RECOGNITION AND MANAGEMENT OF TREATMENT RELATED SIDE EFFECTS OF ANDROGEN DEPRIVATION THERAPY (ADT)

Nikita Ivanov, NP(F), MN-NP
Nurse Practitioner, GU Tumor Group
BC Cancer Agency, Vancouver Centre
Adjunct Professor School of Nursing
University of British Columbia
The program is currently comprised of eight modules:

1. Introduction to Prostate Cancer & Primary Treatment Options
2. Managing the Impact of Prostate Cancer Treatments on Sexual Function and Intimacy
3. Exercise for Prostate Cancer Patients
4. Recognition & Management of Treatment Related Side Effects of Androgen Deprivation Therapy (ADT)
5. Pelvic Floor Physiotherapy for Bladder and Bowel Concerns
6. Counselling Services
7. Metastatic Disease Management
8. Nutrition Advice for Prostate Cancer Patients
INTRODUCTION TO ANDROGEN DEPRIVATION THERAPY (ADT)

• Prostate Cancer Overview

• Androgen Deprivation Therapy

• Treatment Options

• Side Effects and Management
PROSTATE CANCER OVERVIEW

• It is the most common cancer for Canadian men
  • 1 in 9 men will be affected
• Often slow growing and treatable
• Advances in screening, testing, and treatment options have improved prostate cancer outcomes
• 20% of men present with De Novo metastatic disease and about 20% of men will relapse post primary treatment
CERTAIN FACTORS ARE ASSOCIATED WITH INCREASED RISK OF DEVELOPING PROSTATE CANCER

**Age and race/ethnicity**

- ≥65 years old
- Uncommon in men <40 and more common in men aged ≥65 years
- African ancestry
  - Compared to other ethnicities, men of African ancestry have a higher risk of developing prostate cancer; being diagnosed at a younger age; and dying from prostate cancer

**Diet and cigarette smoking**

- Red meat/dairy products are associated with a higher risk of prostate cancer
- Smoking doubles the risk of dying from the disease

**Hereditary and genetic factors**

- Family history of prostate cancer
  - Cancer risk is higher in men with relatives who have been diagnosed with the disease
- History of breast cancer
  - Prostate cancer risk is 19%-24% higher in these men
- Germline HRRm (including BRCA)
  - These mutations have been associated with increased prostate cancer risk

*Results from observational cohort studies

THE PROSTATE CANCER LANDSCAPE

ARAT Androgen-receptor axis-targeted agents  
LHRH Luteinizing hormone-releasing hormone  
mHSPC Metastatic hormone sensitive prostate cancer  
nmCRPC Non-metastatic castration resistant prostate cancer  
mCRPC Metastatic CRPC

LOCALIZED OR LOCALLY ADVANCED PROSTATE CANCER  
BIOCHEMICAL RECURRENCE  
NEWLY DIAGNOSED mHSPC  
PRIMARY PROGRESSIVE mHSPC  
nmCRPC  
mCRPC  
TERMINAL DISEASE (DEATH)

Androgen Deprivation Therapy (ADT) – Foundation of Care (LHRH Agonist or Antagonist)

ARAT/CYP17 Inhibitor Chemotherapy PARP inhibitor

Radiopharmaceuticals

Enzalutamide  
Abiraterone  
Docetaxel  
Enzalutamide  
Abiraterone  
Radium 223  
Enzalutamide  
Apalutamide  
Darolutamide  
Abiraterone  
Cabazitaxel  
Olaparib
Androgens (T) are produced at 3 sites

- Testes
- Adrenal glands
- Prostate tumour cells (occasionally)

In the eugonadal state, 95% of androgens are produced by the testis

**Androgen Receptor (AR) Signalling Pathway**

- Testosterone/DHEA
- 5α-reductase
- DH
- HSP
- Nuclear translocation
- AR
- DNA

Figure adapted from ©Bandyopadhyay M, Muthuirulan P. J Drug Des Devel 2017;1:1-10

**Legends:**
- AR: Androgen receptor
- DHT: Dihydrotestosterone
- HSP: Heat shock protein
- T: Testosterone
GOALS OF ADT

• Achieve and maintain an environment of low T activity
  • Suppress T to “castrate levels” and/or
  • Effectively block AR
• Rapid onset of T suppression
• Block effect of T surge if relevant
• Reduce T to < 0.7 nmol/L (< 20 ng/dL)
• Consistent T suppression
  • No escapes or microsurges while on treatment

• Achieve and maintain low nadir T
• Personalize
  • Tailor to patients’ lifestyles and schedules
• Minimize side effects
• Consider cost
• Improve patient outcomes
  • Reduce morbidity
  • Extend survival
GUIDELINES: TESTOSTERONE TARGETS DURING ADT

There are different definitions of castrate testosterone:

- **Bethesda (US) Consensus 2012**
  \[ T < 20 \text{ ng/dL (0.7 nmol/L)} \]

- **EAU Guidelines 2021**
  \[ T < 20 \text{ ng/dL (0.7 nmol/L)} \]

- **Canadian Consensus 2018**
  \[ T \leq 20 \text{ ng/dL (0.7 nmol/L)} \]

- **NCCN Guidelines 2021**
  \[ T < 50 \text{ ng/dL (1.7 nmol/L)} \]

- **AUA Guidelines 2018**
  \[ T < 50 \text{ ng/dL (1.7 nmol/L)} \]
OPTIONS TO CONTROL TESTOSTERONE LEVELS

• Surgery
  • Orchiectomy

• Human Luteinizing Hormone-Releasing Hormone (LHRH) Agonist
  • Goserelin Acetate (Zoladex)
  • Leuprolide Acetate (Lupron or Eligard)

• Human Luteinizing Hormone-Releasing Hormone (LHRH) Antagonist
  • Degarelix (Firmagon)

• First Generation Non-Steroidal Anti-androgens
  • Bicalutamide (Casodex)
  • Nilutamide (Nilandron)
  • Flutamide (Euflex)
Orchiectomy

1. The surgeon will make a cut (incision) near the groin.
2. The testes are removed through the incision.
3. The incision is closed with stitches and covered with a dressing.
OPTIONS TO CONTROL TESTOSTERONE LEVELS

Androgen Deprivation Therapy

**LHRH agonists**
- Overstimulate the pituitary gland and over-ride the pulsatile control of LH release by natural LHRH
- Result: downregulation of LHRH receptors and desensitization of the gland

**LHRH antagonists**
- Directly bind to the pituitary
- Prevent release of LH + FSH
- Result: Removes stimulus to the testes to produce T

- **ACTH** Adrenocorticotropic hormone
- **FSH** Follicle-stimulating hormone
- **GnRH** Gonadotropin-releasing hormone
- **LH** Luteinizing hormone
- **T** Testosterone

### LHRH THERAPY OPTIONS

<table>
<thead>
<tr>
<th>Attributes</th>
<th>leuprolide SC&lt;sup&gt;1&lt;/sup&gt;</th>
<th>leuprolide IM&lt;sup&gt;2,3&lt;/sup&gt;</th>
<th>goserelin&lt;sup&gt;5,6&lt;/sup&gt;</th>
<th>degarelix&lt;sup&gt;†6,7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Needle Gauges</strong></td>
<td>20 (7.5, 22.5, 30 mg)</td>
<td>23 (all doses)</td>
<td>16 (3.6 mg)</td>
<td>27</td>
</tr>
<tr>
<td>18 (45 mg)</td>
<td></td>
<td></td>
<td>14 (10.8 mg)</td>
<td></td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Subcutaneous</td>
<td>Intramuscular</td>
<td>Subcutaneous Implant</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td><strong>Dosing Intervals</strong></td>
<td>1  3  4  6</td>
<td>1  3  4  6</td>
<td>1  3  4  6</td>
<td>1  3  4  6</td>
</tr>
<tr>
<td><strong>Injection Volume</strong></td>
<td>0.25 0.37 0.50 0.375</td>
<td>1.0 1.5 1.5 0.01 0.03</td>
<td></td>
<td>2x3.0</td>
</tr>
</tbody>
</table>

<sup>†</sup> LHRH antagonist

* Initial dose of 240mg (2 x 3 mL), followed by monthly maintenance doses of 80 mg (4 mL)

IM Intramuscular  SC Subcutaneous

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## HOW DO THEY COMPARE?

<table>
<thead>
<tr>
<th>Items</th>
<th>Surgical Castration</th>
<th>Medical Castration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure</td>
<td>Orchietomy</td>
<td>LHRH Agonists</td>
</tr>
<tr>
<td>Castration</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>Castrate of level of testosterone</td>
<td>3-4 days</td>
<td>3-4 weeks</td>
</tr>
<tr>
<td>Testosterone flare</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prior Anti-Androgens</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Local reaction</td>
<td>N/A</td>
<td>1%</td>
</tr>
<tr>
<td>Administration</td>
<td>Once</td>
<td>3, 4, and 6 months</td>
</tr>
<tr>
<td>Cardiovascular complications</td>
<td></td>
<td>Similar?</td>
</tr>
<tr>
<td>Psychologic preference</td>
<td>22%</td>
<td>78%</td>
</tr>
<tr>
<td>Costs</td>
<td>Hundreds</td>
<td>Thousands</td>
</tr>
</tbody>
</table>
CHOOSING AN ADT REGIMEN

There are many choices of ADT, which are often influenced by coverage, physician preference, or other factors:

**Frequency of administration influenced by:**
- Mobility issues
- Living in remote locations
- Compliance
- Lifestyle
- Availability of home injection program

**Intermittent therapy considered for:**
- nmCSPC with good initial response to ADT
- Low burden mCSPS and complete response to ADT
**PRIMARY THERAPY AND ADT SIDE EFFECTS**

**Androgen Deprivation Therapy**
- Weight gain
- Loss muscle mass
- Gynecomastia
- Testicular atrophy
- Loss of body hair
- Hot flashes
- Fatigue
- Mood disturbances

**Primary Therapy**
- Urinary incontinence
- Climacturia
- Altered or painful orgasm
- Dry ejaculation

**Combined Therapy**
- Erectile dysfunction
- Penile shortening
- Low/no libido
- Depression
- Altered couple relationship
- Partner distress
SIDE EFFECTS OF ADT

What physicians commonly tell patients

- Loss of libido (sex drive)
- Erectile dysfunction
- Hot flashes

LOSS OR LOWERING OF LIBIDO (SEX DRIVE)

- No magic pill to improve libido
- Lower libido is age related

How to enhance your libido?

| Exercise | Enhance Intimacy | Mindfulness | Sensate Focus | Simmering |

Module 2: Managing the Impact of Prostate Cancer Treatments on Sexual Function and Intimacy
ADT can lower your sex drive and cause ED

Erectile Dysfunction Treatments:
- Oral medications (e.g. Viagra or Cialis)
- Vacuum pump erection devices
- Penile injections

Incorporate couple-based coping and education
Psychological and/or relationship counseling

Note! It is still possible to orgasm without an erection
ERECITION=ERECTION, ORGASM=ORGASM, ERECTION≠ORGASM
**HOT FLASHES**

**Commonly occur after the first 2 months of starting ADT**

### What worsens hot flashes?
- **Diet:** avoid alcohol, spicy food, and caffeine (coffee, tea, colas, chocolate…etc.)
- **Heat:** stay cool and hydrated
- **Stress:** try to relieve stress

### What can help with my hot flashes?
- Wear sweat wicking material
- Sleep with layers that can be removed and use a fan
- Massage and acupuncture
- Follow a regular exercise program
- Relaxation and Cognitive Behavioral Therapy (CBT)
HOT FLASHES

Other things people try:

- Soy foods
- Flaxseed
- Vitamin E
- Black Cohosh
- Garlic
- Ginseng

Note! Always ask your doctor before trying a new supplement!

Medications:

- Androcur (cyproterone acetate)
- Depo-Provera (medroxyprogesterone)
- Megace (megestrol acetate)
- Gabapentin 300 mg at bedtime or 100 mg every 8 hours and titrate
- Venlafaxine (Effexor XR) 37.5mg – helps hot flashes and depressive symptoms
## SIDE EFFECTS OF ADT

<table>
<thead>
<tr>
<th>What physicians commonly tell patients</th>
<th>What patients see</th>
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<tbody>
<tr>
<td>Loss of libido (sex drive)</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Gynecomastia</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>(increased breast tissue)</td>
</tr>
<tr>
<td></td>
<td>Loss of muscle mass and strength</td>
</tr>
<tr>
<td></td>
<td>Shrinkage of penis and testicles</td>
</tr>
<tr>
<td></td>
<td>Hair changes</td>
</tr>
</tbody>
</table>

WEIGHT GAIN AND ASSOCIATED CHANGES

- More than 40% of men are overweight at diagnosis
- Common to gain up to 10 kg over 6-9 months due to increased appetite
- Increase in body fat especially at waist, hips, thighs
- Loss of muscle mass and strength
- Weight is difficult to lose even if ADT is stopped!
- Need to be physically active - aerobic and resistance exercise
- Engage in healthy lifestyle habits
- Module 3 and Module 8 : Exercise and Nutrition
SHRINKAGE OF PENIS AND TESTICLES

- Genital shrinkage: penis length, girth and testicular volume
- Apoptosis (cell death) of trabecular smooth muscle
- Impaired veno-occlusive mechanism
- Fibrotic changes
- Usually stops 12-18 months after starting ADT

Work with PCSC Sexual Health Clinician on penile rehabilitation strategies
(Module 2)
HAIR CHANGES

- Thinning or loss of body hair on trunk, arms, legs
- Beard softer
- May or may not be bothersome
- Not a health issue although it can be distressing if not informed

- Reversible if ADT is stopped!
<table>
<thead>
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<th>What patients don’t see</th>
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<td>Loss of libido (sex drive)</td>
<td>Weight gain</td>
<td>Loss of bone density</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Gynecomastia (increased breast tissue)</td>
<td>Diabetes and cardiovascular disease</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Loss of muscle mass and strength</td>
<td>Metabolic syndrome</td>
</tr>
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<td></td>
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LOoss Of Bone Density

Hypogonadal bone loss
- Among the leading causes of osteoporosis in men in the US
- Incidence increases with age
- ADT causes hypogonadal bone loss
  - Increased skeletal response to PTH
  - Low estrogen alters balance of osteoclast/osteoblast activity

NCCN Guidelines 2021:
- Supplemental calcium and vitamin D3
- Additional treatment for men ≥ 50 yrs with low bone mass and:
  - 10-year probability of hip fracture ≥ 3%, or
  - 10-year probability of major osteoporosis-related fracture ≥ 20%
- Baseline BMD test, re-test after 1 year of treatment
- Consider anti-resorptive drugs

BMD Bone mineral density
PTH Parathyroid hormone

1. Bilezikian JP. J Clin Endocrinol Metab 1999;84:3431-4
LOSS OF BONE DENSITY

• All patients on ADT need to ensure they are receiving adequate amounts of Calcium and Vitamin D
  • 1200 mg Calcium (not to exceed 2000 mg/day)
  • 1000 IU Vitamin D (not to exceed 4000 IU/day)
*unless serum vitamin D levels are low and being followed by a physician
• Men with moderate to high risk of fracture at 10-years should be offered drug therapy
  • Denosumab (Prolia) 60mg SC every 6 months (Must have good dental hygiene!)
• Resistance exercises and high impact exercises help preserve BMD
Patients with pre-existing cardiovascular disease (e.g. heart attack and/or congestive heart failure) are at increased risk for cardiovascular events when treated with ADT.
METABOLIC SYNDROME

- Fat mass increases 10-20%
- Lean body mass decreases 2-3%
- Increased insulin levels within months
- Lipids increase in unpredictable ways
- Increases in blood pressure
- Increase in blood sugar levels
- Hemoglobin level could also decline on ADT on average to 125-130g/L (the mechanism is not clearly understood)

NCCN Guidelines:
- Follow traditional assessments of risk factors for diabetes
- Team approach
  - Primary care
  - Nursing
  - Geriatrician
  - Endocrinologist

ABCD Paradigm:
- Awareness and Aspirin
- Blood Pressure
- Cholesterol and Cigarettes
- Diet and Diabetes
- Exercise

3 out of 5
# SIDE EFFECTS OF ADT

<table>
<thead>
<tr>
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<td>Loss of libido (sex drive)</td>
<td>Weight gain</td>
<td>Loss of bone density</td>
<td>Muscle and Joint aches</td>
</tr>
<tr>
<td></td>
<td>Gynecomastia (increased breast tissue)</td>
<td>Diabetes and cardiovascular disease</td>
<td>Depression and emotional lability</td>
</tr>
<tr>
<td></td>
<td>Loss of muscle mass and strength</td>
<td>Metabolic syndrome</td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td></td>
<td>Shrinkage of penis and testicles</td>
<td></td>
<td>Fatigue, lack of energy, lack of initiative</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Hair changes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADT-ASSOCIATED MUSCULOSKELETAL SYNDROME

• Muscle and joint aches and pains within 3 months of initiating ADT
• Could be associated with muscle wasting and tendons and ligaments thinning

Nonpharmacological
• Aerobic and resistance exercise
• Acupuncture x2 per week and then x6 weekly

Pharmacological
• NSAIDS 400 mg Advil x3 day for 5 days (if no contraindications) then 200-400 mg if needed
• Duloxetine (Cymbalta) 300 mg/day can increase to 60 mg/day if needed
DEPRESSION

• Some men report worsening mood on ADT
  • Many men describe feeling more emotional, greater irritability, crying more easily
• In a large US database study,¹ depressive disorders occurred 6 – 60 mos following a cancer diagnosis in:
  • 9.5% of men with PCa but no ADT
  • 13.9% of men with PCa on ADT
    • vs. 9.6% of men without cancer
• Other studies have shown a similar increase in depressive symptoms in men with PCa, regardless of ADT²
• **Monitoring for mood changes is advisable for all patients with PCa**

Exercise impacts mood in a positive way

Module 6: Counselling Services
COGNITIVE FUNCTION

- Impact on a small number of patients
- Typically affects spatial memory (e.g. where did I park the car?)

Counselling services (Module 6)
Exercise! (Module 3)
Reduce clutter in living space
Reduce alcohol and other depressants

FATIGUE

- Feeling of weariness, tiredness, or lack of energy that does NOT always improve with rest
- May affect your ability to do daily activities
- No medication is known to effectively reduce fatigue
- Exercising improves fatigue, social functioning, and mental health
150 minutes per week of moderate-to-vigorous physical activity (aerobic exercise) + 2-3 resistance training sessions

**HEART RATE**

- **Moderate Intensity**
  - 50 - 70%
- **Vigorous intensity**
  - 70 - 85%

**FATIGUE**

<table>
<thead>
<tr>
<th>RPE Scale</th>
<th>Rate of Perceived Exertion</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Max Effort Activity</td>
</tr>
<tr>
<td></td>
<td>Feels almost impossible to keep going. Completely out of breath, unable to talk. Cannot maintain for more than a very short time.</td>
</tr>
<tr>
<td>9</td>
<td>Very Hard Activity</td>
</tr>
<tr>
<td></td>
<td>Very difficult to maintain exercise intensity. Can barely breath and speak only a few words</td>
</tr>
<tr>
<td>7-8</td>
<td>Vigorous Activity</td>
</tr>
<tr>
<td></td>
<td>Borderline uncomfortable. Short of breath, can speak a sentence.</td>
</tr>
<tr>
<td>4-6</td>
<td>Moderate Activity</td>
</tr>
<tr>
<td></td>
<td>Breathing heavily, can hold short conversation. Still somewhat comfortable, but becoming noticeably more challenging.</td>
</tr>
<tr>
<td>2-3</td>
<td>Light Activity</td>
</tr>
<tr>
<td></td>
<td>Feels like you can maintain for hours. Easy to breathe and carry a conversation</td>
</tr>
<tr>
<td>1</td>
<td>Very Light Activity</td>
</tr>
<tr>
<td></td>
<td>Hardly any exertion, but more than sleeping, watching TV, etc.</td>
</tr>
</tbody>
</table>
Multiple Domains of Wellbeing for Survivors

Physical
- Fatigue
- Sleep
- Pain
- Functional

Social
- Family distress
- Roles
- Relationships
- Work
- Finances

Sexual

Psychological
- Fear of recurrence
- Loss of control
- Anxiety
- Depression
- Cognition
- Attention

Spiritual
- Meaning
- Hope
- Inner strength
- Transcendence

Adapted from Ferrell et al 1995, QOL in Long Term Cancer Survivors, Oncology Nursing Forum
MONITORING DURING ADT

- Confirm efficacy
  - Routinely measure PSA and T
- Monitor for Adverse Events
  - CV disease (e.g. lipids, blood pressure, weight, smoking)
  - Glucose
  - Bone mineral density
- Therapy compliance
  - Injection timing
- Compliance with calcium and vitamin D
- Caregiver feedback
- Shared care
Summary

• ADT remains a foundational treatment throughout the prostate cancer journey
• A variety of ADT options are available, and choice is based on a number of patient- and disease-related factors
• The goal of ADT is to lower and maintain testosterone to castrate levels and/or block activity at the androgen receptor
  • This results in a number of side effects that can impact a patient’s QOL
• Patients undergoing ADT for prostate cancer should undergo continuous monitoring for:
  • Efficacy
  • Side effects
  • Compliance to treatment
TAKE HOME MESSAGES

• ADT can have many side effects
• Up to 20% of men DO NOT have any side effects 😊
• Dealing with side effects proactively is the best way to avoid long term problems with ADT
• Exercise and physical activity are the most effective treatments
• Patients must be active participants in prevention strategies
• The PCSC Program is here to help!