Challenges and Questions in the Management of Metastatic Castration Resistant Prostate Cancer

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Introduction

The management of advanced prostate cancer is complicated by continually evolving treatment guidelines and the recently expanded treatment armamentarium with a variety of indications for use within castration-resistant prostate cancer (CRPC). As new data surrounding the care of patients with metastatic CRPC (mCRPC) emerge, oncologists and urologists who treat men with this condition are challenged to keep pace with changing therapeutic paradigms. In this manuscript we will addresses the clinical challenges in management of mCRPC.

How Do You Define Treatment Resistance and Disease Progression in mCRPC?

Because prostate cancer typically metastasizes to bone, it can be challenging to measure response to treatment using the traditional Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.1 Moreover, prostate-specific antigen (PSA) levels can be inconsistent during therapy; increases or decreases in PSA may be influenced by treatment and are not necessarily an accurate depiction of disease status [1,2]. Increases in pain may indicate treatment resistance but can be difficult to quantify; additionally, transient increases in pain are common during treatment initiation [1-3].

In 2008, the PCWG2 released criteria for defining disease progression that marked a shift in focus from trial protocol criteria to patient needs. They note that although the guidelines were developed for clinical trials, they can be adapted for use in clinical practice as long as clinicians remain cognizant of progression criteria in the context of each patient’s situation.3 Notably, the guidelines specify the importance of confirming that serum testosterone is in the castrate range (<50 ng/dL) [3].

In their recommendations for cytotoxic therapies, the PCWG2 updated and clarified the following (Table 1) [3]:

- The criteria for reporting post-treatment PSA changes
- Strategies for applying RECIST to prostate cancer
- Methods for describing post-treatment bone-scan changes

Version 3 of the PCWG2 guidelines is now in development and will be published in Early 2016 (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>PSA</td>
<td>obtain sequence of rising values at a minimum of 1-week intervals</td>
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<tr>
<td></td>
<td>Must report minimum starting value of 2.0 ng/mL</td>
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<td></td>
<td>Estimate pre-therapy PSA-DT if ≥ 3 values are available ≥ 4 weeks apart</td>
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<tr>
<td>Target Lesions</td>
<td>Nodal or visceral progression is sufficient for trial entry independent of PSA</td>
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<tr>
<td></td>
<td>Measurable lesions are not required entry</td>
</tr>
<tr>
<td></td>
<td>Use RECIST to record soft-tissue (nodal and visceral) lesions as target or nontarget</td>
</tr>
<tr>
<td></td>
<td>Lymph nodes ≥ 2 cm in diameter only should be used to assess for change in size</td>
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<tr>
<td></td>
<td>The presence of nodal and/or visceral diseases should be recorded separately</td>
</tr>
<tr>
<td>Prostate/prostate bed</td>
<td>Record prior treatment of primary tumour</td>
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<tr>
<td></td>
<td>Perform direct pelvic imaging (eg. CT, MRI, PET/CT, endorectal MRI, transrectal ultrasound) to document the presence or absence of disease</td>
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<tr>
<td>Bone</td>
<td>Progression=appearance of ≥ 2 new lesions</td>
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<td></td>
<td>Confirm ambiguous results by other imaging modalities (eg. CT or MRI)</td>
</tr>
<tr>
<td>Other Sites of Disease</td>
<td>patients with treated epideral lesions and no other epideral progression are eligible</td>
</tr>
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CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography; PSA=prostate-specific antigen, PSA-DT=prostate-specific antigen doubling time, RECIST=Response Evaluation Criteria in Solid Tumors. Adapted with permission from Scher et al.; Prostate Cancer Clinical Trials, Working Group. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group.

Table 1: Prostate Cancer Working Group 2 Criteria Regarding Progression for Clinical Trial Eligibility by Disease Manifestation.
Although rising PSA may indicate disease progression, PCWG2 authors warn against modifying therapy based on PSA changes alone, which vary according to each patient’s drug regimen [1-3]. In fact, a gradual but steady rise in PSA over months or years in the absence of other signs of in disease progression is frequently observed [1-3]. Thus, “treating through” slow increases is PSA acceptable and recommended in many cases [3]. “Treating through” should be accompanied by regular clinical assessments for pain and performance status decline, as well as regular imaging (every 12-16 weeks in standard practice) to determine whether objective progression has occurred.

The most important aspect of measuring disease progression is examining each patient’s overall symptoms and status before changing therapies. For instance, “We may see a lymph node in the pelvis, which increases by 50% from 2 cm to 3 cm. If that patient has bone dominant disease and had pain from those metastases, and the drug that patient is on is controlling those bone lesions, then from a prognostic and therapeutic point of view, control of his bone lesions is more important than (treating) the lymph node.” Remember to consider “the big picture.”

What is the Role of Immunotherapy in mCRPC?

Oncology clinicians are showing a growing interest in immunotherapy, though few agents have been approved to date, despite more than a decade of clinical trials. Sipuleucel-T is the only immunotherapy approved by the United States Food and Drug Administration (FDA) for the treatment of mCRPC. It can be used as first-line treatment for mCRPC or following androgen-deprivation therapy, secondary hormone therapy (but prior to docetaxel therapy) if disease burden is low and patients are not likely to undergo chemotherapy for at least 3 months, or docetaxel therapy [4]. The pivotal IMPACT trial (Immunotherapy for Prostate Adenocarcinoma Treatment) included patients who had minimal or asymptomatic disease and no visceral metastases; most were chemotherapy naïve [5,6]. It was designed as a crossover study, with the majority of placebo patients receiving other therapies during the course of the trial after completion of the study treatment. The primary endpoint was overall survival [5,6].

The trial data showed the following [5,6]:

- No significant difference in progression-free survival between groups (progression was measured by PSA and radiographic imaging)
- A 22% reduction in mortality risk for patients on sipuleucel-T (median survival, 25.8 months sipuleucel-T vs. 21.7 months placebo; HR, 0.78; 95% CI, 0.61-0.98; P=0.03)
- An overall survival difference between the placebo and treatment groups that was greatest at approximately 3 years
- Minimal and mild adverse events (eg: fever, chills) reported by patients on sipuleucel-T; a low rate of cerebrovascular events (2.4% sipuleucel-T vs. 1.8% placebo)
- The utility of sipuleucel-T is limited in clinical practice. The most recent version of the National Comprehensive Cancer Network guidelines recommend prescribing immunotherapy for a small percentage of men who meet the following criteria [7]:
  - Good performance status (Eastern Cooperative Oncology Group [ECOG] score=0 or 1)
  - Estimated life expectancy of more than 6 months No hepatic metastases
  - No or minimal symptoms

More research is needed to determine whether sipuleucel-T will play a vital role in the treatment of mCRPC.

Investigational immunotherapies: Several promising immunotherapies, such as the poxviral vaccine and ipilimumab, are in late-stage clinical trials.

Poxviral vaccine: A small phase 2 study of PROSTVAC-VF, a poxvir vaccine composed of two recombinant viral vectors (vaccinia and fowlpox) and three immune costimulatory molecules (B7.1, ICAM-1, and LFA3), included chemotherapy-naive patients with minimally symptomatic mCRPC (N=125) [8].

The investigators reported that long-term overall survival rates were significantly improved for the poxviral vaccine group compared with the placebo group; at 3 years, poxviral vaccine patients had [8]:

- Better overall survival with 25 of 82 (30%) poxviral vaccine patients alive versus 7 of 40 (17%) controls
- Longer median survival by 8.5 months (25.1 months for poxviral vaccine patients vs. 16.6 months for controls; HR, 0.56; 95% CI, 0.37-0.85; P=0.0061)

Few adverse events were seen in either group; most were injection-site reactions, with only a subset of patients experiencing associated systemic adverse events such as fatigue, fever, and nausea.8 PROSTVAC-VF is now in phase 3 development; enrollment was completed in December 2014, and data are currently being collected [9].

Ipilimumab: Ipilimumab is a biologic therapy that is currently FDA approved for the treatment of melanoma and is now under investigation for the treatment of prostate cancer [10]. A 2014 article in Lancet reported the results of a multicenter phase 3 trial involving men with mCRPC (indicated by ≥1 bone metastases) that had progressed following docetaxel treatment (N=799) [11]. The primary endpoint — overall survival in the intention-to-treat population — was not met. Median overall survival was 11.2 months (95% CI, 9.5-12.7) in the ipilimumab group and 10.0 months (95% CI, 8.3-11.0) in the placebo group (HR, 0.85; 95% CI, 0.72-1.00; P=0.053). The most frequently reported adverse events in the ipilimumab group were diarrhea and fatigue. Four deaths that occurred during the study period were attributed to ipilimumab [11].

Further data analysis revealed that certain subgroups — such as men in the earlier stages of disease — responded better to ipilimumab [11]. However, patients with visceral metastases fared considerably worse, suggesting that an immunosuppressive environment in the liver may render immunotherapies less effective in this setting [11]. Near a dozen additional clinical trials are currently examining ipilimumab in combination with other therapies for the treatment of prostate cancer.

How are Prognostic and Predictive Tests used in Prostate Cancer?

Prognostic markers in oncology care examine individual patient factors to provide information about patients’ overall outcomes and identify high-risk patients. Predictive biomarkers are used as indicators of the likely benefit of a specific treatment for a specific patient [12].

The Halabi nomogram is a prognostic test for men with mCRPC that was recently revised in 2014 [13]. The updated nomogram was validated for use in clinical practice to predict overall survival in
patients with mCRPC receiving first-line chemotherapy and includes 8 prognostic markers of overall survival [13]:

- ECOG performance status
- Disease site
- Lactate dehydrogenase (LDH; defined as >1 × upper limit of normal)
- Opioid analgesic use
- Albumin
- Hemoglobin
- PSA
- Alkaline phosphatase

Clinicians can evaluate their patients regarding each of these factors to derive a prognostic score that can provide insight about outcomes.

Many clinicians do not have time to review and calculate each risk factor at every patient visit, but keeping the 8 prognostic factors in mind can help identify trends. Most of them use this nomogram unconsciously more than they do consciously, which is to say that after studying this nomogram and treating a lot of patients with this disease...we know these things to be true. The man with the high LDH, the poor performance status, the low albumin, and the low hemoglobin has a poor prognosis. And so we know directionally the way that all those things go. Do we sit there and [draw] the lines and say to a patient, you know, (you may have) a 22.5-month median survival? No. But we will routinely order all of these tests as we are evaluating patients over time, and that can be very helpful in terms of knowing the pace that the patient's course is taking and where he is in the spectrum of the disease.

No known predictive markers are currently available to guide CRPC treatment; however, the androgen receptor splice variant 7 (AR-V7) is now being studied as a potential predictive factor for resistance to androgen receptor–signaling inhibitors. Researchers at Johns Hopkins tested the hypothesis that detecting AR-V7 in circulating tumor cells. Overall survival and progression-free survival were better for men in the enzalutamide and abiraterone groups who were AR-V7 negative [15]. Further investigation into AR-V7 and the identification of other possible predictive biomarkers will shape the future of targeted therapy in mCRPC.

Conclusion

The therapeutic options for mCRPC are expanding and evolving rapidly. The next decade is sure to bring continued advances in treatment as the armamentarium grows and targeted therapies for prostate cancer begin to emerge.

References