Symptom assessment to guide treatment selection and determine progression in metastatic castration-resistant prostate cancer: Expert opinion and review of the evidence

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Cite as: *Can Urol Assoc J* 2018;12(9):E415-20. http://dx.doi.org/10.5489/cuaj.5154

Published online May 14, 2018

Abstract

Multiple new agents to treat metastatic castration-resistant prostate cancer (mCRPC) have become available in recent years; however, the appropriate timing and sequencing of these agents have yet to be elucidated. Until accurate biomarkers become available to allow more focused therapeutic targeting for this population, treatment selection for men with mCRPC will continue to be driven largely by close assessment of patient-related factors and symptoms. Pain, as the predominant symptom of mCRPC, is often the focus when assessing progression and the need for a change in treatment. A myriad of other symptoms, including fatigue, impact on activities of daily living, sleep, and lower urinary tract symptoms, also affect men with mCRPC, and assessment of the composite of these symptoms provides an earlier signal for the need to adjust treatment. A number of tools are available for assessing symptoms in patients with advanced prostate cancer, but they are not routinely used, given their complexity and length. A new simplified questionnaire is proposed for the assessment of symptoms, beyond pain, to inform treatment decisions for men with mCRPC.

Introduction

Prostate cancer is the most common cancer among Canadian men, with approximately 21 300 new cases estimated in 2017. Approximately 10% of all male cancer deaths are attributed to prostate cancer, making it the third most common cause of cancer death in males.[1] While the majority of men with prostate cancer present with localized disease, 19–74% of men with prostate cancer will develop metastases within 10 years, depending on the grade of disease.[2] Initial treatment for advanced prostate cancer involves androgen-deprivation therapy (ADT), but progression of disease despite castrate testosterone levels, termed "castration-resistant prostate cancer" (CRPC), is inevitable. CRPC diagnosis is based on a continuous rise in serum levels of prostate-specific antigen (PSA), progression of pre-existing disease, the development of new metastases, or a combination of these features, despite treatment with ADT. If the diagnosis of metastatic CRPC (mCRPC) is delayed, symptoms may go unmanaged or be inadequately managed, impacting quality of life (QoL).

Pain, fatigue, functional impairment, and diminished health-related QoL (HRQoL) are important considerations in clinical decision-making for men with mCRPC.[3] Symptoms are often an indicator of disease progression in patients with advanced prostate cancer, and pain in particular is identified as an important indicator of overall survival in men with mCRPC.[4,5] The pain of prostate cancer is largely attributable to the high incidence of bone metastases, lumbosacral invasion, and nerve root compression.[6] Among men who develop metastatic disease, bone is most commonly involved, affecting an estimated 90% of this population.[7] Bone metastases are associated with increased mortality,[8,9] as well as increased disability, pain, and impaired QoL.[10-12] Up to half of patients with mCRPC will develop bone pain and other skeletal-related complications during the course of their disease, such as pathological fractures, spinal cord or nerve root compression, surgery to bone, or palliative radiation to bone.[7,13] Still, symptoms are often under-recognized and patients may be hesitant to communicate symptoms to their healthcare providers. A survey of 927 patients with advanced prostate cancer and 400 caregivers revealed that 99% of those with bone metastases experienced one or more symptoms and 73% of those with bone metastases noticed pain prior to diagnosis with advanced prostate cancer.[14] This suggests a need for improved guidance on symptom assessment in this patient population and a need for better understanding of the impact of symptoms on the lives of patients and their caregivers.

Before 2010, docetaxel was the only agent that demonstrated a survival benefit in men with mCRPC. Since then, the number of treatment options with survival benefits for mCRPC has exploded, with the development of cabazitaxel, abiraterone acetate, enzalutamide, and radium-223. The availability of multiple treatments for men with mCRPC within a short time span has led to unresolved questions around appropriate timing and sequencing of treatments. As a result, the type and severity of symptoms have become increasingly important considerations in individualized treatment plans, which also must consider type of metastases (bone/visceral), treatment history, response/progression on prior treatment (including ADT), performance status, comorbidities, potential side effects of the available therapies, and patient preferences. A number of tools are available for assessing symptoms in patients with advanced prostate cancer, but they are not used routinely given their complexity and length. To some extent, there is also a lack of awareness of available tools and their utility. Tools that facilitate effective communication between the clinician and patient (and caregiver) are necessary to ensure earlier symptom recognition and individualization of treatment to optimize QoL and outcomes.[14] Symptom assessment tools must not only provide useful information to guide treatment choices, but also be easy to use and interpret by the treating physician.

This article summarizes the opinions of the authors based on the current evidence and proposes a new simplified questionnaire for assessing symptoms in men with mCRPC.

Role of symptoms in guiding treatment selection

Despite the availability of a number of treatments with survival benefits in mCRPC — including docetaxel, cabazitaxel, abiraterone acetate, enzalutamide, and radium-223 — these treatments are not curative. The goal of treatment selection and sequencing is, therefore, to optimize QoL as well as survival. Many of the new agents for the treatment of mCRPC were developed simultaneously; therefore, head-to-head comparisons are lacking and the optimal sequencing and/or combination of these therapies remain unknown. In addition to the side-effect profiles of various treatments and provincial access issues, treatment selection is largely guided by the presence or lack of symptoms, performance status, and burden of disease, according to patient populations studied in the registration trials.[15-18] Table 1 summarizes the current treatment guidelines for the management of CPRC in Canada, based on the presence or absence of metastases and symptoms.

Chemotherapy

Docetaxel has been evaluated in the first-line treatment of both asymptomatic and symptomatic mCRPC.[19,20] The TAX-327 trial showed a significant survival benefit of docetaxel + prednisone compared with mitoxantrone,[19] and the SWOG 99-16 trial reported a survival benefit of docetaxel + estramustine over mitoxantrone.[20] Because of the toxic effects associated with the addition of estramustine and the lack of additional efficacy, docetaxel in combination with prednisone became the standard of care. However, 26% of patients in the TAX-327 trial experienced one or more serious adverse event and 11% discontinued treatment because of adverse events. Docetaxel is, therefore, generally reserved for patients with more symptomatic mCRPC, to provide both survival benefit and pain palliation.[15] In select cases, docetaxel may be offered in asymptomatic/minimally symptomatic men with evidence of metastases.[21] Consideration of docetaxel warrants a comprehensive discussion of the risks and benefits with an oncologist. A second chemotherapeutic agent, cabazitaxel, demonstrated an overall survival benefit compared with mitoxantrone following docetaxel treatment in the TROPIC trial.[22]

Androgen receptor (AR)-targeted hormonal therapies

The AR-targeted novel hormonal agents abiraterone acetate and enzalutamide were both evaluated as first-line agents in asymptomatic or minimally symptomatic patients with mCRPC.[23,24] The COU-AA-302 trial showed a significant improvement in both overall survival and radiographic progression-free survival with abiraterone acetate compared with placebo in 1088 men with mCRPC who had not received prior docetaxel treatment.[23] The PREVAIL study showed decreases in the risk of radiographic progression and death, and a delay in the need for chemotherapy with enzalutamide compared with

Table 1. Summary of treatment options for castration-resistant prostate cancer (CRPC)*†‡

CRPC without metastases	– Secondary hormonal therapy – Screen for metastases based on PSADT
mCRPC with minimal or no symptoms	– Abiraterone – Enzalutamide – Docetaxel
mCRPC with symptoms	– Docetaxel – Radium-223§
Post-docetaxel	– Abiraterone – Enzalutamide – Cabazitaxel – Radium-223§
In the presence of bone metastases	– Denosumab or zoledronic acid – Consider palliative radiation therapy if pain is present

*The optimal sequence of available options remains unknown. †Patients who have had little or no response to hormonal agents OR who progress with minimal change in PSA or with significant visceral metastases should be considered for early chemotherapeutic options. ‡Whenever possible, clinical trials should remain the first choice in patients with CRPC. §Radium-223 is not approved for patients with visceral metastases. mCRPC: metastatic CRPC; PSADT: prostate-specific antigen doubling time. Adapted from Saad F, et al. *Can Urol Assoc J* 2015;9:90-6.

placebo in 1717 chemotherapy-naive men with mCRPC.[24] Both of these studies enrolled men who were asymptomatic or mildly symptomatic, and the survival advantage of these agents has not been well-documented in patients with significant symptoms in the chemo-naive state.

Targeted alpha therapies

Radium-223, an alpha emitter, was studied in the ALSYMPCA trial, which enrolled 921 patients with bone-predominant, symptomatic mCRPC and no visceral metastases. Compared with placebo, radium-223 improved overall survival, time to first symptomatic skeletal event (defined as the first use of external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic vertebral or non-vertebral bone fractures, spinal cord compression, or tumour-related orthopedic surgical intervention), and QoL.[25] These results led to the approval of radium-223 in mCRPC patients with symptomatic bone metastases without evidence of visceral metastases.

Role of symptoms in defining progression and the need for a change in treatment

In addition to guiding original treatment selection, symptoms also play a key role in defining disease progression and determining whether a change in treatment is needed. Although a change in treatment is generally prompted by clinically significant progression, the definition of progression is variable and usually includes a composite of biochemical (i.e., a rise in PSA), radiographic (changes on computed tomography and bone scans), and symptomatic progression.[26] The clinical significance of changes to these parameters also varies, and it is not always clear when a change in therapy is warranted. For patients on chemotherapy or AR-targeted therapies, PSA progression is an important factor, but must be interpreted in combination with patient characteristics, such as age and performance status, as well as the remaining therapeutic options. The St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) Expert Panel has recommended stopping treatment if at least two of three criteria (PSA progression, radiographic progression, and clinical deterioration) are fulfilled, and changing treatment if there is significant clinical progression without a rise in PSA or radiographic progression.[27]

Radiographic progression and symptoms are also used to inform treatment decisions, depending on whether the primary goal of therapy is to prolong survival or to maintain QoL. For patients on radium-223, progression is determined largely by symptoms, and biomarkers such as alkaline phosphatase and lactate dehydrogenase may be more useful to monitor than PSA, as PSA response does not accurately predict extent of skeletal metastases or treatment effects on disease progression in bone.[28]

It should be noted that in Canada, the timing and sequence of treatment decisions are also shaped by different reimbursement policies in each province, such that access to some agents or specific sequences may be limited.

Symptom assessment in patients with mCRPC

Definition of "symptomatic"

Since symptoms play a role in guiding the treatment of men with mCRPC, accurate symptom assessment is important for this patient population. Unfortunately, there is currently no standard definition of "symptomatic." In the context of bone metastases, the majority of physicians define "symptomatic" by the presence of pain. Pain is the symptom that has consistently been associated with reduced survival in clinical trials; it is also the easiest to address and to focus on, as it is generally self-reported by the patient. However, defining and measuring pain can be challenging due to its subjective nature. Clinical trials have generally defined symptomatic according to medications taken by patients for pain, but many patients do not take any medications despite suffering from significant pain. Some may be reluctant to take opioid pain medications such as morphine due to side effects and perceived associations with addiction and terminal care. Furthermore, pain is only one symptom in a spectrum of symptoms that may reflect disease progression and have a negative impact on QoL. Advanced prostate cancer may also be associated with other symptoms, including fatigue, numbness or weakness, vomiting, loss of appetite, weight loss, lower urinary tract symptoms (LUTS), hematuria, cognitive changes, anxiety, and difficulty sleeping.[14,29] Complicating matters is that different stages of disease may be associated with the predominance of a different spectrum of symptoms.

A recent survey revealed several barriers preventing men from speaking with physicians about their prostate cancer symptoms.[14] More than one-third admitted difficulty talking about their pain and that doing so makes them feel weak. More than half stated that they do not always know whether their pain is related to their cancer. Many patients are reluctant to associate pain with progression of their cancer and try to relate symptoms to other causes (i.e., aging, arthritis, exertion, etc.); they therefore do not always report these symptoms to their physician. More than half of the patients surveyed felt that daily pain/discomfort is simply something they have to live with.[14]

Symptom assessment and monitoring

There are currently several symptom assessment tools available to evaluate symptoms in patients with advanced prostate cancer. Some are useful for understanding trends in research, while others are more useful in the clinical setting, to track an

individual patient's QoL through their treatment. The Brief Pain Inventory (BPI) is widely used to assess pain and its impact on function in people with cancer and other diseases.[30] The BPI is available in two formats — the BPI short-form (BPI-SF), which is used for clinical trials and has been translated into several languages, and the BPI long-form, which includes additional items that allow for more detailed descriptions of pain. The BPI uses a visual analogue scale, and can either be used in a clinical interview or self-administered by the patient. For assessing symptoms beyond pain, the Edmonton Symptom Assessment System (ESAS) was developed to assess nine symptoms that are common in palliative care patients: pain, tiredness, drowsiness, nausea, lack of appetite, depression, anxiety, shortness of breath, and well-being.[31] A blank scale is also included for patient-specific symptoms. Benefits of the ESAS tool are that it is brief and easy to use in the clinic, with the ability to prospectively identify areas of concern in real time, engage patients in symptom assessment, and monitor symptom changes over time.[32] A limitation of the ESAS is that it is only used during clinic visits, not on an ongoing, real-time basis, and assumes that changes in symptoms are associated with a clinic visit, which is not always the case.

The Expanded Prostate Cancer Index Composite (EPIC) is a validated patient-reported instrument that measures urinary incontinence, urinary irritation, and the bowel, sexual and hormonal HRQoL domains for patients with prostate cancer. Like the ESAS, the EPIC instrument is relatively easy to use during a clinic visit to provide real-time feedback. However,

Name: **Date: mm/dd/yy**

1. Mobility
Rate your ability to move and walk (circle one number)

0	1	2	3	4	5	6	7	8	9	10

I have no problems walking — I am unable to walk

2. Usual activities
(e.g., work, study, housework, family or leisure activities)
Rate your ability to do your usual activities (circle one number)

0	1	2	3	4	5	6	7	8	9	10

I have no problem doing my usual activities — I am unable to do my usual activities

3. Sleep
Rate your quality of sleep (circle one number)

0	1	2	3	4	5	6	7	8	9	10

Best quality sleep — No sleep at all

4. Quality of life
Rate how good or bad your overall quality of life has been in the past month (circle one number)

0	1	2	3	4	5	6	7	8	9	10

Best quality of life — Worst quality of life

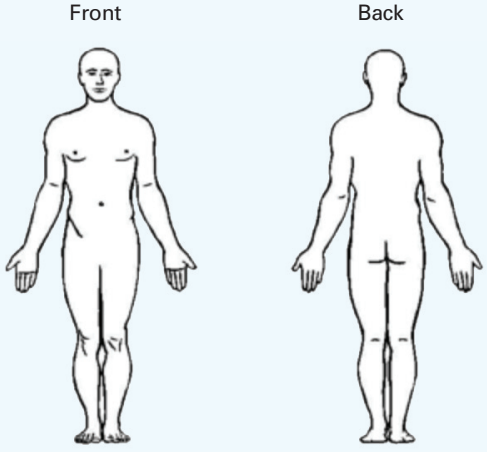
5. Pain
Have you felt any pain in your bones (e.g., spine, back, shoulder or hip) or joints since your last visit? (circle 1 Yes or No)
Yes No

6. Level of pain
How would you rate your pain? (circle one number)

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as I can imagine

7. Location of pain.
Draw an x on the pictures below to show where you have pain.



8. Urination
How would you rate your level of discomfort when urinating? (circle one number)

0	1	2	3	4	5	6	7	8	9	10

No discomfort — Discomfort as bad as I can imagine

9. Current medication/treatment for pain
Do you take any medication to relieve your pain?
Yes No

a) If yes, are you taking (circle as many as apply):
- NSAIDs (e.g., aspirin, acetaminophen, ibuprofen)
- Opioids (e.g., codeine, hydrocodone, oxycodone, morphine)

b) If you take medication, is it:
- Every few days
- 1–2 times/day
- >2 times/day

Fig. 1. Symptom checklist for patients with advanced prostate cancer.

it was developed to measure the impact of treatment-related symptoms on QoL and fails to capture changes in status that occur outside of a clinic visit.

Because of the limitations of existing assessment tools, we propose a simplified checklist developed in collaboration with clinicians from various disciplines to evaluate symptoms among patients with advanced prostate cancer (Fig. 1). This simple checklist asks patients to rate their mobility, ability to conduct usual activities, sleep, overall QoL, and pain levels on a 10-point scale, with higher numbers corresponding to worsening symptoms. It can be easily used in non-academic centres and everyday clinics and easily completed by patients of any age or level of education. We recommend that information on symptoms be collected prior to each appointment, allowing clinicians to devote their time to adequate interpretation of the symptoms reported.

Regardless of how symptoms are assessed, pain and symptom assessment may be easier if the patient is accompanied by a caregiver or close relative, who may be able to comment on the patient's change in activities over time. In a recent survey of men with prostate cancer, half of the respondents admitted that they rely on their caregivers to ask the most important questions regarding their prostate cancer issues.[14]

Conclusion

The availability of multiple agents to treat mCRPC has resulted in substantial improvements in QoL for these patients. Nevertheless, until accurate biomarkers are developed and validated to allow more focused therapeutic targeting in men with mCRPC, treatment selection will continue to rely heavily on close assessment of patient-related factors and monitoring of symptoms to ensure an early change in treatment is offered in the case of progression.

Although pain is considered the predominant symptom in mCRPC and is consistently associated with reduced survival, algorithms to assess progression and treatment selection should incorporate symptoms beyond pain and include a composite measure of symptoms. Other important symptom domains include lack of appetite, weight loss, sleep loss, fatigue, LUTS, interference with daily activities, and social and emotional well-being. Assessment tools should acknowledge that pain can manifest in different ways, such as declining level of activities to avoid pain. Symptom assessment should also focus on the evolution of symptoms over time — not necessarily their absolute level at a specific point. Initial symptom data should be collected before appointments so that clinicians can focus on the interpretation of reported symptoms. We propose an easy-to-use checklist that can be used in physicians' offices, prior to each appointment, to track changes in symptoms over time.

Competing interests: Dr. Saad has attended advisory boards for and has received payment/honoraria from AbbVie, Amgen, Astellas, Bayer, Janssen, and Sanofi; and has participated in clinical trials supported by Astellas, Bayer, Janssen, and Sanofi. Dr. Pouliot has attended advisory boards for Amgen, Astellas, and Pfizer; has been a speaker for Sanofi; has received payment from Amgen, Astellas, Astra Zeneca, Janssen, and Sanofi; and has received honoraria/grants from Amgen, Astellas, Astra Zeneca, Janssen, Pfizer, and Sanofi. Dr. Danielson has received advisory board honoraria, speaker fees, and conference support from Astellas, Bayer, BMS, Janssen, Sanofi, and Pfizer. Dr. Catton has attended advisory boards for and received honoraria from AbbVie, Bayer, Janssen, and Sanofi; has received institution grant support for a fellowship program from AbbVie; and has participated in clinical trials: OCOG PROFIT, CCTG PR13, and NRG 0323. Dr. Kapoor has attended advisory boards for and participated in clinical trial supported by Amgen, Astellas, GSK, Janssen, Novartis, Pfizer, and Sanofi.

Acknowledgments: The authors thank Maryka Hladki of Science & Medicine Canada Inc. for editorial and administrative assistance in preparing the review, and Bayer Canada for providing funding for this support. The authors recieved no honorarium.

This paper has been peer-reviewed.

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