
MEETING REVIEW

Risks, benefits, and approaches to hormonal blockade in prostate cancer

Highlights from the European Association of Urology Meeting, March 20-24, 2015, Madrid, Spain

Jack Barkin, MD

University of Toronto, Humber River Hospital, Toronto, Ontario, Canada

BARKIN J. Risks, benefits, and approaches to hormonal blockade in prostate cancer. Highlights from the European Association of Urology Meeting, March 20-24, 2015, Madrid, Spain. *Can J Urol* 2015;22(3): 7847-7852.

Several abstracts presented at the 2015 European Association of Urology Meeting highlighted new developments in hormone therapy for prostate cancer management. One abstract described how the luteinizing hormone-releasing hormone (LHRH)/gonadotropin-releasing hormone (GnRH) agonist leuprolide, but not the LHRH/GnRH antagonist degarelix, induced plaque instability in a mouse model. A second abstract showed that

in patients with a history of severe cardiovascular disease, degarelix was associated with fewer cardiovascular events than treatment with an LHRH agonist. A third abstract showed how primary androgen-deprivation therapy was linked with increased all-cause mortality in a US registry. A fourth abstract showed that in the ANAMEN study, cognitive performance was not significantly affected by 6 months of treatment with GnRH agonists. Last, a fifth abstract showed that low-dose prednisone, with or without abiraterone, was associated with an overall low incidence of corticosteroid-associated adverse events.

Key Words: hormone therapy, prostate cancer

Background

In 1941, Charles Brenton Huggins and colleagues published a paper describing their discovery of the impact of estrogens on prostate cancer—work that led to Huggins being a co-recipient of the Nobel Prize in Physiology or Medicine in 1966. Following the publication of this seminal work, hormonal manipulation became the main type of treatment for aggressive or advanced prostate cancer.¹

Thus, the first-line approach to locally advanced or aggressive prostate cancer, where attempt for primary curative therapy was not an option, became surgical castration. This worked very well, but because a significant percentage of men, if given the option, preferred to keep their testicles, and because the immediate side effects of surgical castration were devastating for some men, there was a tremendous desire for and acceptance of the more gradual and “less abrupt” medical castration.

For almost 30 years, gonadotropin-releasing-hormone (GnRH) agonists have been used as first-line therapies to reduce testosterone levels, instead of using surgical castration or estrogen therapy, to manage different stages of prostate cancer.^{2,3}

In 2008, the introduction of the GnRH antagonist degarelix (Firmagon, Ferring Pharmaceuticals), which has some unique properties, represented a valuable new treatment option for patients with hormone-sensitive, advanced prostate cancer.^{4,5}

Extensive use and cumulative clinical experience with androgen deprivation therapy (ADT) has identified a number of insignificant to potentially significant possible side effects.^{3,6} Men receiving long term ADT therapy may have alterations in body composition (increased body fat mass and decreased lean body mass),^{7,8} increased weight, decreased bone mineral density,⁹ changes in fasting-serum-lipid profiles,¹⁰ decreased insulin sensitivity,¹¹ a higher risk of diabetes,¹² metabolic syndrome,¹³ increased cardiovascular events,¹⁴⁻¹⁶ and sexual dysfunction, hot flashes, anemia, and cognitive decline.¹⁶

In a recent issue of *European Urology*, the journal of the European Association of Urology (EAU), a group

Address correspondence to Dr. Jack Barkin, Department of Surgery, University of Toronto, 404-960 Lawrence Avenue West, Toronto, ON M6A 3B5 Canada

of North American and European authors published a comprehensive review of the current literature on the adverse effects of ADT along with strategies that

can help mitigate these effects.¹⁶ Figure 1 shows the potential adverse effects of ADT and the evidence-based strategies aimed at reducing them.

Adverse effect	Features	Evidence-based strategies aimed at reducing adverse effects
Decreased bone health	↓ bone mineral density and ↑ risk of fracture	Calcium from daily diet and supplements; vitamin D; denosumab for men with FRAX risk of hip fracture > 3% (alternative: zoledronic acid or alendronate)
Metabolic consequences	↑ weight gain, ↑ body fat percentage, ↓ lean body mass, ↓ insulin sensitivity, ↑ fasting glucose, ↑ insulin resistance; metabolic effects of ADT shares some features of the hallmarks of metabolic syndrome	Exercise (aerobic and resistance); ATP III and AHA/ACC guidelines for lipids
Increased diabetic risk	Large population-based studies show 16%-44% ↑ risk	Closer monitoring for patients with pre-existing diabetes; ADA guidelines for screening high-risk patients
Cardiovascular events	ADT results in unfavorable metabolic changes and may increase risk for CV events; however most published studies report that ADT is not linked to greater CV mortality. Recent studies suggest that GnRH antagonists could be a good alternative to GnRH agonists for men with pre-existing CV disease.	-
Sexual dysfunction	Affects > 90% of men. Decrease in testosterone due to ADT results in both loss of libido and a decrease in erectile function due to venous leakage, decreased arterial flow, and impaired nitric oxide	Intermittent ADT for rising PSA after radiation; use shortest acceptable duration of ADT
Gynecomastia	Gynecomastia and breast pain can be bothersome; as high as 85%	Prophylactic radiation; prophylactic tamoxifen
Reduced penile/testis size	Can be very distressing and associated with greater treatment regret for patients who experience it without warning	Should be discussed with patients before initiating ADT. There are currently no known ways to mitigate this side effect
Fatigue	A noticeable and frequent side effect	Exercise (aerobic and resistance)
Hot flashes	Can be a significant impediment	Medroxyprogesterone, venlafaxine, gabapentin, cyproterone acetate
Cognitive changes	Hypogonadism has been linked to cognitive declines in several studies. The exact impact of ADT on cognition remains unclear	-
Anemia	Very common (in a study, 78% of men with orchiectomy had a median decrease in Hb ≥ 1 g/dl).	-

Figure 1. Evidence-based strategies to mitigate the adverse effects of androgen deprivation therapy.

The only significant concern that is still controversial and where no suggestions were made was that related to potential cardiovascular side effects; the studies investigating ADT and possible increased risk of cardiovascular disease or cardiovascular mortality have reported conflicting results.¹⁶

These inconsistencies were evaluated by a scientific advisory group comprised of members of several medical societies (the American Urological Association, the American Heart Association, the American Cancer Society, and the American Society of Radiation Oncologists) who concluded that ADT may be associated with an increased incidence of cardiovascular events.¹⁷

Based on the existing evidence, in 2010 the US Food and Drug Administration (FDA) and Health Canada notified the manufacturers of GnRH agonists to update the labelling of these drugs and include a warning about the potential increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, and stroke).

A recent study looked at pooled data from six phase 3, prospective, randomized trials in 2328 men comparing the efficacy of GnRH agonists with GnRH antagonists, to examine the relationship between ADT and cardiovascular events.¹⁴ The study showed that in 705 men with pre-existing cardiovascular disease, compared to treatment with the GnRH agonist leuprolide, treatment with the GnRH antagonist degarelix appeared to halve the number of cardiac events experienced during the first year of ADT (HR 0.476; 95% CI: 0.260-0.871, $p = 0.016$). There were no differences between the two treatment types in men without a history of cardiovascular disease,¹⁴ suggesting that GnRH antagonists could be a good alternative to GnRH agonists for men with pre-existing cardiovascular disease.

Background summary

Different ADT modalities have different adverse-event profiles, and therapeutic choices should be made in an individualized manner. Most potential side effects can be prevented or treated. GnRH antagonists have emerged as a viable alternative to GnRH agonists, particularly in men with a history of cardiovascular disease, since they appear to be associated with a lower risk of cardiovascular events.

Selected EUA abstracts

An overarching theme of abstracts presented at the EUA 2015 meeting was that hormone therapy for managing prostate cancer is here to stay.

Five of these abstracts are summarized below. The abstracts included preclinical and clinical studies. Some studies supported the use of first-line, traditional hormone therapy and explored tailored treatments to address concerns about cardiovascular risk. Other important studies reported on “second-line hormone therapy” approaches using abiraterone and enzalutamide, which are now both approved for men with pre-chemotherapy castrate-resistant prostate cancer.

1. LHRH agonist, but not degarelix, induces plaque instability in mice

Knutsson and colleagues¹⁸ investigated the effect of different ADT modalities, specifically the LHRH agonist leuprolide and the luteinizing hormone-releasing hormone (LHRH antagonist) degarelix, on atherosclerotic plaque stability, in an ApoE^{-/-} mouse model.

Analyses of carotid atherosclerotic plaque were performed after 14 weeks of diet and 4 weeks of treatment, when mice reached 30 months of age.

Larger, unstable necrotic cores and increased inflammation were found in plaques from leuprolide-treated mice compared with control mice and degarelix-treated mice. See Table below.

	Leuprolide	Control	Degarelix	p value
Fibromuscular necrosis area (%)	11.0 (0.98-19.8)	0.58 (0-3.1)	0.16 (0-4.39)	$p < 0.05$, respectively
Plaque inflammation* (%)	12.9 (9.25-17.55)	1.79 (1.06-10.57)	10.81 (1.67-15.5)	$p < 0.05$, respectively

*macrophage immune staining

Abstract summary

In preclinical animal models, when compared with GnRH antagonists, GnRH agonists have an increased risk of causing plaque instability. These findings may explain the higher cardiovascular risk in prostate cancer patients treated with GnRH agonists.

2. Risk of cardiovascular events in prostate cancer patients treated with an LHRH agonist versus an LHRH antagonist

While not all studies have found an association between ADT use and increased risk of cardiovascular disease in patients with prostate cancer with no comorbidities or a single coronary artery disease risk factor, there is a significant association between ADT and an increased risk of all-cause mortality among men with a history of coronary artery disease-induced congestive heart failure or myocardial infarction.¹⁹

Nilsson and colleagues²⁰ performed a pooled analysis of phase 3 trials of 1737 men (1118 men without prior cardiovascular disease and 619 men with a history of cardiovascular disease at baseline) to evaluate the risk of cardiovascular events in men with prostate cancer who received ADT (LHRH agonists or degarelix) for longer than 6 months.

They stratified the risk of cardiovascular events according to baseline cardiovascular disease risk factors and severity. Baseline cardiovascular disease, if present, was classified as severe (confirmed coronary or cerebral event and/or surgical intervention) or non-severe (e.g. myocardial ischemia or coronary artery disease not considered severe).

A cardiovascular event was defined as an arterial embolic or thrombotic event, a hemorrhagic or ischemic cerebrovascular condition, myocardial infarction, or other ischemic heart disease. A high-risk patient was defined as having two or more traditional cardiovascular disease risk factors.

Men with prostate cancer receiving ADT had an increased cardiovascular event rate if they had a history of severe cardiovascular disease and/or a high cardiovascular disease-risk status at baseline.

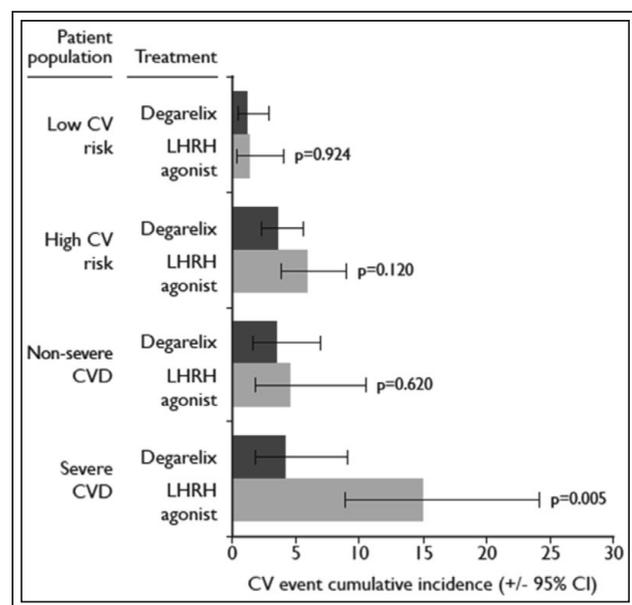


Figure 1. Cumulative incidence of cardiovascular (CV) events in patients with low or high CV risk and non-severe or severe cardiovascular disease (CVD), who were being treated with degarelix versus an LHRH agonist.²⁰

Abstract summary

In patients with a history of severe cardiovascular disease, degarelix treatment was associated with fewer cardiovascular events compared with LHRH-agonist

treatment. The cumulative incidence of cardiovascular events was 4.1 (95% CI: 1.6-8.3) with degarelix versus 14.7 (95% CI: 8.2-22.9) with an LHRH agonist ($p = 0.005$).

3. Primary androgen-deprivation therapy increases all-cause mortality in US registry study

Sammon and colleagues²¹ studied the relationship between primary androgen-deprivation therapy and all-cause mortality in a cohort of 46,376 elderly men residing in the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry areas. The patients had been diagnosed with localized or locally advanced prostate cancer and had undergone therapy. In this cohort, 17,873 men (39%) had received primary androgen deprivation therapy.

The effect of primary androgen-deprivation therapy on overall survival was assessed using a propensity score. The comorbidity-adjusted life expectancy was estimated, to account for the effect of the patient's illness on life expectancy.

A secondary analysis was performed on a contemporary population, using the D'Amico risk stratification.

Primary androgen-deprivation therapy was associated with a higher risk of all-cause mortality in the earlier cohort (HR 1.37; 95%CI: 1.20-1.56) and in the contemporary cohort (HR 1.48; 95%CI: 1.12-1.95).

Abstract summary

Primary androgen-deprivation therapy increases all-cause mortality in populations matched by comorbidity adjusted life expectancy and disease risk. This adverse effect was most evident in men with prolonged life expectancy (comorbidity-adjusted life expectancy > 10 years).

4. Cognitive changes in prostate cancer patients undergoing LHRH analog treatment

Morote and colleagues reported their findings from ANAMEM, an observational, prospective, multicentre, open-label study designed to evaluate cognitive performance at baseline and after 6 months of treatment with GnRH agonists, in a large cohort of patients with prostate cancer ($n = 384$; median age, 71 years).²²

The men's cognitive performance was evaluated using the following validated tests: the Digit Subtest of the Wechsler Adult Intelligence Scale (WAIS III-1), the Matrices (WAIS III-2) test, the Visual Memory test, the Line Orientation test (Woodward abridged version), and the Mental Rotation of Tridimensional Objects test.

Abstract summary

In the ANAMEM study, the cognitive performance of patients with prostate cancer was not significantly affected by 6 months of androgen suppression with GnRH agonists. Longer studies are needed.

5. Corticosteroid-associated adverse events with long term, low dose prednisone plus abiraterone acetate

Abiraterone acetate is a CYP17 inhibitor indicated in combination with prednisone to treat patients with metastatic castration-resistant prostate cancer. In vivo, abiraterone acetate is converted to abiraterone, an androgen biosynthesis inhibitor, which inhibits 17 α -hydroxylase and C17, 20-lyase, which are involved in androgen biosynthesis and mineralocorticoid production.

Miller and colleagues²³ investigated whether long term use of low dose prednisone with or without abiraterone acetate led to corticosteroid-associated adverse events.

The most common adverse events occurring in 0.1% to 0.4% of patients were cataract, type 2 diabetes, gastrointestinal hemorrhage, adrenal insufficiency, hip fracture, melena, and spinal osteoporotic compression fracture. Hyperglycemia occurred in 2% of patients.

Grade ≥ 3 corticosteroid-associated adverse events were seen in 1% to 2% of patients, and there was no long term (up to 30 month) trend in these events. There was also no long term increase in weight from baseline.

Abstract summary

Low dose prednisone given with or without abiraterone acetate is associated with an overall low incidence of corticosteroid-associated adverse events.

Summary

Owing to its overall safety and efficacy profile, GnRH therapy remains a first-line treatment for advanced hormone-sensitive prostate cancer.

While it is uncertain whether there is a link between ADT and an increased risk of a decline in cognitive function, the link between ADT and other side effects is well established. However, there are specific existing or evolving approaches to pre-empt and mitigate those side effects.

If not managed properly, in certain patients, an increased risk of cardiovascular disease may lead to an increased rate of all-cause mortality and thus negate the survival benefit associated with the use of ADT.

In men with metastatic castrate-resistant prostate cancer, long term use of low dose prednisone as monotherapy or in combination with abiraterone is linked with an overall low incidence of corticosteroid-associated adverse events.

In patients who may receive hormone therapy for prostate cancer, there is preclinical and clinical evidence that the GnRH antagonist degarelix is effective and maybe safer, with a lower incidence of cardiovascular events, than GnRH agonists, particularly in patients with previous cardiovascular disease risk factors.

Disclosure

This meeting review was supported by Ferring Pharmaceuticals Inc.

References

1. Carneiro A, Sasse AD, Wagner AA et al. Cardiovascular events associated with androgen deprivation therapy in patients with prostate cancer: a systematic review and meta-analysis. *World J Urol* 2014 Nov 12. Epub ahead of print.
2. Wilson AC, Meethal SV, Bowen RL, Atwood CS. Leuprolide acetate: a drug of diverse clinical applications. *Expert Opin Investig Drugs* 2007;16(11):1851-1863.
3. Klotz L, Toren P. Androgen deprivation therapy in advanced prostate cancer: is intermittent therapy the new standard of care? *Curr Oncol* 2012;19(Suppl 3):S13-S21.
4. Steinberg M. Degarelix: a gonadotropin-releasing hormone antagonist for the management of prostate cancer. *Clin Ther* 2009; 31(Pt 2):2312-2331.
5. Van Poppel H. Evaluation of degarelix in the management of prostate cancer. *Cancer Manag Res* 2010;2:39-52.
6. Alibhai SM, Mohamedali HZ. Cardiac and cognitive effects of androgen deprivation therapy: are they real? *Curr Oncol* 2010;17 (Suppl 2):S55-S64.
7. Smith MR, Finkelstein JS, McGovern FJ et al. Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metab* 2002;87(2):599-603.
8. Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. *Urology* 2004;63(4):742-745.
9. Lee H, McGovern K, Finkelstein JS, Smith MR. Changes in bone mineral density and body composition during initial and long-term gonadotropin-releasing hormone agonist treatment for prostate carcinoma. *Cancer* 2005;104(8):1633-1637.
10. Yannucci J, Manola J, Garnick MB, Bhat G, Bublely GJ. The effect of androgen deprivation therapy on fasting serum lipid and glucose parameters. *J Urol* 2006;176(2):520-525.
11. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. *J Clin Endocrinol Metab* 2006;91(4):1305-1308.
12. Alibhai SMH, Duong-Hua M, Sutradhar R et al. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. *J Clin Oncol* 2009;27(21):3452-3458.

13. Braga-Basaria M, Dobs AS, Muller DC et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *J Clin Oncol* 2006;24(24):3979-3983.
14. Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. *Eur Urol* 2014; 65(3):565-573.
15. O'Farrell S, Sandstrom K, Garmo H et al. Risk of thromboembolic disease in men with prostate cancer undergoing androgen deprivation: Follow-up study in PCBaSe Sweden. EAU 2015, Madrid Spain, Abstract 561.
16. Nguyen PL, Alibhai SM, Basaria S et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur Urol* 2015;67(5):825-836.
17. Levine GN, D'Amico AV, Berger P et al. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *CA Cancer J Clin* 2010;60(3):194-201.
18. Knutsson A, Hsiung S, Celik S, Wigren M, Nilsson J, Hultgårdh- Nilsson A. Treatment with an LHRH agonist, but not the LHRH antagonist degarelix, induces atherosclerotic plaque instability in ApoE^{-/-} mice. EAU 2015, Madrid Spain, Abstract 558.
19. Nanda A, Chen MH, Braccioforte MH, Moran BJ, D'Amico AV. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. *JAMA* 2009;302(8):866-873.
20. Nilsson J, Borre M, Bosnyak Z, Malmberg A, Davey P, Neijber A. Association between baseline cardiovascular (CV) status and the development of CV events in prostate cancer (PCa) patients treated with luteinizing hormone-releasing hormone (LHRH) agonist versus antagonist: Results of a pooled analysis. EAU 2015, Madrid Spain, Abstract 559.
21. Sammon JD, Abdollah F, Reznor G et al. Primary androgen deprivation therapy increases all cause mortality in populations matched by comorbidity adjusted life expectancy and disease risk. EAU 2015, Madrid Spain, Abstract 560.
22. Morote J, Tabernero A, Ledo MJ et al. ANAMEM: Prospective and observational study to evaluate cognitive changes in prostate cancer patients undergoing luteinizing hormone-releasing hormone analogue treatment. EAU 2015, Madrid Spain, Abstract 566.
23. Miller K, Chi K, De Bono JS et al. Assessment of corticosteroid (CS)-associated adverse events (AEs) with long-term (LT) exposure to low-dose prednisone (P) given with abiraterone acetate (AA) to metastatic castration-resistant prostate cancer (mCRPC) patients (pts). EAU 2015, Madrid, Spain, Abstract 564.