Discuss the complications of long term Androgen Deprivation Therapy with LHRH agonist in the treatment of Prostate Cancer

Vikramjit Saren
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MCQ

• Which of the following statements about the complications of ADT is TRUE?
  
  – a) Most men undergoing ADT have normal BMD before initiating therapy, and it usually takes at least a decade of Rx before developing **osteopenia**
  
  – b) **Hot flashes** occur in about ¼ but should always be Rx because of the associated rare but life-threatening cardiovascular side effects
  
  – c) **ED** after surgical or medical castration is common but not inevitable: although 1:5 maintain some activity, only 1 in 20 maintain high levels of libido
  
  – d) Because most men on ADT maintain **lean muscle mass**, the increase in weight is due to increase in adipose tissue.
  
  – e) **Gynaecomastia and mastodynia** are common with oestrogenic compounds and antiandrogens but are effectively Rx by external-beam radiation after they occur
Introduction

- ADT as a form of treatment for prostate cancer
  - discovered by Huggins and Hodges in 1941,
    - Nobel Prize for medicine in 1966.

- Initially, AD was achieved via orchidectomy, then later by using estrogen.
  - Poor patient acceptance and problems of thromboembolism and cardiovascular events with the early use of estrogen

- Fortunately, in the mid-1980s the FDA approval of LHRH analogues
  - Alternative for ADT
Charles Huggins and Hormonal Treatment of Prostate Cancer
LHRH agonist

- [leuprolide](#) (Lupron, Eligard, Lucrin)
- [buserelin](#) (Suprefact, Suprecor)
- [nafarelin](#) (Synarel)
- [histrelin](#) (Supprelin)
- [goserelin](#) (Zoladex)
- [deslorelin](#) (Suprelorin, Ovuplant)
Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>Hot flashes</td>
<td>50–80%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.4–2.6%/year</td>
</tr>
<tr>
<td>Anemia</td>
<td>Common</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>50–100%</td>
</tr>
<tr>
<td>Muscle wasting</td>
<td>Common</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Common</td>
</tr>
<tr>
<td>Depression</td>
<td>Common</td>
</tr>
<tr>
<td>Decline in vitality and physical activity</td>
<td>Common</td>
</tr>
<tr>
<td>Increase in fat apposition</td>
<td>Common</td>
</tr>
<tr>
<td>Decline in cognitive function</td>
<td>Common</td>
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</tbody>
</table>
Hot flashes

• One of the most common symptomatic side effects associated with ADT.
  – Up to 80% will experience hot flashes  
    Karling et al 1994, Charig 1989

• NOT life-threatening - significantly affect the patient's QoL.

• Intense sensation of warmth in the face and upper portion of the body.

• May be associated with nausea and sweating or during sleep.
  – Several seconds up to an hour, but most commonly occur for less than 5 min.

• Triggers - heat, stress, changes in body position, or ingestion of hot liquids,
  – many patients cannot identify any inciting factors  
    Smith 1996
Hot flashes

• Spontaneous resolution may occur,
  – many continue to suffer as long as they are receiving ADT
    Karling et al 1994

• Aetiology
  – alteration in the feedback mechanism to the hypothalamus due to lack of testosterone.
  – An increase in catecholamine secretion in response to decreased endogenous peptide secretion
    • stimulates the nearby thermoregulatory center of the hypothalamus resulting in the perception of increased heat
    Smith et al 1996
Treatment of Hot Flashes

• Oestrogens
• Medroxyprogesterone acetate (MDPA)
• Megesterol acetate
• Clonidine
• Antidepressants
• Alternative therapies
Hot Flashes

- Oestrogen
  - Transdermal estrogen - 83% improvement
    - Complications - Mild, painless breast swelling or nipple tenderness
      Gerber et al, 2000
  
  - Diethylstilbestrol (DES) - excellent results
    - Complete RR of 70% & partial RR of 20%
      Miller JL, 1992
  
  - Lower doses (0.25mg/day)
    - effective in relieving hot flashes &
    - used to avoid the cardiovascular complications associated with higher doses of estrogen.
Hot Flashes

- Medroxyprogesterone acetate (MDPA)
  - Langenstroer et al. - either 400 mg or 150 mg intramuscularly of Depo-Provera in 48 men.
  - 81% on 400 mg dose had a significant improvement and 48% had complete resolution
  - Side effects mainly limited to sexual dysfunction.
  - 150mg dose - ineffective
Hot Flashes

• Megestrol acetate

  - 20mg/day effective in reducing hot flashes by up to 85%  
    Loprinzi et al 1994

  - Side effects include chills, weight gain, and carpal tunnel type pain  
    Loprinzi et al 1994, Quella et al 1998

  - Sartor et al 1998 showed an increase in PSA associated with but declined after discontinuation of megestrol acetate.
Hot Flashes

• Clonidine

  – Initially thought to have some efficacy in the treatment of hot flashes.

  – A randomized prospective, double-blind, placebo-controlled, crossover study of transdermal clonidine demonstrated no advantage over placebo.

Loprinzi et al 1994
Hot Flashes

- **Antidepressants**
  - SSRI (*Venlafaxine hydrochloride*) – has been shown to be effective in the treatment of hot flashes
    
    Loprinzi, Kugler & Sloan 2000

  - 63% reduction in hot flashes of > 50%
    
    Loprinzi et al 1998

  - Side effects - mild GI symptoms

  - Lack placebo controlled trials
Hot Flashes

• Alternative therapies

  – Acupuncture was examined by Hammar et al.

  – Acupuncture twice weekly for 2 weeks then once a week for 10 weeks.

  • 6/7 had decrease in hot flashes (average of 70% after 10 weeks).
  • 3/12 post-therapy, hot flashes were 50% lower

Hammar et al, J Urol 1999
Hot Flashes

• Alternative therapies
  – Soy products have also been used with some success in men and women suffering from hot flashes.
  – Women – decrease up to 45% compared with only 30% for placebo
    Albertazzi et al 1995
  – Vitamin E - effective in reducing hot flashes, mechanism unknown
  – Barton et al. 1998
    • placebo-controlled study of vitamin E in women with breast cancer suffering from hot flashes
      – 30% reduction in symptoms.
Treatment of Hot Flashes
(Summary)

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Estrogens (transdermal or DES)</td>
</tr>
<tr>
<td>Megestrol acetate</td>
</tr>
<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Antidepressants (venlafaxine)</td>
</tr>
<tr>
<td>Progesterone (MPA)</td>
</tr>
<tr>
<td>Vitamin E</td>
</tr>
<tr>
<td>Soy products</td>
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</tbody>
</table>

DES, diethylstilbestrol; MPA, medroxyprogesterone acetate.
Osteoporosis

• Stepan et al. 1989 - first reported the association between androgen deprivation and osteoporosis.
  – progressive loss of bone mineral content in the lumbar spine
  – undergone orchidectomy for sexual delinquency

• Melton et al. 2003 - looked at 429 men treated with bilateral orchidectomy for PCa from 1956 to 2000.
  – overall fracture risk increased by twofold.
Osteoporosis

- More than ½ of men have BMD criteria for osteopenia or osteoporosis
  - Before initiation of ADT  
    - Wei et al 1999, Conde et al 2004

- Longer the ADT, > risk of fracture

- Estimated that 4 yrs of ADT
  - Places the average man in the osteopenic range
BMD chart

Results Summary:

<table>
<thead>
<tr>
<th>Region</th>
<th>Area [cm^2]</th>
<th>BMC [g]</th>
<th>BMD [g/cm^2]</th>
<th>T-Score</th>
<th>PR (Peak Reference)</th>
<th>Z-Score</th>
<th>AM (Age Matched)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>6.12</td>
<td>4.61</td>
<td>0.752</td>
<td>-1.3</td>
<td>81</td>
<td>-0.2</td>
<td>96</td>
</tr>
<tr>
<td>Troch</td>
<td>16.48</td>
<td>12.65</td>
<td>0.768</td>
<td>-0.1</td>
<td>99</td>
<td>0.3</td>
<td>104</td>
</tr>
<tr>
<td>Inter</td>
<td>26.32</td>
<td>43.55</td>
<td>1.655</td>
<td>2.5</td>
<td>138</td>
<td>3.0</td>
<td>149</td>
</tr>
<tr>
<td>Total</td>
<td>48.92</td>
<td>60.81</td>
<td>1.243</td>
<td>1.4</td>
<td>120</td>
<td>1.9</td>
<td>131</td>
</tr>
<tr>
<td>Ward's</td>
<td>1.10</td>
<td>0.58</td>
<td>0.525</td>
<td>-1.8</td>
<td>67</td>
<td>-0.1</td>
<td>99</td>
</tr>
</tbody>
</table>

Total BMD CV 1.0%, ACF = 1.022, BCF = 1.014

Fracture Risk: Not Increased; WHO Classification: Normal
Osteoporosis

• Stoch et al. 2001 - evaluated 60 men with PCa.
  – 19 LHRH vs 41 no LHRH (control 197 men)
  – The BMD was statistically significantly lower in the LHRH group.
  – Furthermore, biochemical markers of bone turnover were significantly altered compared with untreated patients.
  – This study confirms that LHRH agonists can lead to osteoporosis, and that the changes in bone are not due to PCa alone.

• Higano et al. 1999 - examined the effects of intermittent androgen deprivation on BMD;
  – @ 9 months on ADT there was a significant loss of BMD.
Correlation between the duration of ADT and total body BMD
Osteoporosis

- The greatest concern regarding osteoporosis and LHRH agonists is increased risk for bone fractures.

- Osteoporotic bone fractures have become a major health concern due to the increasing elderly population.

- A mortality rate of 30% has been associated with hip fractures in men over 75 years of age.

  Townsend et al 1997

- According to recent studies, the risk of osteoporotic hip fractures is as high as 5% and 20%, 5 and 10 years after initiation of ADT.

  Morote et al, Eur Urol 2003
Prevention of Osteoporosis

• Preventive measures of ADT-associated osteoporosis include:
  – smoking cessation,
  – moderating alcohol and caffeine consumption,
  – vitamin D and calcium supplementation, and
  – regular weight bearing or resistance exercise.

• Seeman et al. 1983 - demonstrated that smoking and excessive alcohol consumption were independent risk factors for osteoporosis.
  – Interestingly, obesity had a protective effect, presumably due to the increased peripheral conversion of testosterone to estrogen.

• Some reports have shown a significant deficiency in vitamin D and calcium in men with PCa.
  – Maintain calcium intake at 1200-1500 mg per day and supplement vitamin D with 400-600 IU per day.

Bilezikian JP 1999
Prevention of Osteoporosis

• More effective options for the prevention and treatment of osteoporosis;
  – Bisphosphonates (alendronate, pamidronate and zoledronate) inhibit osteosclastic activity
    Heidenreich A 2003

• Alendronate
  – first drug to be approved by FDA for the Rx of male osteoporosis
  – Increases BMD
    Orwoll et al 2000
  – Taken on empty stomach in the upright position for 30 mins
  – risk of GI side effects such as epigastric pain, severe esophagitis, and gastroesophageal ulceration
    Body JJ 2001
• Pamidronate
  – Smith et al 2001 demonstrated - 60 mg of IV Pamidronate every 12 weeks did not show a loss in BMD in contrast to patients on LHRH agonist therapy alone.

• Zoledronate is the most potent bisphosphonate
  – up to 850 times potency of Pamidronate in animal studies
  – IV 4 mg every 3 weeks decreases SRE (including fractures) in men with HRPC and bone metastases
  – Also demonstrated efficacy in decreasing pain due to bone metastases and their complications

  Saad, Gleason, Murry 2002

• Prospective RCT using 4 mg of IV Zoledronate was shown to prevent bone loss in men on LHRH agonists for PCa that had no evidence of metastases

  Smith 2003
## Bisphosphonate studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug/dose</th>
<th>No. of patients</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. [36]</td>
<td>Pamidronate 60 mg i.v.</td>
<td>47 men on ADT</td>
<td>BMD no change from baseline</td>
</tr>
<tr>
<td>Orwoll et al. [34]</td>
<td>Alendronate 10 mg oral</td>
<td>241 men with osteoporosis</td>
<td>Increased BMD</td>
</tr>
<tr>
<td>Saad et al. [37**]</td>
<td>Zolendronate 4 mg i.v.</td>
<td>643 men with prostate cancer and osteoporosis</td>
<td>Decreased SRE</td>
</tr>
<tr>
<td>Smith et al. [38**]</td>
<td>Zolendronate 4 mg i.v.</td>
<td>106 men on ADT no metastases</td>
<td>Increased BMD</td>
</tr>
</tbody>
</table>

i.v., intravenous; ADT, androgen deprivation therapy; BMD, bone mineral density; SRE, skeletal related event.
Gynaecomastia

• Gynecomastia - Increase in breast tissue

• Mastodynia - Breast tenderness
  – May occur together or independently

• DES – induces gynaecomastia in 40%  
  Smith, 1996

• Antiandrogens – 66.3% gynaecomastia (150mg bicalutamide) & 72.7% mastodynia
Gynaecomastia

- Prophytlactic radiation therpy
  - Prevent/reduce painful gynaecomastia
  - esp with DES or antiandrogen therapy

- DXT – no benefit ONCE gynaecomastia begins

- Liposuction & subcutaneous mastectomy
  Higano,2003 – established cases

- Selective oestrogen receptor modulator (Tamoxifen) – treat Mastodynia

Payne et al,2002

Higano,2003

Serels and Melmann,1998
Changes in Body Mass and Lipid profiles

- Weight gain - increase in sedentary activity secondary to fatigue, increase in appetite, or the decrease in serum testosterone levels.

- Higano et al. 1996 - examined the effect of CAB on weight and found a median increase in weight of 6 kg.

- Smith et al. 2002 - showed a 9% increase in total cholesterol and a 26.5% increase in Sr TG’s.

- The Cancer Prevention Studies I & II (1959-1996)
  - Risk of death in obese men with PCa – 34% & 36% cf normal
Anaemia

- Normocytic, normochromic anemia
  - due to the lack of testosterone and 5β DHT stimulation of erythroid precursors, and a decrease in erythropoietin production

- Strum et al. 1997 - examined the incidence and severity of anemia in patients on CAB.
  - 90% had Hb drop > 10%
  - ~1 month after the initiation of ADT

- Treatment - subcutaneous recombinant human erythropoietin (EPO).

- Resolution of the anemia on long-term ADT
  - often took > 1 year after the discontinuation of ADT

Strum 1997
Sexual dysfunction

• Sexual dysfunction is a well recognized adverse effect of most ADTs.
  – decrease in libido is usually within the first year of therapy
  – due to the decreased levels of testosterone leading to a decrease in potency

• The lack of testosterone may have a direct effect on the nerves involved in erections

Baba et al 2000
Cognitive function

- There has been information objectively detailing the effect of ADT on memory and cognition.

- Tan 2002 - reported that testosterone replacement in hypogonadal elderly men with no h/o PCa resulted in;
  - improved spatial ability, verbal memory, and fluency.

- Green et al. 2002 - demonstrated a detrimental effect on memory, attention and executive functions (verbal fluency)
  - after 6 months of ADT.
Conclusion

• Side effects of ADT are
  – broad and may potentially be serious.

• Counseling patients who are starting ADT
  – the first step in recognizing and preventing complications associated with the treatment.

• Patients who are not informed may not recognize the significant fatigue or hot flashes as treatable side effects and therefore may not seek proper treatment.

• Lifestyle modifications - exercise, cessation of smoking, diet, and vitamin D and calcium supplementation may have significant benefits;
  – should be recommended when patients are started on therapy.