Prostate Cancer: Managing Side-effects of Androgen Deprivation Therapy

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Prostate Cancer: Managing Side Effects of Androgen Deprivation Therapy

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Richard Wassersug, PhD
Disclosures

• None
Outline

1. Androgen deprivation therapy therapy definitions
2. Case examples
3. Rationale: Why knowing the side effects of ADT is important in your practice
4. What do your patients want to know?
5. What do your colleagues want patients to know?
6. The facts about ADT side effects
7. Counseling and treating your patients with ADT side effects: back to the cases
8. Questions
Testosterone Biosynthesis
Testosterone: Target Organs

- brain
  - libido, mood, cognition

- heart
  - cardiovascular health

- liver
  - protein synthesis

- kidney
  - stimulation of erythropoietin production

- bone
  - strength and density

- skin
  - hair growth, balding, sebum production

- muscle
  - strength, volume, energy reduction in visceral fat

- male sexual organs
  - penile growth, spermatogenesis, erection, prostate growth and function

- bone marrow
  - stimulation of stem cells
ADT

- Suppresses the production of the androgen dihydrotestosterone (DHT) by limiting the amount of available testosterone

**Three ways**

1) **LHRH agonists** (Leuprolide, Goserelin, Triptorelin) - overstimulate the hypothalamic-adrenal-gonadal axis, stopping production of T via a feedback loop

2) **LHRH antagonists** (Cetrorelix, Ganirelix, Abarelix, Degarelix) inhibit the activation of the total axis

3) **Adjuncts to ADT**
   - Androgen receptor antagonists (Casodex, Flutamide, MDV3100)
   - 5 alpha-reductase inhibitors (Dutasteride, Finasteride)
   - CYP17A1 inhibitors (Abiraterone, Ketoconazole)
Case 1

Michael is a 72 yo male who has been on ADT for the past year for recurrent prostate cancer (CaP). Over the past 3 months you have noticed that he has elevated fasting blood glucose and an increase in waist circumference despite his efforts to eat healthy and keep active 3-4 days a week. Today he presents with a fasting blood glucose of 14.
Case 2

Peter is a 52 yo male married to Jill, his second wife. He started ADT with his radiation treatment 1 year ago. The couple has struggled a great deal with maintaining sexual intimacy. Jill is very much interested in maintaining penetrative intercourse and other sexual activities. Whenever Peter engages in sexual activities, he becomes frustrated by his struggle to become aroused and to achieve an erection. Jill is interested in sex a few times a week and often starts to engage in these activities on her own. Though she appreciates it when he joins her in these activities, she perceives it to be a chore for him. With great effort, he has been able to achieve a partial erection and occasionally orgasm with lots of physical stimulation. Jill is very much attracted to Peter; however, she is beginning to doubt that he finds her attractive. She reports feeling guilty about her interest in sex when he isn’t interested.
**Case 3**

**Joseph** is an active 82 yo male who has been on ADT for the past 5 years for metastatic CaP. His PSA remains undetectable and he is tolerating ADT well. He has been taking calcium and vitamin D supplementation for many years but comes to you today to discuss his bone health.
Rationale

- Approximately 50% of all men treated for CaP will be on ADT at some time in their life\(^1\).
- More than 600,000 men in North America are on ADT at any given time\(^1\).
- Side effects of ADT are known to reduce the quality of life (QOL) of patients with CaP\(^2\).
- ADT was previously administered to prevent symptoms associated with advanced cancer, so side effects which reduced QOL were seen as less significant in light of delaying disease progression – however, ADT is now commonly used to treat biochemical relapse\(^2\).

• Walker et al. surveyed 79 newly prescribed ADT patients and 54 of their partners and found that both patients and their partners were poorly informed about the side effects of ADT$^3$. 

$^3$Walker LM. Urologic Oncology 2013.
Soeyonggo et al. surveyed 92 primary care physicians in Canada, who had patients on ADT; >50% of whom administered ADT annually\(^4\).

38% of the MDs felt their knowledge of ADT side effects was inadequate and 50% felt uncomfortable counselling patients on ADT\(^4\).

The majority surveyed “expected their specialist colleagues to monitor [their patients’] ADT side effects\(^4\).”

\(^4\)Soeyonggo T. Locke JA. Canadian Urol Assoc J 2014.
• In a study conducted in the United Kingdom Moule et al. found similar results:

![Table 2: GP confidence in their own knowledge](image)

<table>
<thead>
<tr>
<th>Area of knowledge</th>
<th>Very confident n (%)</th>
<th>Fairly confident n (%)</th>
<th>Not very confident n (%)</th>
<th>Total number n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision making regarding treatment options</td>
<td>4 (5.6)</td>
<td>25 (34.7)</td>
<td>29 (40)</td>
<td>58 (80.6)</td>
</tr>
<tr>
<td>Recovery from radiotherapy</td>
<td>5 (6.9)</td>
<td>23 (31.9)</td>
<td>32 (44.4)</td>
<td>60 (83.3)</td>
</tr>
<tr>
<td>Managing urinary continence</td>
<td>3 (4.2)</td>
<td>19 (26.4)</td>
<td>36 (50)</td>
<td>58 (80.6)</td>
</tr>
<tr>
<td>Sexual function</td>
<td>5 (6.9)</td>
<td>21 (29.2)</td>
<td>31 (43.1)</td>
<td>57 (79.2)</td>
</tr>
<tr>
<td>Relationship issues</td>
<td>4 (5.6)</td>
<td>24 (33.3)</td>
<td>30 (41.7)</td>
<td>58 (80.6)</td>
</tr>
</tbody>
</table>

• The authors also found that general practitioners preferred learning about ADT side effects through education face-to-face (72%)\(^5\).

\(^5\)Moule P et al. Education for Primary Care 2014.
What do your patients want to know?

• Only 11% of men with nonmetastatic CaP starting continuous ADT were recommended lifestyle interventions by their physicians despite patients wanting this information\textsuperscript{6}.

• Patients generally want to be involved in treatment decisions, however, some felt that they had missed out on hormonal treatment options (26%) and or were unaware of all the treatment options available (29%)\textsuperscript{7}.

• Lebret \textit{et al.} created a educational tool kit containing written detailed guidance on diet and physical exercise for patients about to receive ADT
  • 82% of the patients receiving the kit were glad to have it
  • 57% had started implementation of the activities\textsuperscript{8}.

What do your colleagues want patients to know?

- Tran et al. demonstrated that the uro-oncologists, who start patients on ADT, have little consistency in what they feel patients starting on ADT need to know about ADT side effects.

- Physicians agreed that osteoporosis, erectile dysfunction, hot flashes, loss of libido, and loss of muscle mass were drug responses that were essential or important to warn patients about.

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Tran S. Walker LM. Jour of Oncology Pharmacy Practice 2013.
## The facts about ADT

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Prevalence Rate (%)</th>
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<tbody>
<tr>
<td>Genital shrinkage: penile length loss &gt; 1cm</td>
<td>93.00%</td>
</tr>
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<td>Mild anemia</td>
<td>82.00%</td>
</tr>
<tr>
<td>Cessation of sexual activity</td>
<td>80.2-93.0%</td>
</tr>
<tr>
<td>Erectile dysfunction/impotence</td>
<td>73.3-95.0%</td>
</tr>
<tr>
<td>Weight gain</td>
<td>70.00%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>65.00%</td>
</tr>
<tr>
<td>Concern about body image</td>
<td>60.20%</td>
</tr>
<tr>
<td>Loss of libido/sexual interest/drive</td>
<td>58.0-91.4%</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>55.00%</td>
</tr>
<tr>
<td>Metabolic syndrome (risk as early as 3-6 mos)</td>
<td>55.00%</td>
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<tr>
<td>Osteoporosis 2 years on ADT</td>
<td>53.30%</td>
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<tr>
<td>Perceived loss of masculinity</td>
<td>50.00%</td>
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<tr>
<td>Hot flashes</td>
<td>44.0-80.0%</td>
</tr>
<tr>
<td>Decline in executive functioning</td>
<td>38.0-48.0%</td>
</tr>
<tr>
<td>HDL cholesterol &lt; 40mg/dL</td>
<td>35.00%</td>
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<td>Fatigue or decreased energy</td>
<td>33.0-46.8%</td>
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<td>Breast swelling</td>
<td>24.90%</td>
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<td>Decline in spatial ability</td>
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<td>Decline in verbal memory</td>
<td>19.0-48.0%</td>
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<td>Breast tenderness</td>
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<td>Increase in arterial stiffening</td>
<td>17.10%</td>
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<td>Osteoporosis</td>
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<td>Average HDL rise</td>
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<td>Diabetes type II risk</td>
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<td>Night sweats</td>
<td>4.60%</td>
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10Walker LM. Clinical Genitourinary Cancer 2013.
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Considerations when counseling and treating your ADT patients

• Cases
  1. Metabolic syndrome / insulin resistance
  2. Sexual health / erectile dysfunction / relationship issues
  3. Bone health / fracture risk
Case 1

**Michael** is a 72 yo male who has been on ADT for the past year for recurrent prostate cancer (CaP). Over the past 3 months you have noticed that he has elevated fasting blood glucose and an increase in waist circumference despite his efforts to eat healthy and keep active 3-4 days a week. Today he presents with a fasting blood glucose of 14.
ADT and metabolic syndrome / insulin resistance

- Patients starting radiation therapy and ADT had a transient increase in waist circumference at 9 months and significant changes in measures of insulin resistance at 3 months\textsuperscript{11}.

ADT is correlated with increased prevalence of metabolic syndrome

treatment for localized prostate cancer, and 20 aged-matched control subjects. The prevalence of metabolic syndrome was higher in the ADT than in the non-ADT (P < .01) and control (P = 0.03) groups\textsuperscript{13}.

Metformin and ADT

- Nobes et al. (n=40) demonstrated a significant improvement in abdominal girth, weight, body mass index and sBP after 6 months of metformin as compared to control.

- Margel et al. (n=3837) found that increased cumulative duration of metformin exposure after CaP diagnosis was associated with decreases in both all-cause and CaP-specific mortality among diabetic men.

- Bensimon et al. (n=935) found that the use of metformin in patients with non-metastatic CaP was not associated with a decreased risk of CaP-specific mortality.

- In a literature review by Clements et al. the authors found supportive evidence for metformin in combating metabolic syndrome and anti-cancer activity.

There exists conflicting evidence for metformin in non-diabetic patients but metformin is likely beneficial in patients with a known diagnosis of diabetes.

*Current clinical trials: NCT01796028, NCT01620593, NCT01215032, NCT01677897, NCT01077479

• In a literature review by Gardner et al. found that exercise training had benefits in muscular strength, cardiorespiratory fitness, functional task performance, lean body mass, and fatigue, with inconsistent effects observed for adiposity.

Focht et al. has launched a clinical trial (Individualized Diet and Exercise Adherence Pilot Trial (IDEA-P)) to contrast the effects of a lifestyle intervention designed to promote independent self-management of exercise and dietary behavior with those of standard care disease management approach in the treatment of prostate cancer.

Exercise is beneficial in patients on ADT
**Case 2**

Peter is a 52 yo male married to Jill, his second wife. He started ADT with his radiation treatment 1 year ago. The couple has struggled a great deal with maintaining sexual intimacy. Jill is very much interested in maintaining penetrative intercourse and other sexual activities. Whenever Peter engages in sexual activities, he becomes frustrated by his struggle to become aroused and to achieve an erection. Jill is interested in sex a few times a week and often starts to engage in these activities on her own. Though she appreciates it when he joins her in these activities, she perceives it to be a chore for him. With great effort, he has been able to achieve a partial erection and occasionally orgasm with lots of physical stimulation. Jill is very much attracted to Peter; however, she is beginning to doubt that he finds her attractive. She reports feeling guilty about her interest in sex when he isn’t interested.
Incontinence
Climacturia
Altered or painful orgasm
Dry ejaculation
Erectile dysfunction
Penile shortening
Low/no libido
Depression
Altered couple relationship
Partner distress

Weight gain
Loss muscle mass
Gynecomastia
Testicular atrophy
Loss of body hair
Hot flashes
Fatigue
Lack of initiative
Mood disturbances
ADT and sexual health / erectile dysfunction

Three possible outcomes for patients²⁰:

1. Decide that sexual activity is a thing of the past:
   • Assume sex is impossible
   • Decide there are other ways of being intimate (i.e. shared mutual interests)

2. Motivated to maintain sexual activity and continue to experiment and persist in finding solutions that work for them,

3. Motivated to maintain sexual activity but become discouraged and demoralized and continue to struggle for years.

²⁰Walker LM. Psycho-Oncology 2010.
Sexual health counseling and ADT

- Often providing an opportunity to open up conversation within the couple is enough to get them talking to each other\textsuperscript{20}.

\begin{quote}
It is important to have an open conversation with your patient and his partner about their sexual relationship
\end{quote}

- Those seeking pro-erectile aids may benefit from use of a vacuum erection device or intra-cavernous injections (PDE5i are less likely to work in the ADT population)\textsuperscript{20}.

\textsuperscript{20}Walker LM. Psycho-Oncology 2010.
Walker et al. share a description of the common challenges that couples face when trying to be sexual while on ADT\textsuperscript{21}.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
Category & Struggles & Strategies to Overcome Struggle & Exacerbating the Struggle \\
\hline
Adjusting to changes to sexual relationship & Changes to sex\textsuperscript{*} & Embrace new experiences & Hold on to the idea that sex has to be as it was \\
& & Acknowledge loss and grief of previous sexual relationship & Assume that sex of a different nature is inferior \\
& & Focus on intimacy & Judge the other person’s attempts to improve the situation or to adapt the sexual encounter \\
& & Use of erectile aids/sex toys & \\
& & Remain lighthearted and laugh & \\
& & Both partners participate and enjoy the sexual experience & \\
& & Look for positive changes & \\
Fatigue\textsuperscript{*} & Make sex a priority & Fail to engage in sexual activity because of fatigue & \\
& Schedule activities earlier in day & Persist in having sex late in the evening when energy is low & \\
& Allow lots of time for activities & \\
& Engage in modified/assisted sexual activities & \\
Absence of sex\textsuperscript{^A} & Replace sex with other activities & Fail to share other interests/activities & \\
& Find other ways to maintain intimacy & Fail to maintain sense of intimacy & \\
& Reprioritize & \\
\hline
\end{tabular}
\end{table}

\textsuperscript{21}Walker LM. Psycho-Oncology 2010.
Case 3

**Joseph** is an active 82 yo male who has been on ADT for the past 5 years for metastatic CaP. His PSA remains undetectable and he is tolerating ADT well. He has been taking calcium and vitamin D supplementation for many years but comes to you today to discuss his bone health.
ADT and bone health / fracture risk

• ADT is associated with reduced bone mineral density and a higher risk for fractures\textsuperscript{22}.
• It is important to test for bone mineral density changes in patients on ADT\textsuperscript{23}.
• Men over 50 who have had one fragility fracture, or those with a T score of $-2.5$ or lower at the lumbar spine, total hip or femoral neck, are considered to have at least a moderate 10-year risk of fracture\textsuperscript{23}.
• Those at moderate to high risk should be offered pharmacologic therapy\textsuperscript{22}.

\textsuperscript{22}\textsuperscript{Cheung A. CUAJ 2014. 23Papaioannou A. CMAJ 2010.}
ADT and bone health / fracture risk

- Calcium and Vitamin D should be offered to all patients on ADT

Choo et al. (n=104) demonstrated in a randomized trial that patients on ADT and radiation therapy who were treated with weekly risodronate had significantly less bone loss and bone turnover markers after 2 years as compared to control.

Smith et al. (n=645) found that early zoledronic acid use in castration-sensitive prostate cancer and bone metastasis was not associated with lower risk of skeletal-related events.

ADT and bone health / fracture risk

• Smith et al. (n=1438) demonstrated in non-metastatic CaP patients on ADT and twice yearly treatment with denosumab had increased BMD at all sites as well as fewer vertebral fractures at 2 years of treatment

• Fizazi et al. (n=1904) demonstrated that denosumab is better than zoledronic acid for prevention of skeletal-related events in patients with castration-resistant CaP

Denosumab should be offered to your patients at moderate to high-risk of fracture

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Take home points

- ADT is commonly prescribed to patients in your practice and have several associated side effects.
- Metformin can be used in patients on ADT who have diabetes.
- Exercise is extremely important in preventing metabolic syndrome and insulin resistance.
- It is important to have an open conversation with patients and their partners about sexual intimacy.
- All patients on ADT should be taking calcium and vitamin D.
- Patients on ADT who are at moderate to high risk of fracture should be offered denosumab.
How to help your patient on ADT and help yourself...

- **Be proactive**: do complete history, physical and bloodwork prior to initiation of ADT therapy – patients want to know beforehand about these side effects.
- **Regular monitoring**: at regular intervals and institute appropriate therapies (learn so you are prepared!)*
- **Exercise** is the single most beneficial therapy for ADT side effects and prevent the mental and metabolic snowball effect.
- **Goal is QoL**: watch for medical AND psychological issues.
- **Listen to the patient** – what is most bothersome – encourage the use of blogs and community support group.
- **Listen to the partner**: they are often the thermostat to their partner’s wellbeing.
- **Use your local and online resources** to help.
Resources

• Use the resources available to you:
  • Vancouver Prostate Centre Supportive Care Program
  • Self-help book and group-based educational class promoting active lifestyle management
  • Lebret et al.’s ADT educational tool kit for diet and physical exercise\(^7\)
    • http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-hormone-therapy
    • http://www.medscape.com/viewarticle/738378
  • LIFEonADT.com

\(^7\)Lebret T et al. Urology 2010.
Acknowledgements

Dr. John Robinson, PhD.
Dr. Tony Soeyonggo, MD.
Dr. Padraig Warde, MD.
Questions?
ADT and hot flashes

• Irani et al. (n=919) demonstrated that leuprolelin, venlafaxine, cyproterone and medroxyprogesterone are effective at reducing ADT associated hot flashes. However, cyproterone and medroxyprogesterone are significantly more effective\textsuperscript{28}.

• Loprinzi et al. (n=214) demonstrated that gabapentin decreases hot flashes to a moderate degree in men on ADT\textsuperscript{29}.

\textsuperscript{28}Irani J. Lancet Oncol 2010. \textsuperscript{29}Loprinzi CL. Ann Oncol 2009.
ADT and fatigue

• Cormie et al. randomized 63 men scheduled to receive ADT to a 3-month supervised exercise program or usual care and found that those in the exercise program had better preserved fatigue (p=0.042), social functioning (p=0.015) and mental health (P=0.022)\(^\text{30}\).

• Gardner et al. conducted a literature review of exercise training and found that exercise training demonstrated benefits in fatigue amongst other side effects of ADT\(^\text{31}\).

• Although the single site clinical trial was closed early due to poor accrual Richard et al. demonstrated that methylphenidate was associated with improved fatigue as compared to placebo (p=0.0220 and also improved QOL (p=0.04))\(^\text{32}\).

Exercise is beneficial for patients on ADT

ADT and cardiac disease

- Nanda et al. found in a retrospective study that men with cardiac induced CHF or MI who were treated with neoadjuvant ADT had a significantly increased risk of all-cause mortality (HR 1.96, p=0.04)\(^{33}\).
- Ziehr et al. found no association between ADT and cardiac-specific mortality in a retrospective study. However, ADT was associated with significantly increased cardiac-specific mortality in men with CHF previous MI (p=0.048)\(^{34}\).
- Nguyen et al. conducted a systematic review of 8 randomized clinical trials and found that cardiovascular death in patients receiving ADT vs control was not significantly different\(^{35}\).
- Albertsen et al. pooled data from six phase 3 prospective trials and found that among men with preexisting cardiovascular disease, the risk of cardiac events within 1 year of initiating therapy was significantly lower in men treated with a GnRH antagonist as compared with a GnRH agonist (HR 0.44, p=0.002)\(^{36}\).

In patients with pre-existing heart disease ADT increases risk of mortality