Changing face of metastatic prostate cancer: the law of diminishing returns holds true

Ulka N. Vaishampayan

Purpose of review
Prostate cancer presents with a multitude of faces. It ranges from localized cancers staying quiescent for many years during active surveillance to the raging diffuse liver metastases causing terminal disease. The incidence of metastatic disease is increasing. This review will highlight some of the recent developments as well as ongoing challenges of managing advanced prostate cancer.

Recent findings
Significant strides are being made in managing metastatic prostate cancer. With the evolution of multiple new therapies, now the optimal use of these therapies and their proper sequencing is being addressed. Research is ongoing for mapping out pathways of resistance to therapies and for discovering new targets. Genomic alterations and abnormalities in circulating tumor DNA are being detected and will hopefully lead us more toward biomarker based therapies. The next era in oncology belongs to immune therapy. However, in prostate cancer the immune checkpoint inhibitors have shown modest responses and a phase III trial of radiation therapy ± ipilimumab revealed no benefit. Efforts are ongoing with combination trials of enzalutamide and atezolizumab or pembrolizumab. PARP inhibitors are gradually being established for therapeutic purposes, with olaparib achieving breakthrough status for prostate cancer patients with BRCA1 and 2 and ATM mutations.

Summary
The future will bring an era of personalized medicine in advanced prostate cancer as well as optimization and more strategic sequencing of existing therapies.

Keywords
castration resistance, immunotherapy, prostate cancer, targeted therapy, treatment optimization

INTRODUCTION
The decline in prostate-specific antigen (PSA) screening has significantly increased the incidence of prostate cancer presenting de novo as metastatic disease. The proportion of men over the age of 75 diagnosed with metastatic prostate cancer in 2013 increased to 12% as compared to 7.8% in 2011. The proportion of men diagnosed with aggressive cancer has also increased from 68.9% to 72%.

In addition to the rising incidence of metastatic prostate cancer, it seems that the nature of the disease may be changing. For example, recently, I saw three patients in my practice with metastatic prostate cancer who had been on an androgen receptor axis–targeted (ARAT) therapy and whose disease had responded for a duration ranging from 1 to 3 years. Each of these patients has now progressed, presenting with liver metastases. Unfortunately, this is not an uncommon scenario in medical oncology offices caring for patients with advanced prostate cancer. Patients not infrequently are presenting with aggressive, rapidly progressing prostate cancer and visceral metastases. The management of such patients represents a perplexing challenge. In many men, the prostate cancer can be fairly well controlled initially on a second-generation hormonal agent, so both the patient and the physician may be lulled into a false sense of security because of the temporary reprieve hormonal therapy provides. Then the ‘bubble’ may burst, and the patient develops a rapidly progressive, poorly differentiated cancer that is incredibly difficult to treat. Some of...
Genitourinary system

KEY POINTS

- Despite progress in the treatment of metastatic castration-resistant prostate cancer in the past 10 years, we are still seeing patients for whom second-generation hormonal agents work initially, only to lose their effectiveness, leading to rapidly progressive, poorly differentiated cancer that is difficult to treat.
- We must set realistic expectations and educate patients and families on the variety of therapeutic options for prostate cancer treatment and their limitations, efficacy, and toxicities.
- Alternating effective therapies to minimize toxicity and potentially maintain prolonged efficacy by delaying resistance should continue to be an area of active investigation.
- We owe it to our patients to not limit our research to only developing novel agents, but also be creative in optimizing outcomes from existing therapies.

these patients may be too ill to tolerate chemotherapy, and may also have a minimal chance of responding to chemotherapy. Bone marrow metastases that induce cytopenias, presence of synchronous cranial metastases, or impaired liver function are additional hurdles facing patients being considered for the next lines of therapy.

Contrast this with the symptomatic patient with diffuse bone metastases who we have all treated and who get a welcome, but again temporary, reprieve from the morbidity of their prostate cancer. Why is it then that despite many areas of progress, we are getting a sense of frustration in managing advanced prostate cancer? The reasons for this phenomenon are multifactorial and include the following:

1. Patient and physician expectations have escalated, making chemotherapy administration a relative taboo in metastatic prostate cancer,
2. Lead time bias from early detection of metastases by advances in imaging,
3. Easily tolerated therapies that prompt the use of effective treatments in the asymptomatic phase of metastatic disease,
4. Patient and physician reluctance to switch therapies too soon,
5. The medical oncologist’s delayed involvement in prostate cancer care, and
6. Underestimating the lethal and aggressive forms of metastatic prostate cancer.

It is imperative to adopt measures to address these problems and continue to build upon the upward trajectory in outcomes in advanced prostate cancer. If patients have a rapid PSA doubling time, then different therapeutic options should be discussed. Oncologists must set realistic expectations and educate patients and families on the variety of therapeutic options and their limitations, efficacy, and toxicities. Alternating effective therapies to minimize toxicity and potentially maintain prolonged efficacy by delaying resistance should be an area of continued active investigation. Periodic imaging studies to assess disease status and not relying entirely on PSA for monitoring is important. In addition, development of novel strategies continues to be essential in the treatment of metastatic castration-resistant prostate cancer (mCRPC).

NOVEL TARGETS IN PROSTATE CANCER

Hormone therapy–based targets

Multiple novel hormone agents are in various stages of development. Some of them, such as ODM-201 (NCT02200614) and ARN-509 (SPARTAN trial; NCT01946204), are in double-blind, placebo-controlled phase III trials to evaluate efficacy in non-mCRPC. ODM-201 is also being evaluated in metastatic hormone-sensitive disease (NCT02799602). ARAT therapies, such as enzalutamide, ODM-201, and TAK-700, are also being tested in randomized trials in the metastatic hormone-sensitive setting [1].

Resistance to androgen receptor (AR)–targeted therapies has been commonly associated with either AR gene amplification or AR splice variant or gain-of-function mutations in AR [2]. EPI-506 is a small-molecule N-terminal domain inhibitor that has demonstrated inhibition of AR, including splice variants such as AR-V7, in preclinical studies and is currently in phase I clinical trials. ASN-001 is a CYP17 lyase inhibitor with selective activity against the testosterone production pathway and, hence, does not require steroid coadministration. This agent is also currently undergoing clinical trial testing [3].

Chemotherapy-based advances

Cabazitaxel therapy was compared with docetaxel in the frontline setting in mCRPC with no difference in overall survival (OS; median 25.2 months with cabazitaxel, 24.3 months with docetaxel) and with expected distinct toxicity profiles noted [4**]. Cabazitaxel demonstrated a response rate of 42% compared with 31% for docetaxel. Cabazitaxel at a dose of 20 mg/m² showed favorable toxicity, with the lowest incidence of cytopenias, neuropathy, and alopecia compared to docetaxel 75 mg/m² or cabazitaxel 25 mg/m² in a three-arm study (each
treatment was given every 21 days as intravenous infusion) [5].

Since docetaxel is now often being used in hormone-sensitive metastatic prostate cancer with concurrent androgen deprivation therapy, particularly among patients with high-volume disease, cabazitaxel is likely to emerge as the default standard chemotherapy in mCRPC. Phase III trial data indicate that cabazitaxel at a dose of 20 mg/m² can improve toxicity without compromising efficacy and suggest that this should be the preferred starting dose. Platinum-based chemotherapy is also a valid option in mCRPC, especially if neuroendocrine features are noted or if docetaxel and cabazitaxel are not feasible because of hepatic dysfunction. The combination of cabazitaxel and carboplatin was well tolerated and showed promising efficacy with a response rate of 52% in patients with measurable disease and a median progression-free survival of 5.7 months [6]. Cabazitaxel and targeted therapy–based combinations would be attractive for future clinical trial testing.

**Immunotherapy**

Immune checkpoint therapies have taken the oncology world by storm, and advanced prostate cancer is no exception. Metastatic prostate cancer was the first malignancy amongst solid tumors in which an OS benefit was demonstrated in a placebo-controlled randomized trial favoring immunotherapy (sipuleucel-T) [7]. However, the advent of other, easier-to-use effective immunotherapies, and the cumbersome nature of using sipuleucel-T that involves leukapheresis, have been major hurdles in the widespread clinical application of sipuleucel-T.

The potential synergy between the CTLA-4 inhibitor ipilimumab and radiation therapy was explored in mCRPC and showed initial promise, but disappointingly no OS benefit was observed with this combination in a phase III trial. KEYNOTE-028 is a phase IB multi-cohort trial of the PD-1 inhibitor pembrolizumab as single agent in patients with different histologic tumor types. Among 245 patients 35 (14.3%) mCRPC patients were PD-L1–positive, and 20 who were response evaluable were treated. Objective response rate was noted in five patients, with a median response duration of 58.7 weeks [8].

Immune checkpoint blockade with pembrolizumab in patients with enzalutamide-resistant disease demonstrated promising efficacy, with three of the first 10 treated patients demonstrating a response with PSA decline and decrease in size of measurable target lesions. Two responders who had tissue available for analysis were positive for PD-L1 expression, and one demonstrated microsatellite instability [9*].

A randomized trial of enzalutamide with or without atezolizumab is planned, and a combination of radium-223 and atezolizumab is currently in phase I testing in mCRPC patients with measurable disease.

Vaccine-based immunotherapy strategies are also promising, especially if given in combination with immune modulators. The intriguing OS benefit seen in the phase II randomized trial of rilimogene galvacirepvec/rilimogene glafolivec (median OS 25.1 months in the vaccine arm versus 16.6 months in the placebo arm; HR 0.56; P = 0.0061) has heightened interest in the awaited results of the phase III placebo-controlled trial. The ease of administration, tolerability, and the possibility of prolonged durable remissions are among the biggest assets of vaccines. Although immunotherapy may hold the key to inducing durable remissions in mCRPC, it cannot be relied upon for rapid control of symptomatic disease; thus, it is likely that combinations of agents will be required for optimal responses.

A phase I trial of a sequential combination of multipronged immune modulators, including an adenoviral vector vaccine (administered via electroporation); tremelimumab, a CTLA-4 inhibitor; and myeloid-derived suppressor cell inhibition via sunitinib maintenance, is in progress (NCT02616185). The development of cellular immunotherapy consists mainly of armed activated T cells, which have demonstrated safety and preliminary proof-of-principle activity. A phase II trial of bispecific antibody-armmed activated T cells in combination with the PD-1 inhibitor pembrolizumab is planned in mCRPC after our initial phase I trial demonstrated safety and preliminary efficacy [10*].

**Targeted therapy**

Robinson et al. reported on genomic testing of biopsy specimens from 150 patients with mCRPC, and found that approximately 89% had actionable mutations. Of the actionable mutations, 62% were in the AR gene, and 8% had actionable germline mutations [11**]. The frequency of DNA repair mutations (BRCA and ATM) was 19.3%.

The proportion of patients being enrolled on clinical trials of matched targeted therapies is rapidly expanding and will soon provide results on the impact of specific targeted therapies in mCRPC. PARP inhibitors have already demonstrated significant durable response rates in mCRPC with DNA repair mutations [12**]. The promising efficacy of PARP inhibitors has recently resulted in the breakthrough designation of olaparib by the U.S. Food and Drug Administration for BRCA1/2 or ATM gene mutation–positive prostate cancer. Clinical trials evaluating several other PARP inhibitors such as rucaparib and niraparib are ongoing.
Phosphatase and tensin homolog (PTEN) loss (present in approximately 14% of prostate cancers tested) in advanced prostate cancer signifies unchecked activity of the Mammalian Target of Rapamycin (mTOR) and PI3K pathways. PI3K mutations are reported in approximately 27% of prostate cancer cases [13]. Inhibitors of the PI3K pathway are in ongoing clinical trials, especially in patients with PTEN loss or ARAT-resistant disease. The IGF-1 receptor is another target that has been evaluated in clinical trials but has yielded disappointing results [13]. mTOR inhibition has been explored in mCRPC and has demonstrated modest clinical efficacy at best [14]. The Bromodomain and Extra-terminal-1 inhibition pathway is also under active clinical investigation [15].

CONTEMPORARY MANAGEMENT OF mCRPC
The three patients with liver metastases mentioned earlier were treated with different therapeutic regimens. One of them had elevated transaminases, and because he was unable to receive docetaxel- or cabazitaxel-based chemotherapy or qualify for any clinical trial, he was treated with carboplatin and etoposide chemotherapy—similar to a regimen that would be used for neuroendocrine prostate cancer. The second patient had an ATM gene mutation and, hence, was considered for a clinical trial with PARP inhibitor. The third patient had PTEN loss noted on tissue genomic testing and was therefore evaluated for a study with a PI3K inhibitor (Fig. 1).

Multiple decision dilemmas persist regarding optimal management and therapeutic sequencing in prostate cancer. The questions regarding which therapy to start and the odds of it actually helping or improving the life expectancy of a patient who is symptomatic are important and must be discussed in detail with the patient and their family.

Although median survival in mCRPC has nearly doubled in the past 10 years and to a large extent we have achieved the goal of less therapy-related toxicities, work remains in terms of need for optimization of the systemic therapies. Early risk stratification and genomic characterization of tumors will help create appropriate plans of attack. DNA repair mutations, PI3K mutations, or PTEN loss can be identified before starting hormone agents, and then proactive planning for targeted therapies such as PARP inhibitors or PI3K inhibitor–based

![FIGURE 1. State-of-the-art therapy options in mCRPC. ARAT, androgen receptor axis targeted; mCRPC, metastatic castration-resistant prostate cancer.](image-url)
CONCLUSION

At present, we are using therapies with the hope that they will help curb disease progression during the patient’s lifetime. A global and comprehensive therapeutic plan should be considered, and both the patient and their oncology care team should have candid discussions about the role of the various treatments and how these should be used and sequenced for optimal therapeutic effect. We owe it to our patients to not just limit our research to developing novel agents, but also be creative in optimizing outcomes from the existing therapies.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

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