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Review Article

Critical questions in metastatic castration-resistant prostate cancer: Integrating emerging clinical evidence and guideline recommendations

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Abstract. Metastatic castration-resistant prostate cancer (CRPC) typically confers a poor prognosis, however, novel advances in treatment options, as well as biomarkers for monitoring disease response and progression, have recently helped improve survival rates. Additionally, new guidelines provide some direction on incorporating these new treatments but some confusion still exists among clinicians about best methods for initiating treatment and the optimal sequencing of agents to prolong survival. In this article, we review the literature and answer some frequently asked questions about treating men with metastatic CRPC, including choosing a first-line treatment, monitoring treatment response, and proceeding to additional lines of therapy.

Keywords: Prostate cancer, metastasis, castration-resistant, treatment, guidelines

Introduction

Prostate cancer is the second-leading cause of cancer-related deaths in men in the United States, accounting for approximately 30,000 deaths in 2013 [1]. Roughly one in seven men develops prostate cancer in his lifetime [2]. Metastatic castration-resistant prostate cancer (CRPC) typically confers a poor prognosis, with a median survival of about 2 years; however, novel advances in treatment options, as well as biomarkers for monitoring disease response and progression, have recently helped improve survival rates [3]. Additionally, new guidelines provide some direction on incorporating these new treatments and biomarkers in clinical practice, but some confusion still exists among clinicians about best methods for initiating treatment and the optimal sequencing of agents to prolong survival [4, 5].

Here, we review the literatures and answer some frequently asked questions about treating men with metastatic CRPC, including choosing a first-line treatment, monitoring treatment response, and proceeding to additional lines of therapy.

Choosing First-Line Therapy

In patients with non-metastatic CRPC, the American Urological Association (AUA) recommends observation and androgen deprivation as the current standard of care [5]. In patients who are not comfortable with simple observation, first-generation antiandrogens, such as flutamide, bicalutamide, and nilutamide, or the combination of ketoconazole and a steroid are recommended [5]. Clinical trial entry should be encouraged for these patients.

When prostate cancer progresses to metastatic CRPC, the prognosis worsens, with a median survival of 9 to 30 months [6, 7]. For metastatic CRPC, docetaxel had long been recommended as a first-line therapy since the 2004 pivotal TAX327 and SWOG9916 trials [8, 9]. However, along with docetaxel, several other agents have recently become available, resulting in prolonged overall survival [6]. In patients with disease progression who have previously received docetaxel, the AUA recommends treatment with abiraterone plus prednisone, enzalutamide, or cabazitaxel [5]. In those with symptomatic bone metastases, radium-223 is recommended as standard treatment. In the rare event that one of these agents is contraindicated or unavailable, patients should be treated with ketoconazole plus a steroid.

In patients with asymptomatic/minimally symptomatic metastatic CRPC who have not previously received treatment with docetaxel, the AUA suggests treating with abiraterone plus prednisone, docetaxel, or sipuleucel-T. If standard therapies are not available, patients should be treated with either a first-generation antiandrogen, ketoconazole plus a steroid, or continued observation [5]. Enzalutamide was also recently approved by the

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United States Food and Drug Administration for use in this setting.

Current American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) guidelines state that pharmaceutical or surgical ADT should be continued indefinitely in combination with additional therapies [4]. ASCO recommends first-line treatment with abiraterone plus prednisone, enzalutamide, or radium-223 (for patients with bone metastases) or a limited course of docetaxel plus prednisone. If docetaxel/prednisone is given, patients should be counseled about the potential for toxicity. Sipuleucel-T may also be offered to patients who are experiencing no or minimal symptoms. In men previously treated with docetaxel but who experience disease progression, cabazitaxel plus prednisone may be offered [4].

Mitoxantrone plus prednisone may also be offered, but studies have shown that mitoxantrone confers a quality-of-life benefit without a demonstrated survival benefit [4]. Additionally, it is important to note that this drug is now rarely used - typically only in patients who have exhausted all other treatment options.

Hormonal agents such as antiandrogens, ketoconazole, and corticosteroid monotherapy may sometimes be recommended for men with metastatic CRPC, but ASCO/CCO guidelines caution that these agents have unknown survival and quality-of-life effects [4]. Additionally, ASCO/CCO guidelines caution against the use of bevacizumab, estramustine, and sunitinib based on insufficient evidence of either survival or quality-of-life benefit with these agents [4].

Of course, patient preference and the balance among quality of life, survival benefit, cost, and other factors should always be taken into account when making treatment decisions.

Measuring Response to Therapy

Once treatment of metastatic CRPC has begun, it is important to measure the patient's response to therapy. Serum PSA is the leading indicator of active disease and should be monitored every 3 to 6 months [10, 11]. Unfortunately, aside from PSA, there is a lack of reliable biomarkers that clinicians can use to determine which treatment may be most effective for each patient, decide when to switch therapies, or even identify patients who might be best served by monitoring alone [11].

PSA is a marker for active prostate cancer, and its elevation is often the first sign that cancer is recurring. Serum PSA is almost always detectable before a clinical recurrence. There are limitations, however, to using PSA as a biomarker for the progression of metastatic CRPC. Although PSA does mark the presence of cancer cells, it can also be found in patients with normal prostate cells or benign prostatic hyperplasia (BPH) [11]. Therefore, PSA tests have limited specificity for clinically significant prostate cancer, and many men may be subjected to unnecessary biopsies or treatments based on the PSA test results. Additionally, some forms of prostate cancer, particularly those that are poorly differentiated or have small cell histology, do not secrete PSA. Patients with these forms often have visceral disease. Efforts have been made in recent years to improve the accuracy of PSA-based monitoring, including considering the rate of PSA changes over time as well as the ratios of free PSA (fPSA) to bound PSA [11]. Although the use of PSA decline as a marker of response to CRPC is controversial, PSA progression has been correlated with disease progression, both in androgen-sensitive prostate cancer as well as in CRPC. A PSA increase of at least 25% above the nadir and an absolute increase of at least 2 to 5 ng/mL are predictors of poor overall survival in hormone-sensitive and castration-resist ant disease [12].

PSA isoform p2PSA, a 2-amino-acid leader sequence of the PSA proenzyme, has been found to be a more specific indicator of prostate cancer than fPSA, complexed PSA, or total PSA [13]. High levels of p2PSA in radical prostatectomy patients have also been shown to be a predictor of final prostate cancer pathology [14].

In addition to PSA and PSA derivatives, several other emerging biomarkers may also hold promise in active surveillance of response to metastatic CRPC therapy. For instance, prostate cancer antigen-3 (PCA3) is currently being studied as a potential biomarker [15]. Expression of PCA3 is associated with PSA levels and is highly overexpressed in metastatic CRPC. Its expression also strongly correlates with tumor volume [11]. Furthermore, PCA3 is expressed only in prostate tissue, and higher PCA3 levels have been found to correspond to metastatic disease and poorer prognosis [15].

Emerging data also support the use of androgen-receptor mutations as biomarkers in deciding whether patients should be treated with enzalutamide or abiraterone combined with prednisone, either initially or sequentially [16]. Splice mutations in the ligand binding domain of the androgen receptor lead to both intrinsic and acquired resistance to these hormonal agents. One such mutation is the AR-V7. A recent publication by Antonarkis et al. [16] demonstrated that CRPC patients who harbor AR-V7 in circulating tumor cells experience primary and acquired resistance to both enzalutamide and abiraterone. This splice variant is not only intrinsic in approximately 19% to 39% of patients, but it can emerge with treatment over time. Further prospective evaluation will be crucial in determining when the sequential use of these hormonal agents is appropriate or whether other agents such as investigational drugs, radium, docetaxel, or cabazitaxel should be selected for treatment [16].

Imaging patients for metastatic disease is particularly important when considering starting or changing treatment for CRPC. A recent publication from the RADAR (Radiographic Assessments for Detection of Advanced Recurrence) group reviewed the indications for scanning for the detection of metastatic disease [17]. Initial scanning should include technetium bone scintigraphy and a CT scan of the chest/abdomen/pelvis. Additional recommended tests are plain radiography, MRI, and sodium fluoride PET scanning to be conducted at the physician's discretion when necessary. For patients with non-metastatic CRPC, the first scan should be performed when the PSA is 2 ng/dL or greater. Repeat scanning

should be performed when the PSA is 5 ng/dL and upon every doubling of PSA thereafter [17].

Sequencing Therapies

With the emergence of biomarkers and novel therapies for the treatment of metastatic CRPC comes the challenge of knowing how to best sequence these therapies to optimize overall survival and quality of life. Although no strong evidence regarding the sequencing of treatments is available, it is suggested that the clinical state of the metastatic CRPC be the guiding factor in this decision [4, 5], specifically: 1) In patients with non-metastatic prostate cancer, ADT should be used as first-line treatment, 2) In asymptomatic or minimally symptomatic and chemo-naïve metastatic CRPC, sipuleucel-T, enzalutamide, or abiraterone plus a steroid should be offered, 3) In symptomatic metastatic CRPC, docetaxel or abiraterone plus a steroid should be offered, 4) If docetaxel fails, abiraterone plus a steroid, enzalutamide, cabazitaxel, or mitoxantrone may be offered and 5) For patients with bone metastases but no known visceral disease, radium-223 should be administered.

Unfortunately, no consensus or guidelines currently define the optimal sequence of treatments for metastatic CRPC; in fact, both the AUA and ASCO/CCO guidelines state that there is insufficient evidence to support specific sequencing or combinations of these therapies [4, 5]. There are currently no biomarkers or clinical parameters to predict who will benefit from which specific therapy first[18]. Future research efforts should focus on defining the optimal sequencing of therapies, while also taking into account safety, efficacy, and cost, to confer the greatest benefit to patients with metastatic CRPR.

Conclusion

Decisions regarding the initial treatment and management of metastatic CRPC can be difficult. Although recently published guidelines and clinical studies with novel agents do offer guidance, it is difficult and sometimes confusing to incorporate this rapidly evolving information in clinical practice. Clinicians are encouraged to individualize treatment plans based on specific patient populations and patient needs. Quality of life and overall survival must be considered, and clinicians should communicate clearly with their patients regarding the potential risks and benefits of metastatic CRPC treatment. every doubling of PSA thereafter [17].

Conflict of interest

The authors declare no conflicts of interest.

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