Prostate Cancer Treatment and Cardiovascular Effects

Ana Barac, MD, PhD, FACC
Associate Professor of Medicine and Oncology, Georgetown University
Director, Cardio-Oncology Program, MedStar Heart and Vascular Institute

Charleston Cardio-Oncology Symposium, November 2019
Disclosures

• Associate Editor: JACC Cardio-Oncology
• Co-Director: ACC Live Course on Advancing CV Care of Oncology Patient
• Research support, investigator-initiated study: Genentech, Inc
• Honoraria: Bristol Myers Squibb
• DSMB: CTI Biopharma
Objectives

- Epidemiology of Prostate cancer
- Oncology treatment approaches
- CV and Cardiometabolic effects: morbidity and mortality
- Prevention and CV risk treatment
# Prostate Cancer Epidemiology

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2019</th>
<th>Estimated Deaths 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast Cancer (Female)</td>
<td>268,600</td>
<td>41,760</td>
</tr>
<tr>
<td>2. Lung and Bronchus Cancer</td>
<td>228,150</td>
<td>142,670</td>
</tr>
<tr>
<td>3. Prostate Cancer</td>
<td><strong>174,650</strong></td>
<td><strong>31,620</strong></td>
</tr>
<tr>
<td>4. Colorectal Cancer</td>
<td>145,600</td>
<td>51,020</td>
</tr>
<tr>
<td>5. Melanoma of the Skin</td>
<td>96,480</td>
<td>7,230</td>
</tr>
<tr>
<td>6. Bladder Cancer</td>
<td>80,470</td>
<td>17,670</td>
</tr>
<tr>
<td>7. Non-Hodgkin Lymphoma</td>
<td>74,200</td>
<td>19,970</td>
</tr>
<tr>
<td>8. Kidney and Renal Pelvis Cancer</td>
<td>73,820</td>
<td>14,770</td>
</tr>
<tr>
<td>9. Uterine Cancer</td>
<td>61,880</td>
<td>12,160</td>
</tr>
<tr>
<td>10. Leukemia</td>
<td>61,780</td>
<td>22,840</td>
</tr>
</tbody>
</table>

Prostate cancer represents 9.9% of all new cancer cases in the U.S.
Prostate Cancer Epidemiology

- >3 million men living with prostate cancer in the US in 2016
- > 75% treated with curative intent
- Mean age 66
History of Antiandrogen Therapy (ADT)

Prostate cancer is androgen-driven disease

1966 Nobel prize in medicine to Dr. Charles Huggins "for his discoveries concerning hormonal treatment of prostatic cancer"
# Classes of Antiandrogen Drugs

<table>
<thead>
<tr>
<th>GnRH Agonists</th>
<th>GnRH Antagonists</th>
<th>Anti-Androgens</th>
<th>Adrenal Androgen Inhibitors</th>
<th>Estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuprolide</td>
<td>Degarelix</td>
<td>Flutamide</td>
<td>Ketoconazole</td>
<td>Estradiol</td>
</tr>
<tr>
<td>Goserelin</td>
<td>Bicalutamide</td>
<td></td>
<td>Corticosteroids</td>
<td>Premarin</td>
</tr>
<tr>
<td>Triptorelin</td>
<td></td>
<td>Nilutamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histrelin</td>
<td></td>
<td>Enzalutamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>( Abiraterone acetate )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Circulation. 2016 Feb 2; 133(5): 537*
ADT in Prostate Cancer Treatment

- Standard therapy for all patients with metastatic prostate Ca
- Adjuvant therapy with curative intent radiation for high risk non-metastatic disease
- Abirateron in combination with GnRH agonist
Adverse Side Effects of ADT

- Hot flushes
- Fatigue
- Loss of libido
- Gynecomastia
- Testicular atrophy

- Metabolic Syndrome
- Weight gain
- Increased fat mass
- Increased insulin resistance
- Hypertriglyceridemia
- Increased risk of Fractures
ADT Increases CV Mortality?

Tsai et al.
JNCI 2007
No Effect of ADT on CV Mortality in Randomized Setting

Association of Androgen Deprivation Therapy With Cardiovascular Death in Patients With Prostate Cancer
A Meta-analysis of Randomized Trials

Paul L. Nguyen, MD
Youjin Je, MS
Fabio A. B. Schutz, MD
Karen E. Hoffman, MD, MPH, MHSc
Jim C. Hu, MD, MPH
Arti Parekh, BA
Joshua A. Beckman, MD, MSc
Toni K. Choueiri, MD

Context: Whether androgen deprivation therapy (ADT) causes excess cardiovascular deaths in men with prostate cancer is highly controversial and was the subject of a joint statement by multiple medical societies and a US Food and Drug Administration safety warning.

Objective: To perform a systematic review and meta-analysis of randomized trials to determine whether ADT is associated with cardiovascular mortality, prostate cancer-specific mortality (PCSM), and all-cause mortality in men with unfavorable-risk, non-metastatic prostate cancer.

Data Sources: A search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials databases for relevant randomized controlled trials in English be-
No Effect of ADT on CV Mortality Clinical Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Relative Risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 22863 (Bolla)</td>
<td>1.30 (0.71-2.38)</td>
<td>.39</td>
</tr>
<tr>
<td>DFCI 95-096 (D’Amico)</td>
<td>1.02 (0.50-2.09)</td>
<td>.96</td>
</tr>
<tr>
<td>TROG 96.01 (Denham)</td>
<td>0.79 (0.48-1.31)</td>
<td>.37</td>
</tr>
<tr>
<td>RTOG 85-31 (Efstatliou)</td>
<td>0.79 (0.56-1.11)</td>
<td>.17</td>
</tr>
<tr>
<td>ECOG EST-3886 (Messing)</td>
<td>3.26 (0.35-30.2)</td>
<td>.30</td>
</tr>
<tr>
<td>RTOG 86-10 (Roach)</td>
<td>1.24 (0.76-2.01)</td>
<td>.40</td>
</tr>
<tr>
<td>EORTC 30846 (Schroder)</td>
<td>0.97 (0.42-2.24)</td>
<td>.94</td>
</tr>
<tr>
<td>EORTC 30891 (Studer)</td>
<td>0.91 (0.70-1.18)</td>
<td>.47</td>
</tr>
<tr>
<td>Overall (fixed-effects model)</td>
<td>0.93 (0.79-1.10)</td>
<td>.41</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Q=5.12, p=.645, I-squared=0.0%
Why is There a Difference with Observational Data?

Quantifying Observational Evidence for Risk of Fatal and Nonfatal Cardiovascular Disease Following Androgen Deprivation Therapy for Prostate Cancer: A Meta-analysis

Cecilia Bosco a,*, Zsolt Bosnyak b, Anders Malmberg b, Jan Adolfsson c, Nancy L. Keating d, Mieke Van Hemelrijck a

a King’s College London, Division of Cancer Studies, Cancer Epidemiology Group, London, UK; b Ferring Pharmaceuticals, Clinical R&D, Copenhagen, Denmark; c Karolinska Institute, Stockholm, Sweden; d Harvard Medical School and Brigham and Women’s Hospital, Boston, MA, USA

Observational Data:
HR for ADT and CVD = 1.57 (1.26-1.94)
ADT no longer significantly improves OS, possibly due to harms of ADT in some men.

JAMA: Sept 22 2015
Select Cohorts of Susceptible Men?

B. None or minimal comorbidity (n = 157)³

- Radiation therapy and androgen deprivation therapy
- Radiation therapy alone

C. Moderate or severe comorbidity (n = 49)³

- Radiation therapy alone
- Radiation therapy and androgen deprivation therapy

Me 78 76 76 71 68 60 52 38 18 24 21 16 11 6 4 2 2 1

sed on You
Men at Risk: 2 or More Recent CV Events

Risk and Timing of Cardiovascular Disease After Androgen Deprivation Therapy in Men With Prostate Cancer

Sean O’Farrell, Hans Garino, Lars Holmberg, Jan Adolfszon, Per Stattin, and Micke Van Hembrijck

See accompanying editorial on page 1232

ABSTRACT

Purpose
Findings on the association between risk of cardiovascular disease (CVD) and the duration of androgen-deprivation therapy (ADT) in men with prostate cancer (PCa) are inconsistent.

Methods
By using data on filled drug prescriptions in Swedish national health care registers, we investigated

A

Hazard Ratio

0.00
0.50
1.00
1.50
2.00

0.6
6-12
12-18
18-36

No previous CVD event
1 previous CVD event
≥ 2 previous CVD events, ≥ 1 year since last
≥ 2 previous CVD events, < 1 year since last

Time Since GnRH Start (months)
Decision-Making in the Clinic

Comorbidity Level

- Low Risk
- Intermediate Risk
- High Risk
- Locally Advanced
- Node Positive

Risk of Prostate Cancer Death

- CHF/MI
- Multiple CM Mod/Severe CM
- Single CM Mild CM
- No CM

Avoid ADT

- ????????????

Give ADT

COURTESY OF PAUL NGUYEN
Conclusions

• ADT is associated with a multitude of metabolic effects
• ADT did not increase CVD mortality in randomized clinical trials
• However, there is a signal of increased CV mortality/morbidity among patients with prior HF/MI or multiple CVRFs
• Recommended to optimize CV risk treatment, exercise and referral to CV specialist in patients with high CV risk
Advancing the Cardiovascular Care of the Oncology Patient

JANUARY 25 – 27, 2019
The Ritz Carlton
Washington, DC

COURSE DIRECTORS
Ana Barac, MD, PhD, FACC
Bonnie Ky, MD, MSCE, FACC

For more information and to register visit ACC.org/CVOncology

THANK YOU!

ACC.org/CVOncology
Feb 14-16, 2020
The Ritz Carlton, Washington DC

JACC CardioOncology
Online, Open Access
Launching September 2019

Bonnie Ky, MD, FACC
Editor-in-Chief

JACC.org/CardioOncology
Submissions: JACCSUBMIT-CardioOncology.org