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# The primary care physician's role in the monitoring and management of the potential sequelae of the medical treatment of prostate cancer: early and late

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*Significant progress has been made in the management of aggressive prostate cancer. The established old and new treatments have resulted in the significant delay in progression of disease, improvement of the quality of life, as well as the increase in the overall survival of men*

*with advanced prostate cancer. However, these therapies carry with them possible adverse effects that primary care physicians are experienced in managing. Thus, there is an increasing need for the urologist to involve and partner closely with the primary care practitioner to prevent, identify and manage the potential side effects of these life-changing therapies.*

**Key Words:** prostate cancer, medical treatment, castration resistant prostate cancer

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## Introduction

Prior to 2010, there were only two therapeutic strategies for patients with advanced prostate cancer who fail surgery and/or radiation: blockers of testicular testosterone synthesis and docetaxel chemotherapy. The traditional approach of androgen suppression was with the use of luteinizing hormone-releasing hormone (LHRH) agonist/antagonist injection therapy with or without oral anti-androgen (or orchiectomy) in order to achieve castrate levels of serum testosterone, defined as < 50 ng/dL.<sup>1</sup>

New evidence has shown that androgen precursors in the tumor cell microenvironment may be converted to testosterone and dihydrotestosterone (DHT). Castration resistant prostate cancer (CRPC) tumor cells may also increase the production of androgens de novo to fuel their growth.<sup>2-4</sup>

While traditional and recently approved therapies for advanced prostate cancer can improve quality of life as well as progression-free and overall survival, treatment related adverse events have been documented; therefore, it is important for urologists to work closely with their patients' primary care physicians to monitor treatment response, as well as the physical and biochemical side effects of the therapies.

## Androgen deprivation therapy (ADT)

There is an increasing number of published studies demonstrating an association between ADT and an increased risk of myocardial infarction, cerebrovascular accident, sudden cardiac death, QTc prolongation, diabetes mellitus, and metabolic syndrome.<sup>5</sup> Patients on ADT are encouraged to engage in physical exercise daily and maintain a healthy weight. Where appropriate, patients might benefit from statin, glucose-lowering, anti-hypertensive, and/or anti-platelet therapy.<sup>6</sup> It has become very important for the family doctor to be

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informed when these often older patients are placed on LHRH therapy. This therapy as previously stated can cause or aggravate the conditions as defined as part of the metabolic syndrome. They should also be reminding and encouraging the patient to be compliant with their regular ingestion of calcium and vitamin D.

Studies suggest that the LHRH antagonist degarelix (Firmagon) may offer the advantage over LHRH agonists such as leuprolide for reducing the risk of cardiovascular events in men with pre-existing cardiovascular disease; therefore, patients with pre-existing cardiovascular conditions requiring ADT should perhaps be preferentially treated with degarelix.<sup>7,8</sup>

Recently, Sun et al reported a study that assessed the adverse effects of ADT for prostate cancer delivered as gonadotropin-releasing hormone (GnRH) agonists or bilateral orchiectomy. Patients treated surgically had a significantly lower risk for any fracture, peripheral arterial disease, and cardiac complications than those treated medically. There was no difference in the rate of diabetes or cognitive disorders between the two groups initially, but the risk for diabetes increased in those taking GnRH agonists for greater than 35 months. The authors concluded that for patients with prostate cancer requiring ADT, medical treatment with GnRH agonists carried higher risks of significant complications than surgical treatment with bilateral orchiectomy.<sup>9</sup>

Recent studies have also suggested a link between ADT and cognitive impairment,<sup>10</sup> Alzheimer's,<sup>11</sup> and acute kidney injury.<sup>12</sup>

### Castration resistant prostate cancer (CRPC)

The term CRPC emphasizes the resistance of the prostate cancer to castration levels of testosterone (typically resulting in a serum testosterone level of less than 50 ng/dL).<sup>13</sup> Recently, there has been significant

advances in the pharmacologic management of CRPC, Table 1. By definition, CRPC refers to the patient on hormone therapy to keep the testosterone levels castrate, who exhibits a rising prostate-specific antigen (PSA) with or without evidence of progression of disease as shown by local extension and/or soft tissue or bony metastases. Presently, there is no recommended treatment if there is no evidence of spread. These patients should be monitored frequently, depending on the PSA doubling time, with repeat bone scans or CT scans to detect the earliest evidence of progression.

Traditionally, the treatment of metastatic CRPC was with the oral agents ketoconazole and/or prednisone. Previously, if these agents failed, the management primarily would have been with intravenous taxotere (docetaxel-chemotherapy). There have been some innovative approaches to re-attacking the androgen receptor through new testosterone suppressors. In the "pre-chemotherapy space", we now have the oral agent abiraterone (Zytiga) plus prednisone (5 mg PO bid or 10 mg PO daily) or enzalutamide (Xtandi). Benefits from these new hormonal agents are demonstrated by improvements in quality of life (reduced pain/fatigue, increased physical/emotional well-being, and decreased/delayed skeletal related events), and overall patient survival.<sup>13</sup>

#### *Abiraterone acetate (Zytiga)*

Abiraterone acetate (1000 mg PO daily) is an irreversible and specific steroidal inhibitor of CYP17 (P450c17), and is a novel inhibitor of androgen synthesis uniquely blocking testosterone production in the testes, adrenal glands, and intra-tumoral prostatic tissue.<sup>14</sup> This drug exerts its action high up in the steroidogenesis pathway by blocking the production of other steroids; consequently, there is a need for the concomitant use of oral prednisone 10 mg daily.

TABLE 1. Recent advances in castration resistant prostate cancer treatment

- Autologous active cellular immunotherapy
  - \* Sipuleucel-T (Brand name: Provenge) [not available in Canada]
- Semi-synthetic taxane
  - \* Cabazitaxel (Brand name: Jevtana)
- Androgen biosynthesis inhibitor
  - \* Abiraterone acetate (Brand name: Zytiga)
- Androgen receptor inhibitor
  - \* Enzalutamide (Band name: Xtandi)
- Alpha-emitting radiopharmaceutical
  - \* Radium 223 dichloride (Brand name: Xofigo)

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The most common side effects of abiraterone include elevations in triglycerides and cholesterol, liver function tests (LFTs), fatigue, musculoskeletal pain, abnormal electrolyte(s), edema, constipation, and hot flashes. Severe hepatotoxicity has been reported in approximately 7% of patients and is more common in patients with abnormal LFTs at baseline. Most cases of hepatotoxicity appear to be reversible after discontinuation of abiraterone.

Case reports of myopathy and rhabdomyolysis occurred generally within the first month of treatment and resolved following drug discontinuation. Mineralocorticoid effects, which include hypertension, fluid retention and hypokalemia, are commonly reported. Patients on prednisone may require an increased dose of a corticosteroid before, during and after stressful conditions, such as surgery, trauma or severe infections. There were slightly more cardiac events (mainly grade 1/2) reported in the abiraterone group (11%-16%) than in the placebo group (7%-14%).

### *Enzalutamide (Xtandi)*

Enzalutamide (160 mg PO daily) is a very potent androgen receptor inhibitor which competitively inhibits the binding of androgen to the receptor.<sup>15</sup>

The most common side effects for enzalutamide include fatigue, musculoskeletal pain, rise in LFTs, diarrhea, androgen deprivation symptoms, edema, headache, hypertension, dizziness and insomnia.

Enzalutamide is associated with an increased risk of seizure, especially at doses above 160 mg. The lowering of the seizure threshold may be due to enzalutamide and its active metabolite crossing the blood brain barrier and inhibiting GABA gated chloride channel activity. Treatment-emergent hypertension should be managed appropriately. Posterior reversible encephalopathy syndrome (PRES) has been reported rarely, with and without associated hypertension. Enzalutamide should be discontinued in patients who develop PRES. Increases in non-pathological fractures and falls were observed as compared to placebo. Concomitant neurological symptoms or presyncope were rarely reported with the falls.

Caution should be exercised in the following patient populations: history of significant cardiovascular disease, QT prolongation, risk factors for Torsades de Pointes, and/or medications known for QT prolongation. Caution should also be exercised in those with either a history of seizures or those who have known risk factors for seizures (e.g., brain injury with loss of consciousness, recent TIA, CVA, brain metastases, and/or medications that lower the seizure threshold).

Enzalutamide may cause neuropsychiatric events such as cognitive or memory impairment, seizures, hallucinations, etc. Patients should take caution and avoid tasks in which mental impairment or loss of consciousness may harm themselves or others. Monitor INR levels closely for patients on warfarin.

### *Potential drug-drug interactions*

Abiraterone is mainly metabolized by CYP3A4 and SULT2A1. The drug moderately inhibits CYP2C9, 2C19 and P-glycoprotein in vitro (may not be clinically significant), and is a potent CYP1A2 inhibitor (no observed increase in systemic theophylline exposure), potent CYP2D6 and CYP2C8 inhibitor in vitro; therefore, exercise caution with concomitant use of CYP2C8/1A2 substrates and monitor closely.<sup>16</sup>

Enzalutamide is an inducer and inhibitor of several CYP isoenzymes and susceptible to many drug interactions. Since the half-life of enzalutamide is 5.8 days, the effects on enzymes may persist for one month or greater after stopping the drug.<sup>17</sup>

Table 2 summarizes the potential drug-drug interactions of these two new hormonal agents with other commonly prescribed drugs.<sup>18</sup>

### *Other novel compounds used in mCRPC*

#### *Radium 223 dichloride (Xofigo)*

Radium 223 dichloride is a therapeutic alpha particle-emitting pharmaceutical and targets bone metastases by acting as a calcium mimetic. It naturally targets new bone growth in and around bone metastases, and has been shown to reduce skeletal complications. Radium 223 is indicated for the treatment of patients with CRPC with symptomatic bone metastases and no known visceral metastatic disease.<sup>19</sup>

This radiopharmaceutical is excreted by the small intestine. The most common side effects include nausea, diarrhea, vomiting, edema, and bone marrow suppression (notably thrombocytopenia, neutropenia, leukopenia and pancytopenia).

#### *Denosumab (Xgeva)*

Denosumab (120 mg SC q monthly) is indicated for reducing the risk of developing skeletal-related events in patients with bone metastases from prostate cancer. This agent is a fully human IgG2 monoclonal antibody which inhibits osteoclast formation, function and survival, thus decreasing bone resorption and interrupting cancer-induced bone destruction. Patients being treated with denosumab should not be treated concomitantly with bisphosphonates.<sup>20</sup>

TABLE 2. Potential drug-drug interactions of abiraterone and enzalutamide with other commonly used drugs<sup>18</sup>

Rank 2010	Brand name	Generic name	Abiraterone interactions	Abiraterone comments	Enzalutamine interactions	Enzalutamine comments
1/11	Lipitor/ apo-atorvastatin	Atorvastatin	No significant interactions		Avoid/use alternative	Avoid combo or monitor closely: combo may decr. statin levels, efficacy (hepatic metab. induced)
5	Teva-amoxicillin	Amoxicillin	No significant interactions		Caution advised	Combo may incr. risk of seizures (additive effects)
6	Nexium	Esomeprazole	No significant interactions		Avoid/use alternative	Combo may decr. esomeprazole levels, efficacy (hepatic metab. induced)
7	Teva-venlafaxine XR	Venlafaxine	No significant interactions		Caution advised	Combo may incr. risk of seizures (additive effects)
23	Adalat XL	Nifedipine	No significant interactions		Monitor/modify therapy	Monitor BP: combo may decr. calcium channel blocker levels, efficacy (hepatic metab. induced)
26	Ratio-oxycocet	Oxycodone (acetaminophen)	No significant interactions		Avoid/use alternative	Avoid combo or consider oxycodone dose adjustment: combo may decr. oxycodone levels, efficacy (hepatic metab. induced)
27	Tylenol with codeine #3	Codeine (acetaminophen)	Caution advised	Combo may decr. codeine efficacy (hepatic conversion to morphine decr.)	No significant interactions	
33/44	Taro-warfarin/ coumadin	Warfarin	No significant interactions		Avoid/use alternative	Avoid combo or monitor INR: combo may decr. warfarin levels, efficacy (hepatic metab. induced)
36/48	Teva-metoprolol/ apo-metoprolol	Metoprolol	Caution advised	Combo may incr. metoprolol levels, risk of adverse effects (hepatic metab. inhibited)	No significant interactions	
39	Flomax CR	Tamsulosin	Caution advised	Combo may incr. tamsulosin levels, risk of adverse effects (hepatic metab. inhibited)	No significant interactions	
41	Apo-prednisone	Prednisone	No significant interactions		Caution advised	Combo may decr. corticosteroid levels, efficacy (hepatic metab. induced)

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Denosumab can cause symptomatic hypocalcemia. Symptoms and signs of severe hypocalcemia include altered mental status, tetany, seizures and QTc prolongation. Pre-existing hypocalcemia should be corrected prior to initiating therapy. While on therapy, calcium levels should be monitored prior to the initial dose of denosumab, within 2 weeks after the initial dose, and if suspected symptoms of hypocalcemia occur. Administer adequate calcium and vitamin D, and magnesium, as necessary.

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with denosumab. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. The incidence of ONJ was higher with longer duration of exposure. Poor oral hygiene, invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), treatment with anti-angiogenic medication, local gum or oral infection are considered risk factors for ONJ in patients receiving denosumab. Other risk factors for ONJ include infections, older age, concomitant therapies (e.g., chemotherapy, corticosteroids, radiotherapy to the head and neck), smoking, and previous treatment with bisphosphonates.

An examination of the oral cavity should be performed by the prescriber prior to initiation of denosumab treatment, and a dental examination with appropriate preventive dentistry is recommended prior to treatment with denosumab, especially in patients with risk factors for ONJ. Good oral hygiene practices should be maintained during therapy. Patients should receive routine dental assessments, and immediately report any oral symptoms such as dental mobility, pain or swelling. While on treatment, patients should avoid invasive dental procedures.

## Summary

We have made tremendous advances over the last 70 years in managing first castration responsive and now CRPC. These old and new therapies have performed tremendously well in delaying the progression of disease, improving the quality of life, and increasing the survival in a significant number of men suffering from aggressive prostate cancer.

As with any therapy that alters the normal biochemistry and physiology of a man, there is a risk of potential side effects. Some of these adverse effects may aggravate the co-morbidities that the patient is already exhibiting or cause problems that the primary care

physician is experienced in identifying and treating. The primary care practitioner is also well versed in managing the potential drug-drug interactions.

Even though the possible adverse effects of established as well as newer pharmacologic therapies in advanced prostate cancer are relatively infrequent, there is an increasing demand for the urologist to inform and partner closely with the primary care physician to prevent, identify and assist in the management of the potential side effects of these life altering therapies.

## Disclosure

Dr. Victor Mak has received speakers honoraria for Abbott, Abbvie, Actavis, Allergan, Amgen, Astellas, AstraZeneca, Ferring, Janssen, Norrizon, Novartis, Pfizer, and Sanofi.

Dr. Jack Barkin is a speaker and investigator for Glaxo, Actavis, Pfizer, Astellas, Merus Labs, Allergan, Janssen, Ferring, NeoTract and Merck. □

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