomarkers & Prevention, April 2003.
Prostate Cancer: 2015

• Leading solid tumor and second cause of death from cancer in American males

• 233,000 new cases expected (was 238,590)

• 29,480 deaths expected (was 29,720)

• Lifetime risk of prostate cancer in U.S.:
  • Diagnosis: ~17%
  • Death: ~3%
  • 68: Median age at diagnosis
  • 80: Median age at death
Risk of Prostate Cancer by Age and Race

![Bar chart showing percent with prostate cancer by age range and race.]

**Probability of Developing PC**

- Birth to 39: 1 in 9,442
- 40 to 59: 1 in 41
- 60 to 69: 1 in 16
- 70 and older: 1 in 8
- Birth to death: 1 in 7

Jemal et al., CA Cancer J Clin. 2010 Sep-Oct;60(5):277-300
Male Population Trend in the US Challenges Prostate Cancer

~80% of new prostate cancer diagnoses are in men >age 65yrs

Http://www.census.gov/statab/freq/99s0014.text
Prostate Cancer: Risk factors - Family History

- PC with highest proportion of familial cancers among common malignancies
  - Prostate Cancer 20.15%
  - Breast Cancer 13.58%
  - Colorectal 12.80%
- Increased risk among men with a first degree relative with PC (odds ratio 2.5)
- 2 or 3 first degree relatives increases the risk 5 to 11 fold
- Increased risk with relatives with breast cancer

Criteria for Hereditary Prostate Cancer (HPC) Diagnosis

1. Family including prostate cancer in >3 first-degree relatives
2. Family with prostate cancer in three successive generations of the maternal or paternal lineages
3. Family with two first-degree relatives affected at age $\leq 55$ years

To be diagnosed with HPC the family should meet at least one of the three criteria.
“HPC is likely to be caused by multiple genes, interacting among themselves and with the environmental factors and this could explain the difficulty in identifying susceptibility genes in HPC.”

Fusion between the androgen-regulated transmembrane protease serine 2 gene (TMPRSS2) and E twenty-six (ETS) transcription factors

• Present in ~ 50% localized PC.
Prostate Carcinogenesis

Pathway of Prostate Cancer Progression

Normal epithelium → Prostatic intraepithelial neoplasia (PIN) → Invasive carcinoma → Metastasis

- Loss 8p21 NNX3.1
- Loss 10q23, 13q PTEN RB
- Loss 17p p53
- Loss p27 Expression
- SKP2, MDM2 Over-expression
- Loss PML Expression
- Loss TSC1/2
- Loss TTD
- Loss p18 Ink4a

Androgen-responsive cell

SHBG → Testosterone → 5α-reductase → DHT → Ligand binding → HSP AR

Dimerization and phosphorylation

DNA binding → AR → ARA70 → GTA → Target gene activation

Biological responses

- PSA
- Growth
- Survival

Sidney Kimmel Cancer Center
at Thomas Jefferson University
NCI-designated
Table 2  Summary of Enrollment of African American Men Onto Phase III Prostate Cancer Trials

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Total of Trial Participants, n</th>
<th>African American Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone (Before Chemotherapy)(^{44})</td>
<td>1088</td>
<td>30 (2.8)</td>
</tr>
<tr>
<td>Abiraterone (After Chemotherapy)(^{45})</td>
<td>1195</td>
<td>43 (3.6)</td>
</tr>
<tr>
<td>Aflibercept(^{46})</td>
<td>1224</td>
<td>32 (2.6)</td>
</tr>
<tr>
<td>Atrasentan(^{47})</td>
<td>994</td>
<td>137 (13.8)</td>
</tr>
<tr>
<td>Bevacizumab(^{48})</td>
<td>1050</td>
<td>Not reported (88% of patients were white)</td>
</tr>
<tr>
<td>Cabazitaxel(^{49})</td>
<td>755</td>
<td>40 (5.3)</td>
</tr>
<tr>
<td>Docetaxel(^{50})</td>
<td>674</td>
<td>90 (13.4)</td>
</tr>
<tr>
<td>Docetaxel(^{51})</td>
<td>1006</td>
<td>Not reported</td>
</tr>
<tr>
<td>Enzalutamide (Before Chemotherapy)(^{52})</td>
<td>1717</td>
<td>34 (2.0)</td>
</tr>
<tr>
<td>Enzalutamide (After Chemotherapy)(^{53})</td>
<td>1199</td>
<td>47 (3.9)</td>
</tr>
<tr>
<td>Ipilimumab(^{54})</td>
<td>799</td>
<td>21 (2.6)</td>
</tr>
<tr>
<td>Lenalidomide(^{55})</td>
<td>1059</td>
<td>46 (4.3)</td>
</tr>
<tr>
<td>Ortezonel (Before Chemotherapy)(^{56})</td>
<td>1560</td>
<td>Not reported (regions included)</td>
</tr>
<tr>
<td>Ortezonel (After Chemotherapy)(^{57})</td>
<td>1099</td>
<td>27 (2.5)</td>
</tr>
<tr>
<td>Radium-223 chloride(^{58})</td>
<td>809(^{a})</td>
<td>16 (2.0)</td>
</tr>
<tr>
<td>Satraplatin(^{59})</td>
<td>950</td>
<td>Not reported (89% of patients were white)</td>
</tr>
<tr>
<td>Sipuleucel-T(^{60})</td>
<td>737</td>
<td>43 (5.8)</td>
</tr>
</tbody>
</table>

\(^{a}\) Interim study population with available data on African American study participants, final study cohort was 901 treated patients (921 randomized patients), although the number of African American patients was not stated.\(^{58}\)
Strategies to engage African American participants

- Use one-to-one, culturally sensitive contact (including telephone conversations)
- Make contact through existing community groups, e.g., churches or by recruiters identified through local community leaders and groups
- Additional considerations include logistical and financial issues such as transportation, time, and child care. These potentially require flexibility in clinical trial visit locations; move appointments to areas more convenient for participants: community centers, churches, etc.

Solutions targeting physicians and investigators

- Include community-based physicians who treat a racially diverse patient population and are able to encourage trust in the system and provide insights into the local African American population
- Improve communication skills of physicians to increase informed patient consent
- Involve African American physicians
- Increase awareness of cultural differences and sensitivities

Solutions targeting the community and healthcare system

- Build trust in the community with ongoing contact
- Increase funding for African American-specific recruitment measures and for sites located in high African American catchment areas
- Minimize inclusion/exclusion criteria barriers to entry
- Provide financial support for those of low socioeconomic status, or who require health insurers to cover routine costs associated with participation in clinical trials
Obstacles to Clinical Trials Participation for African Americans

- Socioeconomic status
- Lack of education and awareness
- Eligibility barriers
- Willingness to participate
- Cultural barriers
- Types of institutions where patients are treated
Obstacles

- Socioeconomic status
  - Affects awareness and access to clinical trials
  - Poverty results in more complicated health issues
  - Lower SES individuals have a greater inability to participate in clinical trials

- Lack of education and awareness
  - Clinical trials participants tend to have higher levels of education than the general population
  - African Americans are less likely to learn about trials from doctors or the than whites, but more likely to learn about them from other patients
Obstacles, Continued

• Eligibility barriers
  - Comorbidities can restrict eligibility
  - Associated with older age, male sex and African American race
• Willingness to participate
  - Lingering distrust of doctors (Tuskegee Experiment)
  - Fear of enrollment in clinical trials without knowledge or permission
  - Racism
• Lack of perceived benefit
Obstacles, Continued

- Cultural barriers
  - Physicians are not recommending trials to African American patients
  - Patients’ religion or God decides their fate

- Institutions where patients are treated
  - Clinical trials are conducted at academic medical hospitals/institutions
  - Majority of African Americans received treatment at community practices and hospitals
Solutions to Engage African Americans in Prostate Cancer Clinical Trials

- **Personal contact with African American Men**
  - Direct mail, phone calls with physicians, recruitment via survivors or clinical trials leaders, engaging women in the process

- **Engage community**
  - Church-based programs with a physician or health educator and encourage screening
  - Community health fairs
  - Community advisory board

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Additional Solutions

• Change recruitment locations
  • Use community centers or other more accessible locations to remove transportation or childcare barriers to participation
• Use mass media to create awareness
  • Reduce education and awareness gaps in clinical trials knowledge
• Employ patient navigators
  • Use them to increase the number of African Americans receiving screening for prostate cancer and helping survivors transition to clinical trials
Additional Solutions, Continued

• Physicians and Investigators
  • Work more closely with community-based physicians to engage their patients in trials
  • Pharmaceutical companies should expand to sites with significant African American populations
  • Universities should reward researchers for working with small minority populations
  • Employ African American doctors and researchers as clinical trials leaders

• Financial
  • Provide free health care and other financial incentives
President Obama
State of the Union Address
January 12, 2016

- The goal of the Cancer Moonshot is to make a decade’s worth of progress in five years in the prevention, diagnosis, and treatment of cancer

- “I’m putting Joe in charge of Mission Control”

President Obama
Goals of the Cancer Moonshot

- Accelerate progress in cancer, including prevention & screening
  - From cutting edge basic research to wider uptake of standard of care
- Encourage greater cooperation and collaboration
  - Within and between academia, government, and private sector
- Enhance data sharing

(Presidential Memo 2016)
The Vice President’s Cancer Initiative

Vice President’s Office

Cancer Moonshot Federal Task Force

NCI/NIH

NCAB

“Blue Ribbon Panel”

Working Groups
Next Steps for Blue Ribbon Panel Recommendations

- NCI now needs to consider how to implement the Blue Ribbon Panel recommendations
- Extent and rate of implementation will depend on Congressional appropriations
- NCI will look to the Blue Ribbon Panel and its advisory boards for implementation advice
- Continued investments in investigator-initiated research and in research initiatives beyond the scope of the Blue Ribbon Panel remain a high priority for NCI
Where we need to go

- Improve prevention, screening, and treatment to continue to bring down cancer mortality rates, including those cancers for which there has been limited progress
- Redouble our efforts to understand and overcome cancer health disparities
- Take full advantage of the opportunity to accelerate progress by working together on a wide range of projects, from the most basic to the most applied
Thank you for your attention.

Questions?

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