Hormone-refractory prostate cancer: a primer for the primary care physician

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Objective: *To provide a current and evidence-based clinical review of practical value to primary care physicians encountering men with hormone-refractory prostate cancer (HRPC) in their practice.*
Methods: *Evidence-based narrative review by two expert clinicians incorporating results of systematic reviews and randomized trials whenever available.*
Results: *HRPC represents the final common pathway to death from prostate adenocarcinoma, the single most prevalent cancer in Canadian men. However, primary care physicians will not encounter these patients with a frequency adequate to develop confidence in their care. HRPC is defined by progressive disease despite castration, and biologically is a characterized by androgen hypersensitivity. It is important to understand that HRPC is a disease spectrum ranging from asymptomatic patients with only a rising prostatic-specific antigen (PSA) level and a prognosis measured in years to extremely symptomatic patients with widespread metastases requiring end-of-life care. Numerous effective management options are now available for HRPC and are selected based on the phase of the disease natural history, and patient comorbidities and preferences.*
Conclusions: *Men with HRPC have therapeutic options that can improve and maintain both the quality and quantity of their lives. A co-management approach including a medical oncologist and the patient's urologist and primary care physician is preferred.*

Key Words: prostatic neoplasms, drug therapy, review, radiotherapy, metastases

Prostate adenocarcinoma (prostate cancer) is the single most common serious cancer diagnosed in Canadian men. A high survival rate means that prostate cancer survivors comprise 0.8% of the male population.[1] With marked heterogeneity in the natural history of prostate cancer, and the availability of multiple treatment options, the task of providing care and counsel to men with the disease presents a growing challenge. Primary care physicians have the opportunity to play a central role in prostate cancer management. This can range from advice on screening, counseling about treatment options, through to administration of androgen deprivation therapy (ADT), managing adverse effects of treatment, and palliative care.

Although most men diagnosed with prostate cancer will be cured, or die of competing causes, approximately 20%-25% of men will die from their cancer. Hormone-refractory prostate cancer (HRPC) is the final common pathway to death from prostate cancer, and will be the focus of this review. Although a primary care physician may see many men with prostate cancer, the number of patients with HRPC an individual physician may see in their practice will likely be small. This review aims to provide primary care physicians with a summary of the approaches taken by oncologists in the management of these patients. Every effort is made to shape management guidelines from the best available evidence, including

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randomized trials and systematic reviews where available. However, where high-quality studies are lacking, the opinions expressed may reflect the biases of the author based on experience and interpretation of the available evidence—so *caveat lector*!

Pathophysiology

Although some cancer patients die from complications of local recurrence, in the vast majority death is due to the effects of distant metastases. This is also true for prostate cancer, though it remains a puzzle why some prostate cancers are cured with local treatment, while others metastasize. High tumor grade (the Gleason grading system is used most commonly), high pretreatment blood prostatic-specific antigen (PSA) level, and a more advanced tumor (T) stage may provide clues to an increased risk of eventual distant recurrence. However, these predictors are limited in their ability to provide an estimate of the risk of prostate cancer death for any individual patient.

The availability of PSA testing has transformed our understanding of the natural history of prostate cancer over the past 20 years. Most of this effect is due to the clinical "lead time" that an elevated PSA test provides. Historically, men were diagnosed with the disease on tissue examination following transurethral resection (TUR) of the prostate based on the presence of symptoms. In the modern era, men are most commonly diagnosed with prostate cancer by elevated PSA, in the absence of symptoms or palpable disease. Similarly, recurrent disease is most often identified based on an elevated or rising PSA, rather than by symptoms or clinical detection of metastases.

The identification of such PSA or "biochemical" recurrence is often the trigger to initiate androgen deprivation therapy (ADT). Reduction in circulating androgens is achieved by chemical castration with depot luteinizing hormone releasing hormone [LHRH] agonists, or less commonly, with bilateral orchidectomy. ADT is highly effective at reducing PSA levels, as well as relieving the signs and symptoms of metastatic disease. The duration of cancer control is associated with the degree of PSA drop while on ADT.[2] However, ADT is not curative, and progression of cancer is inevitable in all patients that survive comorbid conditions. Typically, progression is first identified as a persistently rising PSA despite ADT.

Such progression represents the first indication of the emergence of "hormone resistant" or "androgen independent" prostate cancer that will ultimately lead to hormone-refractory prostate cancer (HRPC). Although widespread in use, these terms are misnomers. Recent studies point to the progression of prostate cancer in the castrate state as being caused by the emergence of cancer cells that have become hypersensitive to extremely low levels of circulating and intracellular androgens.[3] It remains controversial whether the cells giving rise to these subclones arise spontaneously via mutations, or are present in the earlier stages of the prostate cancer. ADT does not completely eliminate androgen production; the adrenal glands continue to produce androstenedione and dehydroepiandrostenedione, which can activate the androgen receptor. A strong parallel exists in postmenopausal breast cancer, where despite very low levels of sex hormones, hormone-receptor expressing cancer cells remain able to proliferate and potentially thrive, and may respond to further hormonal and non-hormonal interventions.

Clinical assessment

Hormone-refractory prostate cancer is most commonly diagnosed at an asymptomatic stage, with the identification of consistently rising PSA levels in a man with a history of recurrent disease who has been receiving ADT. However, men with HRPC can present anywhere along the spectrum of their natural history, from those with no symptoms or clinical findings, to men with symptomatic disseminated metastases, Figure 1.

When evaluating a patient with suspected HRPC, a history of the prostate cancer and its treatment including current and past use of hormonal therapies should be reviewed. As the natural history of prostate cancer can be lengthy, this can often be complex.

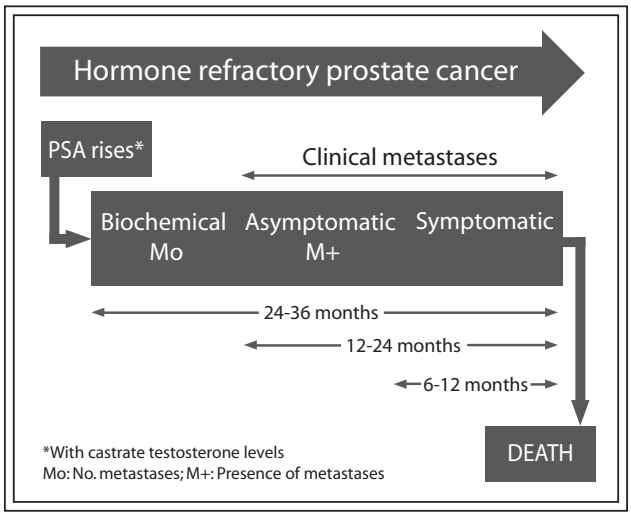

Figure 1. Progression of advanced prostate cancer.

A history of concurrent medical problems should be obtained, as prostate cancer typically affects older men whose comorbidities may influence the treatment options available to them.

Review of systems should include the identification of local and systemic symptoms. Prostate cancer has a proclivity to metastasize to bone and lymph nodes. Focal symptoms include pain, lower urinary tract symptoms, and leg edema. Systemic symptoms such as weight loss, fatigue, and anorexia should be identified, and often reflect a greater disease burden. Often, changes in a patient's activities or behavior patterns can provide clues to the impact of their cancer. Men with HRPC typically die from the systemic effects of their increasing cancer burden, typified by wasting, bone marrow failure, and immunosuppression rather than critical organ failure. The onset of these may be insidious. Rarely, men with HRPC may develop lung or liver metastases. Finally, some patients develop uncontrolled pelvic recurrence, which becomes the major challenge in treating and controlling their cancer.

Physical examination should include inspection for anemia and jaundice, and examination of the lymph nodes areas in the neck, axillae, and groins. Patients receiving chemotherapy may be alopecic. Palpation or percussion of the spine and costovertebral areas may provide clues to bone metastases or hydronephrosis. If the history is unclear regarding bilateral orchidectomy, scrotal examination should be performed. Digital rectal examination to assess for local recurrence at baseline and in the presence of new or worsening lower urinary tract or rectal symptoms is mandatory. The lower extremities should be examined for edema which may be a clue to intra-abdominal or pelvic lymphadenopathy, pelvic mass or deep venous thrombosis. If symptoms suggestive of spinal cord compression, radiculopathy, or focal neurological deficit are present, a focused neurological examination should be performed.

As biochemical (PSA) or clinical progression in the presence of a castrate testosterone level is the *sine qua non* of HRPC, the serum testosterone level should be checked to confirm that the patient's androgen levels are adequately suppressed. This is unnecessary in men treated with bilateral orchidectomy. Anemia is common in men with HRPC, and renal obstruction not uncommon, hence laboratory investigations should include a complete blood count and routine biochemistry including creatinine, bilirubin, and liver enzymes in addition to the PSA. Patients receiving chemotherapy may be neutropenic, and if this suspected a differential white blood cell count should be included. Rarely, disseminated intravascular coagulation can occur; if bleeding stigmata are present, INR, PTT, and fibrinogen level should be checked. Despite the high frequency of bone metastases, hypercalcemia is extremely rare in HRPC.

Usually a routine chest radiograph and whole bone scintigraphy are adequate for restaging. However, the suspicion of intra-abdominal disease generated by symptoms such as unexplained leg edema or abdominal pain may justify investigation with an abdominopelvic computed tomographic (CT) scan. Intractable back pain, leg weakness, or sensory loss in a patient with known bone metastases should prompt urgent magnetic resonance imaging of the spinal cord to rule out spinal cord compression. The high incidence of neurological impingement in HRPC and need for early intervention justify this practice.[4]

Symptom palliation

Symptom control is the first and essential step in managing the patient with metastatic HRPC, Figure 2. Pain is the most important symptom, and the timely use of appropriate non-narcotic and narcotic analgesics titrated to adequately control pain is essential for optimal palliation. Men with prostate cancer are often older and may have other medical conditions which complicate the choices of analgesics.[5] Aggressive prophylaxis of constipation is essential if narcotics are used, as fear of this complication often affects analgesic adherence. When stronger analgesics are required, use of hydromorphone may be preferable to morphine in older patients, or those with impaired renal function, to minimize adverse effects.

Short course external beam radiotherapy may be highly effective for focal areas of bone pain, and is also used for treatment of neurological impingement

Maintain androgen suppression (< 0.7 nmol/l)

If no metastases or symptoms consider:

- Antiandrogen withdrawl and observation
- Secondary hormonal manipulation
- Experimental therapy

Optimize symptoms (analgesics, focal RT)

Prophylactic zoledronic acid

Docetaxel-based chemotherapy

Palliative RT, radio-isotopes, bisphosphonates

Figure 2. Approach to HRPC.

syndromes. Multifocal pain, or pain in previously radiated areas may require consideration of systemic therapies. Lymphedema typically does not improve and may even worsen if treated with radiotherapy and drug therapy. Conservative measures such as elevation and compression may be required. Renal obstruction may require TUR, ureteric stents, or even percutaneous nephrostomy tubes. Chronic fatigue and anorexia are harder to treat. Anemia due to cancer may require packed red cell transfusion or a trial of erythropoietic stimulating agents. Through communication with a patient's oncologist and urologist, the primary care physician can not only identify the need for these palliative interventions, but can also contribute to the delivery and management of treatment in all of these scenarios.

The development of rising PSA levels despite ADT can be alarming to a man used to the regular reassurance of an unchanged PSA. The primary care physician can play an important role in education, counseling, and support to decrease the anxiety and fear that often accompany entry into this ultimately incurable phase of prostate cancer.

Secondary hormonal manipulations

It is a tenet of palliative medicine to use the most effective and least toxic interventions first, and this remains the most compelling argument for trials of secondary hormonal manipulations in men with HRPC. Although there is no data from randomized trials, current practice is to maintain ADT despite the presence of disease progression. Discontinution of LHRH agonist therapy may lead to the recovery of gonadal function and a rise in serum testosterone levels, which may stimulate prostate cancer growth. Androgens have antiapoptotic effects on prostate cancer cells in animal models, and this may contribute to reduced effectiveness of radiotherapy and chemotherapy in the clinic.[6] Case reports of this phenomenon have been reported.[7]

For patients with asymptomatic PSA progression on testicular ADT alone, the addition of an oral antiandrogen is a simple and often effective intervention. Nonsteroidal antiandrogens are preferred since they are more effective in combination with gonadal ADT, as identified in a meta-analysis of complete androgen blockade in men with metastatic prostate cancer when compared to steroidal antiandrogens (e.g. cyproterone acetate).[8] These data are considered generalizable to the hormone-refractory setting. Several nonsteroidal antiandrogens are available (flutamide, nilutamide, and bicalutamide), with bicalutamide considered the optimal choice by most clinicians, based on the convenience of once daily dosing and the most favorable toxicity profile. There is little evidence that switching between these agents, if PSA progression has occurred on one, is beneficial.

For patients receiving treatment with complete androgen blockade (LHRH agonist or bilateral orchidectomy plus oral antiandrogen) who are experiencing cancer progression, discontinuation of the oral antiandrogen may result in a drop in PSA levels and even symptomatic response.[9] This "antiandrogen withdrawal" phenomenon is incompletely understood, but may result from the acquisition of androgen receptor mutations over time and exposure to antiandrogens that may paradoxically stimulate the androgen receptor.[10] As a result, discontinuation of the antiandrogen in effect results in a secondary androgen deprivation effect. However, this phenomenon is typically seen only in patients with prolonged continuous antiandrogen exposure, and is rare in patients only briefly exposed (i.e. less than 2 years). Nevertheless, obvious disease progression on antiandrogen therapy justifies discontinuation of these agents whether antiandrogen withdrawal is anticipated and observed or not.

For patients progressing on oral antiandrogens, therapeutic options include observation, low dose corticosteroids with or without ketoconazole, and investigational agents. The value of corticosteroids in this setting lies in their ability to suppress adrenal androgen production through suppression of ACTH. A PSA response of 21% and subjective response of 56% were reported with prednisone 5 mg qid in one randomized trial.[11] Hydrocortisone and dexamethasone have each been used for this purpose, but typically prednisone 10 mg daily is prescribed in Canada. Few side effects are seen with this low dose; bruising of the forearms due to capillary fragility is common, while worsened glucose tolerance is far less common. Ketoconazole acts directly on gonadal and adrenal steroidogenesis to rapidly and completely inhibit androgen synthesis. Doses of 200 mg orally twice daily have been shown to achieve this, but doses up to 400 mg tid have been used based on hypotheses of direct anticancer effects. Typically ketoconazole is given along with corticosteroids to avoid hypoadrenalism, so the incremental benefits of ketoconazole over prednisone alone are difficult to discern. It is unclear if this if worthwhile in view of the serious potential toxicities of ketoconazole including hepatotoxicity. Men with early HRPC are often excellent candidates for clinical trials of investigational therapies, and this should not be forgotten as a treatment option.

Bisphosphonates

Primary care physicians are familiar with oral bisphosphonate drugs for the treatment of postmenopausal osteoporosis. Bisphosphonates are now commonly used in oncology, although typically more intensive intravenous dosing is used. Over 90% of men with HRPC eventually develop skeletal metastases, and their presence predisposes to skeletal-related events such as pain, pathological fracture, and neurological impingement. As skeletal metastases in prostate cancer tend to occur first in the axial skeleton, advancing disease can also result in cytopenias and ultimately bone marrow failure. The skeleton may also serve as a reservoir for a large burden of metastatic cells that contribute to systemic symptoms and wasting.

Zoledronic acid is the current standard treatment to prevent skeletal-related events in metastatic HRPC. The dose is 4 mg IV every 3 weeks and may require adjustment for renal dysfunction. Adverse effects are modest, but 5%-10% of patients experienced anemia, myalgia, lower limb edema, or dizziness with zoledronic acid in the randomized trial that established its benefits in HRPC.[12] Osteonecrosis of the jaws is a rare complication associated with bisphosphonate potency, duration, IV route of administration, and dental health.[13] Zoledronic acid is probably optimally used in men with demonstrated bone metastases and minimal pain (less than 30 mg morphine equivalent per day). The optimal duration of treatment is uncertain. Bisphosphonates may also have modest effects on bone pain in HRPC. Data from randomized trials suggests modest benefits of intravenous and oral clodronate, intravenous pamidronate, and intravenous zoledronic acid on pain in men with HRPC.[14] It is unclear if one agent is superior to others or to radiation for this indication. Radiotherapy, radioisotopes, and chemotherapy appear to have much greater effectiveness for the relief of pain in this setting, and should be considered first for pain relief along with optimized analgesic therapy.

Chemotherapy

Chemotherapy represents a safe, effective, and probably underutilized treatment option for appropriately selected men with HRPC. Typically mild single agents are used, and most treated men derive some degree of benefit with only mild or modest adverse effects. The use of chemotherapy for palliation of symptoms by disease control in HRPC is a relatively recent development in the oncology world. The delay in adopting use of chemotherapy related to the challenge of determining efficacy in the pre-PSA era. As most patients have bone predominant disease, objective assessment of "response" to treatment was difficult if not impossible. Ground breaking work by Ian Tannock at the Princess Margaret Hospital using palliative response (based on self reported pain and analgesic use) established mitoxantrone as a standard palliative agent for HRPC causing pain in the early 1990's.[15] The subsequent use of PSA to identify active drugs in HRPC has accelerated clinical research.

Docetaxel was first isolated from the needles of the European yew tree, and is currently used to treat many cancer types including those of the breast, lung, and head and neck. Docetaxel was identified as active in HRPC in the late 1990's, and has now become the standard first-line chemotherapy agent for HRPC. Docetaxel demonstrated higher palliative and quality of life response rates, as well as a modest improvement in overall survival, when compared to mitoxantrone in two large randomized trials.[16,17] The optimal timing of the initiation of chemotherapy remains a topic of debate. Currently, men without evidence of metastases should not be offered cytotoxic chemotherapy outside the setting of a clinical trial. Men with unequivocal symptoms should be considered candidates for a trial of docetaxel. In these authors' view, men with metastases, relatively indolent disease, and absent or minimal symptoms should progress through the steps outlined above (symptom palliation, secondary hormonal manipulations, bisphosphonates) prior to proceeding with a trial of chemotherapy. Immediate chemotherapy may be justified for men with metastases and very worrisome PSA kinetics, visceral organ involvement, or who are in failing health at the time they present for assessment. Even though disease progression has occurred on low dose prednisone and ADT, this author usually continues both throughout chemotherapy treatment, as the presence of even low levels of adrenal androgens may antagonize its apoptotic effects.

Barriers to the use of chemotherapy in men with HRPC include misinformation or fixed beliefs of patients and referring physicians, age bias of medical oncologists, and timely referral of patients. A standard approach after the failure of docetaxel remains to be defined, and is an active area of clinical research. Agents currently under study, and of potential future interest in HRPC, include cell-based immunotherapy (APC8015), drugs targeting tumor angiogenesis (bevacizumab and aflibercept), patupilone, the endothelin inhibitors atrasentan and ZD4054, and abiraterone (a selective cytochrome P450 inhibitor).

Radioisotopes

The bone predominance of metastatic HRPC in most patients makes the idea of a "therapeutic" bone scan appealing. Prior to the advent of palliative chemotherapy, hemibody irradiation was often used for palliation of pain in widely symptomatic bone metastases from HRPC. Beta-emitting bone-avid radioisotopes currently available in Canada include strontium-89 and samarium-153. Strontium-89 was observed to confer palliative benefits in a Canadian randomized trial, which has lead to recommendations for its use in men with HRPC.[18] Samarium-153 also has supportive data from randomized trials.[19,20] It has the advantages of less myelosuppression, making repeated treatments more feasible. Both therapies are limited by access, as they are only available at specific centers in Canada. As well, they currently are not preferred for use early in HRPC as they compromise bone marrow reserve, and increase the risk of serious and prolonged cytopenias if chemotherapy is subsequently administered. Radioisotopes are probably best for patients who are not suitable for or refuse chemotherapy, or have exhausted chemotherapeutic options and have diffuse bone pain or pain in previously radiated sites.

Conclusions

Primary care physicians are an important part of the health care team for men with HRPC. They provide familiarity, continuity of care, and an additional point of access to the health system that patients often need and value during their cancer journey. Unfortunately, primary care physicians may lose touch with their patients once they enter the cancer care system. Primary care physicians may also feel excluded due to their lack of familiarity with the disease process, and the increasingly complex and changing array of cancer treatments available for specific cancer types. It is hoped that this expert review can increase the level of comfort of primary physicians as participants in the care of patients with HRPC, by providing a succinct yet comprehensive guide to the natural history of the disease and the general approach to its treatment.

Disclosure

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DISCUSSION

Question (Dr. Greenberg):
What is prostate-specific antigen doubling time (PSADT) and does it have a role in treatment decision-making in HRPC?

Answer (Dr. Winquist):
A number of prognostic factors of potential value in HRPC have been identified including: hemoglobin, lactate dehydrogenase, and alkaline phosphatase levels; age, Gleason sum; performance status; the presence of visceral metastases; and the presence of pain. The total PSA level has not been demonstrated a reliable marker of survival in HRPC; however, the rate of PSA change may be. For example, a drop in PSA level by at least 30% from baseline by 3 months with docetaxel-based chemotherapy appears to be associated with a better prognosis. Shorter PSADTs have been associated with a shorter time to the development of bone metastases and survival in men with HRPC. The value of PSADT in HRPC depends very much on the disease context, and it should not be used in isolation to make treatment decisions. A rapidly shortening PSADT may be of particular value in assisting decisions in asymptomatic patients with and without metastases.

Question (Dr. Miner):
What is a prostate-specific antigen "flare" during chemotherapy for HRPC?

Answer (Dr. Winquist):
Theoretically, a "flare" refers to the apparent worsening of disease due to the initiation of therapy. For example, true "flare" of disease can occur with the initiation of LHRH agonist therapy for hormone-naïve metastatic prostate cancer. Rising PSA levels following chemotherapy may indicate true progressive disease, delayed response, or "marker flare" due to a surge of release of PSA from HRPC cells undergoing rapid apoptosis (an uncommon phenomenon). The pattern of PSA over time following chemotherapy may be highly variable, and the presence of a stable or rising PSA level does not exclude palliative benefits of treatment. Decisions about discontinuing or changing chemotherapy should not be based on serial PSA patterns alone, and never be based on isolated PSA values.