Bipolar Androgen Therapy (BAT) in men with prostate cancer

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Presentation Overview

- Androgen and Androgen Signaling 101
- Rationale For Bipolar Androgen Therapy (BAT)
- Results from the RESTORE study testing BAT in Castration Resistant Prostate Cancer
- The multi-center TRANSFORMER Trial
- Future Directions
- Results of BATMAN trial testing BAT as part of Intermittent Hormone Therapy strategy
Testosterone Replacement

TIME
Manopause?!
Aging, insecurity and the $2 billion testosterone industry

CLICK
To Learn More About
HORMONE REPLACEMENT THERAPY

AXIRON
the only underarm testosterone treatment
Anabolic Steroids

Trenbolone Acetate
(Fina-Finaplix H pellets)
High Dose Testosterone as Treatment for Prostate Cancer
What Are Androgens?

• **Steroid hormone which can bind to Androgen Receptor**
  – Testosterone, Dihydrotestosterone (DHT), DHEA, Androstenedione...

• **Sexual Differentiation**
  – Needed to make a Male (Female is Default)

• **Primary Sex Characteristics:**
  – Spermatogenesis
  – Accessory Sex Tissue Maintenance
    • Penis, Prostate...

• **Secondary Sex Characteristics:**
  – Bone density
  – Muscle mass
  – Libido
  – Hair growth
  – Hematopoiesis
What is a Steroid Hormone?

- Testosterone (T)
- Dihydrotestosterone (DHT)
- Estrogen
- Progesterone
- Cortisol
- Aldosterone
How are Androgens Made?

- Hypothalamus
- LHRH
- Pituitary Gland
- Brain
- Muscle
- Testicle
- Adrenal Gland
- Prostate
- Cholesterol
- Testosterone
- Androgens
- 5α-Reductase
- DHT
- AR
- Growth and survival genes
Androgen Receptor Signaling 101

Androgen Receptor

Androgen
(Testosterone)

Active Androgen Receptor
How Do Androgens Effect the Prostate Cell?

NTD - Signaling Part
DBD - DNA Binding Part
LBD - Androgen Binding Part

Binds and activates genes:
- Cell Growth
- Cell Survival
- Make prostate stuff like PSA, Acid Phosphatase, etc.
The Devilish Prostate

- Physiologic Function unknown
- 80% of American men develop benign prostatic hyperplasia (BPH) by age 80
- ~40% of 40 year olds in autopsy studies have microscopic prostate cancer
- In US ~220,000 annual new cases of clinical prostate cancer
- ~27,000 US deaths annually from prostate cancer
Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Huggins and Hodges Cancer Research 1:293, 1941

STUDIES ON PROSTATIC CANCER

II. THE EFFECTS OF CASTRATION ON ADVANCED CARCINOMA OF THE PROSTATE GLAND

Huggins et al Archive of Surgery 43:209, 1941

Alkaline Phosphatase

Acid Phosphatase
All Current Hormone Therapy for Prostate Cancer Involves Disrupting Androgen Interacting with its receptor

**Get Rid of Testosterone**
- Orchietomy
- Medical Castration
- Zytiga

**Block Testosterone Binding**
- Antiandrogens
  - Casodex
  - Xtandi
# 75 years of Androgen Ablation

## 1940s-60s
- Orchietomy
- Adrenalectomy
- Diethylstilbesterol
- Hypophysectomy

## 1970s-90s
- **LHRH agonists**
  - Goserelin
  - Triptorelin
  - Buserelin
  - Histrelin
  - Nafarelin
  - Leuprolide...
- **LHRH antagonists**
  - Degarelix
  - Abarelix

- **Antiandrogens**
  - Cyproterone Acetate
  - Flutamide
  - Bicalutamide
  - Nilutamide

- **Adrenal Poisons**
  - Aminoglutethimide
  - Ketoconazole

## 21st Century
- Abiraterone
- Enzalutamide
- ARN-509
- Galeterone
- EPI-002...

## Combined Androgen Blockade
Castration Resistant Prostate Cancer (CRPC)

Add More Hormone Therapy
- Bicalutamide (Casodex)
- Abiraterone (Zytiga)
- Enzalutamide (Xtandi)
- Ketoconazole

Provenge Vaccine

Radium 223 (Xofigo)

Docetaxel Chemotherapy

Cabazitaxel

Clinical Trials
- Immunotherapy
- PARP Inhibitors
- PSMA Targeted...
Two opposite sorts of change of the hormonal status can induce regression of hormone dependent cancers:

(a) deprivation of essential hormones
(b) hormone interference with large amounts of critical compounds (i.e. hormones) ...
For an idea that does not first seem insane, there is no hope
-- Albert Einstein
Brine Shrimp *Artemia salina*

- Live in Great Salt Lake, Utah
- Can adapt to levels of salinity from 2.5% to 30% (seawater is 3.5%)
- DEATH by OSMOTIC SHOCK
  - Billions die from rapid change in salinity produced by runoff from melting snow from mountains
Castration is a form of “Shock Therapy” for Prostate Cancer

Castration removes major growth/survival factor

Rapid decline in serum testosterone level

- Rapid pain response
- Extensive cell death
- PSA response
- Clinical response

“Shock Phase” “Adaptation Phase” “Resistance Phase”
Prostate Cancer has an Androgen Receptor “Sweet Spot”
ADAPTATION:
Autoregulatory increase in Androgen Receptor activity leads to resistance to androgen ablative therapies

- AR Protein Overexpression
- AR Gene Amplification
- Ligand independent AR variants
- AR Mutation

“Sweet Spot”
Growth of Castration Resistant AR-Positive Prostate Cancer Models is Inhibited by Androgen

Dr. Shutsung Liao
Ben May U
Chicago

Why does BAT work against Prostate Cancer?

- Disrupt new DNA production preventing cell division
- Induce breaks in DNA
- Turn off important cell growth signals
- Stop cells from making the AR-V7 variant
- Prevent cells from becoming more aggressive in growth in response to potent hormone blockade
- Induce Cell Stress that can activate cell death
Pharmacology: Dose Matters

Androgen Dose-Response

Increasing Amount of Androgen

Hypotheses:

• Men with Castration Resistant Prostate Cancer could respond to rapid cycling between polar extremes of supraphysiologic and castrate testosterone levels [Bipolar Androgen Therapy (BAT)].

• Rapid cycling disrupts adaptive autoregulation of the Androgen Receptor.

• Adaptive decrease in the amount of Androgen Receptor may re-sensitize CRPC to androgen ablative therapies
“Bipolar Androgen Therapy”

Supraphysiologic T-Levels

Rapid Cycling Between Polar Extremes

Castrate T-Levels

High AR-Expressing Cells Vulnerable

Low AR-Expressing Cells Vulnerable

Serum Testosterone (ng/dL)

T-Injections (400 mg/month) Days

>1500

AR-Expressing Cells Vulnerable

High AR-Expressing Cells Vulnerable

Low AR-Expressing Cells Vulnerable

Days

T-Injections (400 mg/month)
A Pilot Study of Parenteral Testosterone and Oral Etoposide as Therapy for Men with Castration Resistant Prostate Cancer

Schweizer et al. Sci Transl Med. 2015;7(269):269ra2
Testosterone + Etoposide  
Testosterone Only (15 cycles)  

Back to Castrate T
Pilot Study Response Summary

- 8 of 14 men had some PSA decline
- 30% had >50% PSA decline
- Median Response was 248 Days
- 4 men received ≥ 12 cycles of T
- 50% Objective Response by RECIST
- 10/10 patients had some PSA decline on abiraterone or anti-androgens post-BAT

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Cycles (N)</th>
<th>Max PSA change relative to baseline %</th>
<th>RECIST Response</th>
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<tbody>
<tr>
<td>15</td>
<td>9</td>
<td>-39</td>
<td>PR</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>-46</td>
<td>SD</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>-48</td>
<td>PR</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>-60</td>
<td>SD</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>-78</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>-86</td>
<td>PR</td>
</tr>
<tr>
<td>13</td>
<td>36</td>
<td>-97</td>
<td>PR</td>
</tr>
<tr>
<td>16</td>
<td>6</td>
<td>-98</td>
<td>CR</td>
</tr>
</tbody>
</table>
**RE-sensitizing with Supraphysiologic Testosterone to Overcome REsistance**
(The RESTORE Study)

- **ADT**
- **PSA**
- **Progression**
- **Enzalutamide**
- **BAT**
- **PSA Decline**
- **PSA Progression**
- **Day 85 Response Evaluation**
- **Continue BAT to PSA Progression**
- **Off BAT Resume ADT**
- **PSA Response?**
- **Abiraterone**
- **Enzalutamide**

Continuous LHRH agonist therapy

NIH-RO1 funded
Trial Eligibility

• Maintained on continuous ADT
• Progression on either Abiraterone, Enzalutamide or both
  • Rising PSA
  • Measurable bone metastases, lymph node or soft tissue metastasis
• No worrisome lesions (spinal cord compression, urinary tract obstruction)
• No pain due to prostate cancer
PSA Response to BAT in Post-Enzalutamide Patients

Percent Change in PSA in Response to BAT

- Post-Enzalutamide
- Post-Abiraterone & Enzalutamide
Androgen Produces Double Strand DNA Breaks in Prostate Cancer Cells

Extreme Responder Case #1

- Biochemical and Radiographic Complete Response
- Inactivating Germline Mutations in DNA Repair-BRCA2 and ATM
**Summary of Response to BAT in Post-Enzalutamide Patients**

<table>
<thead>
<tr>
<th>Category</th>
<th>Rate</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50% PSA Response</td>
<td>30%</td>
<td>9/29</td>
</tr>
<tr>
<td>Any PSA decline</td>
<td>51%</td>
<td>15/29</td>
</tr>
<tr>
<td>Median Cycles of BAT/Patient</td>
<td>6 cycles</td>
<td>3-22+</td>
</tr>
<tr>
<td>Response Rate after 3 cycles BAT</td>
<td>14%</td>
<td>4/29</td>
</tr>
<tr>
<td>Complete Response</td>
<td>4%</td>
<td>1</td>
</tr>
<tr>
<td>Partial Response</td>
<td>10%</td>
<td>3</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>62%</td>
<td>18</td>
</tr>
<tr>
<td>Progression</td>
<td>21%</td>
<td>6</td>
</tr>
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</table>
## Side Effects from BAT

### Adverse Events (n=29 pt)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>n=</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Breast Tenderness</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Lower Extremity Edema</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Decreased Urine Flow</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pain</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Grade 1</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

All are Grade 1-2

### Serious Adverse Events

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>Grade</th>
<th>Relationship to BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary retention</td>
<td>2</td>
<td>Probable</td>
</tr>
<tr>
<td>Disseminated intravesicular coagulation</td>
<td>4</td>
<td>Possible</td>
</tr>
<tr>
<td>Hyponatremia, fluid retention, hydronephrosis &amp; ureteral obstruction</td>
<td>4</td>
<td>Possible</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3</td>
<td>Possible</td>
</tr>
<tr>
<td>Non-ST elevation myocardial infarction</td>
<td>3</td>
<td>Possible</td>
</tr>
</tbody>
</table>
Potential Positive Effects

- Subjective improvement in energy levels, functional activity
- Increased Hemoglobin
- Renewed Sexual Potency
- Increased Libido
Do we RESTORE Sensitivity to Hormone Therapy?

Continuous LHRH agonist therapy

ADT → PSA Progression → BAT

Day 85 Response Evaluation

- PSA Decline → PSA Progression
- PSA Response → PSA Decline

Continue BAT to PSA Progression

- Off BAT Resume ADT
- PSA Response?
  - Yes → PSA Progression
  - No → PSA Decline

Abiraterone → PSA Progression

Enzalutamide → PSA Progression
Changes in PSA Levels After Re-Treatment with Enzalutamide
Extreme Responder Case #2

- Undetectable PSA on Enzalutamide Rechallenge
- Stable Bone-Only Disease for 19 months
- Somatic Mutations of unclear significance in BRCA2 and FANCA
AR-Variant 7 is associated with poor response to hormonal therapies and decreased progression free survival
Preliminary AR-V7 Results from RESTORE Study

Baseline

- 22 samples
- 5/22 CTC Negative
- 11/17 (65%) ARV7 Negative
- 6/17 (35%) ARV7 Positive

3 cycles BAT

- All ARV7- Remain Negative
- All (6/6) ARV7+ become ARV7-
- 2/6 ARV7+ have >50% PSA Response

Post Re-challenge 3 cycles Abi-Enza

- 4/6 ARV7- revert back to ARV7+
- 2/6 awaiting third sample
The RESTORE Study
New Castration-Only Study Arm Opening March 2017

Continuous LHRH agonist therapy

Progression on ADT
No Other Hormone Therapies Allowed
30 patients

Day 85 Response Evaluation
PSA Decline

Continue BAT to PSA Progression

PSA Progression

Continue ADT

Off BAT

NIH-RO1 funded
A Randomized Phase II Study Comparing Bipolar Androgen Therapy vs. Enzalutamide in Asymptomatic Men with Castration Resistant Metastatic Prostate Cancer:

The TRANSFORMER Trial
(Testosterone Revival Abolishes Negative Symptoms, Fosters Objective Response and Modulates Enzalutamide Resistance)
- Designed to detect 50% improvement in Progression Free survival for BAT vs. Enzalutamide
- Number of Patients: 180 (1:1 randomization)
- 17 US sites
- 143 patients enrolled to date
Key Eligibility Criteria

• Good Performance Status
• Treated with continuous hormone therapy
• No prior enzalutamide or other investigational AR targeted therapy
• Documented metastatic disease on scans
• Must have had disease progression while on abiraterone alone or abiraterone in combination with other investigational agents based on:
  – PSA progression And/Or
  – Cancer progression on scans
Exclusion Factors

- PAIN due to metastatic prostate cancer requiring treatment intervention
- Prior treatment with docetaxel or cabazitaxel for metastatic CRPC
- Require urinary catheterization for voiding due to obstruction from prostatic enlargement
- Evidence of disease in sites or extent that, in the opinion of the investigator, would put the patient at risk from therapy with testosterone
<table>
<thead>
<tr>
<th>PI and Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Agarwal --- Huntsman Cancer Institute, Salt Lake City, UT</td>
</tr>
<tr>
<td>Dr. Smith --- University of Michigan, Ann Arbor, MI</td>
</tr>
<tr>
<td>Dr. Denmeade --- Johns Hopkins and Sibley, Washington DC.</td>
</tr>
<tr>
<td>Dr. Stein --- Cancer Institute of New Jersey, New Brunswick, NJ</td>
</tr>
<tr>
<td>Dr. Flaig --- University of Colorado, Denver, CO</td>
</tr>
<tr>
<td>Dr. Schweizer --- University of Washington, Seattle, WA</td>
</tr>
<tr>
<td>Dr. Assikis--- Piedmont Cancer Institute, Atlanta, GA</td>
</tr>
<tr>
<td>Dr. Twardowski --- City of Hope, Duarte, CA</td>
</tr>
<tr>
<td>Dr. Szmulewitz --- University of Chicago, Chicago, IL</td>
</tr>
<tr>
<td>Dr. Holzbeierlein--- Kansas University, Kansas City, KS</td>
</tr>
<tr>
<td>Dr. Sonpavde --- University Alabama, Birmingham, AL</td>
</tr>
<tr>
<td>Dr. Garcia --- Cleveland Clinic, Cleveland OH</td>
</tr>
<tr>
<td>Dr. Hussain --- University of Maryland, Baltimore, MD</td>
</tr>
<tr>
<td>Dr. Sartor--- Tulane University, New Orleans, LA</td>
</tr>
<tr>
<td>Dr. Hauke --- Nebraska Cancer Specialists, Omaha, ME</td>
</tr>
<tr>
<td>Dr. Mao--- Allegheny Hospital, Pittsburgh, PA</td>
</tr>
</tbody>
</table>
Study Enrollment

• 16 sites have enrolled patients
• 143 patients signed consents
  – 15 patients failed screening
  – 120 patients have received treatment
  – Two Safety Board meetings held with no concerns
  – Recommend continue the study
Patient #001

TRANSFORMER

Testosterone

PSA ng/mL

Pre-BAT

Post-BAT x 3
Many Questions to Answer

• Should we move forward?
• How can we move forward? $$$
• How to Identify Responders?
• Optimize Dosing Schedule
• Mechanism of Re-Sensitization?
• Combination therapy?
  o DNA repair inhibitors
  o Other hormones
  o Immunotherapy
  o Bone Marrow Transplant
Points to Take Home

• Pharmacologic testosterone (BAT) can be given safely to asymptomatic men with castrate resistant prostate cancer
• Radiographic Response and PSA response observed in some men
• BAT may re-sensitize CRPC to androgen ablative therapies
• BAT improves Quality of Life in some men
Can BAT be Incorporated into an Intermittent Androgen Deprivation Strategy?

• Prolong Response to Hormonal Therapies?
• Delay Development of Castration Resistance?
• Mitigate Side Effects of Hormone Therapy?
• Positive Effects on Quality of Life?
Hormone Therapy Side Effects

- Depression
- Lack of Focus
- Constant Fatigue
- Decreased Muscle Mass
- Man Boobs
- Abdominal Fat
- No Libido
- Sexual Impotence
- Decreased Bone Mass
Standard Intermittent Hormone Therapy

Androgen Deprivation for 6 months

PSA Response?

YES
Stop Hormone Therapy
Testosterone Recovery (6-9 mos)
PSA Increase >20 ng/ml
Restart Androgen Deprivation
Repeat Until Resistance

NO
Continue Hormone Therapy
Start Second Line Hormone Therapy

Advantage-May Improve Quality of Life and Restore Sexual Function
Disadvantage-Variable and Slow Testosterone Recovery Gives Cancer Cells Time to Adapt
PSA Level after 7 months of ADT Predicts for Survival

(SWOG 9346: Hussain et al. JCO 2006;24:3984)
Bipolar Androgen Therapy in Men with Androgen-ablation Naive Prostate Cancer: The “BATMAN” Study

- Androgen Ablation Naive men with no or minimal metastatic disease and asymptomatic
- First Line Therapy
- N= 33 men, Baseline Avg. PSA 49.7 (5.6-257.3)
BATMAN Study

- Primary endpoint is percentage of men with PSA ≤ 4 ng/ml after 18 months of therapy
- We estimated 40% would have PSA < 4 (IADT studies)
- We predicted 60% would have PSA <4 with addition of BAT cycling
- 33 men completed trial from Jan 2013 to Feb 2014
- Trial Completed May 2015
BATMAN Results

- 29/33 men had declining PSA after 6 months ADT lead-in and allowed to proceed to BAT
- 21/29 (72%) men reached PSA < 4 after 18 months
- Most common side effect low grade swelling in lower legs
- Significantly improved Quality of Life and sexual function

Acknowledgements

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Harry Cao- Study Coordinator
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Hao Wang-Biostatistician
Robert Delaney- Finance Administrator

Co-Investigators
Emmanuel Antonarakis
Mario Eisenberger
Channing Paller
Michael Carducci
Jun Luo- AR-V7

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Presented in Memory of Bruce Hunsicker
Founder- One-in-Six Foundation
Thank You for Your Attention and Your Advocacy

For information about clinical trial enrollment contact Dr. Denmeade

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Phone: 410-955-8875