Optimizing Patient Outcomes in Castration-Resistant Prostate Cancer: Moving Urologists From Knowledge to Action

A CME Activity

OVERVIEW

Evan Ya-Wen Yu, MD, provides his insights into the evolving management of patients with castration-resistant prostate cancer (CRPC) and the implications of the genomic landscape on CRPC. Since clinical trial evidence does not clearly inform sequencing strategies, Dr. Yu weaves his insight into this conundrum using 3 cases, with suggestions to help the urologist individualize treatment. The efficacy and safety of near-horizon investigational agents such as poly ADP ribose polymerase inhibitors and programmed death ligand-1 blocking agents are discussed.

CONTENT AREAS

- National Comprehensive Cancer Network guidelines on prostate cancer
- Clinical trials such as IMPACT, COU-AA-301 and -302, PREVAIL, PLATO, ALSYMPCA, AFFIRM, TROPIC, PROSELICA, FIRSTANA
- Prechemotherapy vs post-chemotherapy
- Sequencing
- Genomic landscape

FACULTY

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CE/CME Information

Target Audience
This activity was developed for urologists, oncologists and other health care professionals who have an interest in castration-resistant prostate cancer (CRPC).

Learning Objectives
At the conclusion of this activity, participants should be better able to:
- Implement a multidisciplinary approach to the management of patients with CRPC that ensures continuity of care
- Integrate current guidelines into the routine clinical care of patients with CRPC
- Evaluate the clinical safety data for current and emerging therapies used for the treatment of CRPC
- Develop individualized management plans for patients with CRPC involving the selection, sequencing and combination of optimal treatment strategies

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1. What role does sipuleucel-T play in the treatment of patients with metastatic castration-resistant prostate cancer?

Answer

The efficacy of sipuleucel-T in improving overall survival (OS) in men with metastatic castration-resistant prostate cancer (mCRPC) was first demonstrated in 2 small phase 3 trials.\(^1,2\) Time to disease progression was not improved, however. To confirm the OS benefit, the phase 3 Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) trial randomized 512 patients in a 2:1 ratio to sipuleucel-T or placebo administered every 2 weeks for a total of 3 infusions.\(^3\)

Initially, only men with Gleason score ≤7 and no symptoms were enrolled, but these criteria were amended following further analysis of the earlier studies to include men with any Gleason score and whose disease was minimally symptomatic. Patients could have undergone no more than 2 chemotherapy regimens.

In the IMPACT trial, median survival was 25.8 months vs 21.7 months in the sipuleucel-T and placebo groups, respectively, over a median follow-up of 34.1 months.\(^3\) Death occurred in 61.6% and 70.8% (hazard ratio [HR] 0.78; \(P=0.03\)) and time to objective disease progression was 14.6 weeks vs 14.4 weeks, respectively. Reduction of the prostate specific antigen (PSA) level ≥50% occurred in 2.6% and 1.3% of sipuleucel-T and placebo patients, respectively.

The most common adverse events (sipuleucel-T vs placebo) were: chills (54.1% vs 12.5%), fatigue (39.1% vs 38.1%), fever (29.3% vs 13.7%), nausea (28.1% vs 20.8%), and headache (16.0% vs 4.8%). A grade ≥3 adverse event occurred in 6.8% and 1.8% of sipuleucel-T and placebo patients, respectively, of which chills and fatigue were the most common.

Post hoc analysis of the IMPACT results showed the PSA level to be the strongest baseline prognostic factor for OS.\(^4\) The OS benefit with sipuleucel-T was greater for patients in the lowest baseline PSA quartile (≤22.1 ng/mL) (HR 0.51; 95% confidence interval [CI] 0.31-0.85) compared with the highest PSA quartile (>134 ng/mL) (HR 0.84, 95% CI 0.55-1.29).

Lower tumor burden in the lowest PSA quartile may explain this finding. The greatest difference in OS was seen at 3 years following treatment, although only a third of the study population experienced survival of this length. While not prospectively validated, the results of IMPACT suggest that sipuleucel-T should be used selectively for asymptomatic patients with more indolent, lower volume mCRPC as opposed to patients with rapidly progressive or extensive disease.
2. What should be done if a patient progresses on either abiraterone or enzalutamide? Should he be switched to the other or move on to a therapeutic agent with a very different mechanism of action?

Answer
Algorithms such as the one developed by the National Comprehensive Cancer Center2 provide guidance regarding systemic therapy for metastatic castration-resistant prostate cancer (mCRPC).

However, the algorithms provide no clear pathway regarding sequencing because of limited evidence from randomized clinical trials. Results of 3 trials have shown a prostate specific antigen (PSA) response ≥50% ranging from 3% to 13% with abiraterone in patients who have progressed on second-line enzalutamide.6-8

Median overall survival (OS) ranged from 7 to nearly 12 months.7,8 A better, albeit modest, response has been observed with enzalutamide following progression on docetaxel and/or abiraterone.9-14 PSA response ≥50% ranged from 13% to 40%, with 46% experiencing a 30% PSA response in 1 trial.12

Median OS ranged from 4.8 months to 12.2 months in 5 of the 6 trials and was not reached in the other trial.9

While these results do not provide a clear pathway for sequencing, they suggest that there must be many mechanisms of resistance in common between abiraterone and enzalutamide. Consequently, when a patient’s disease progresses, it would be reasonable to switch class of therapy, e.g., hormone to radiopharmaceutical or chemotherapy.
Consideration should also be given to offering the patient the option to enroll in a clinical trial. The benefits and limitations of each option, along with consideration of potential side effects and cost of treatment, should be included in a discussion with the patient as part of the shared decision-making process. Other team members may be involved to provide further support to the patient, to answer questions, and to help the patient successfully transition to a new treatment plan. This can be particularly helpful when care may be provided by team members previously unfamiliar to the patient.

3. Should radium-223 be used before or after chemotherapy?

Answer

Radium-223 is an alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases, and no known visceral metastatic disease. Previous treatment with docetaxel was associated with a higher incidence of adverse events after receiving radium-223 than the no previous docetaxel subgroup (95% vs 90%, respectively). A grade 3/4 adverse event occurred in 62% and 54% of patients, respectively. The previous docetaxel group had a higher incidence of grade 3/4 thrombocytopenia with radium-223 than with placebo (9% vs 3%, respectively). In contrast, the incidences of grade 3/4 anemia and neutropenia were similar between radium-223 and placebo within each docetaxel subgroup.

Significant baseline predictors for grade 2-4 hematologic toxicities related to radium-223 were identified using logistic regression analysis. Predictors for anemia were extent of disease (6-20 vs <6 bone metastases, odds ratio [OR] 2.76; P=0.022), total alkaline phosphatase (OR 2.00; P=0.019), and elevated prostate specific antigen (PSA) level (OR 1.65; P=0.006).
Predictors for thrombocytopenia were prior docetaxel (OR 2.16; \( P = 0.035 \)), elevated PSA level (OR 1.83; \( P = 0.016 \)), decreased platelets (OR 1.44; \( P = 0.030 \)), and decreased hemoglobin (OR 1.35; \( P = 0.008 \)).

Overall, these data indicate that adequate hematologic parameters are more important for choosing radium-223 than a prior history of docetaxel. Thus, strict eligibility criteria for radium-223 include an initial absolute neutrophil count (ANC) \( \geq 1500/\mu\text{L} \), platelet count \( \geq 100,000/\mu\text{L} \), and hemoglobin \( \geq 10 \text{ g/dL} \).

### Radium-223 Before or After Chemotherapy? Practical Considerations

- Only FDA-approved for patients who lack visceral metastasis
- Stringent eligibility requirements for treatment
  - Initial ANC \( \geq 1500/\mu\text{L} \) with subsequent \( \geq 1000/\mu\text{L} \)
  - Hb \( \geq 10 \text{ g/dL} \)
  - PLT \( \geq 100,000/\mu\text{L} \) with subsequent \( \geq 50,000/\mu\text{L} \)
- Requires preauthorization, while chemotherapy with docetaxel does not

Prior to subsequent administration of radium-223, the ANC should be \( \geq 1000/\mu\text{L} \) and platelet count \( \geq 50,000/\mu\text{L} \).

### 4. What strategies are effective to prevent toxicity related to cabazitaxel?

**Answer**

Febrile neutropenia, diarrhea, and hematuria were the adverse events most commonly observed in phase 3 clinical trials of cabazitaxel in patients with metastatic castration-resistant prostate cancer (mCRPC). \(^{19-21}\)

### The PROSELICA Study– TEAEs

<table>
<thead>
<tr>
<th>Any grade TEAE</th>
<th>CBZ 20 + PRED (n=840)</th>
<th>CBZ 25 + PRED (n=395)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3–4 TEAE</td>
<td>10.7%</td>
<td>8.4%</td>
</tr>
<tr>
<td>TEAE leading to permanent treatment discontinuation</td>
<td>14.4%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Most frequent grade 3-4 TEAEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2.1%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1.5%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.4%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.6%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1.7%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Bone pain</td>
<td>1.7%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.3%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.2%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.7%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

*TEAE, treatment-emergent adverse events.*

As recommended in the 2015 American Society of Clinical Oncology guidelines, febrile neutropenia is best prevented with prophylactic granulocyte colony stimulating factor. \(^{22}\) It is best to administer pegfilgrastim the same day as cabazitaxel, compared with 24 hours after cabazitaxel, as same-day administration has been shown to significantly reduce the infection rate during cycle 1 (6% vs 26%, respectively; \( P = 0.01 \)).

Modifying the dose of cabazitaxel is also appropriate to minimize the toxicities associated with cabazitaxel. The dose can be lowered from 25 mg/m\(^2\) to 20 mg/m\(^2\) since the incidences of most adverse events are less with the lower dose. \(^{20,21}\) Moreover, results of the PROSELICA trial showed overall survival (OS) to be similar at the 2 dose levels (13.4 vs 14.5 months),
while grade 3/4 adverse events were more frequent with the higher dose (39.7% vs 54.5%). The most frequent grade 3/4 adverse events in the 20 mg/m² vs 25 mg/m² groups were febrile neutropenia (2.1% vs 9.2%), hematuria (1.9% vs 4.2%), and diarrhea (1.4% vs 4.0%). Similar observations have been observed in the FIRSTANA trial. In FIRSTANA, efficacy outcomes of median OS (24.5 months vs 25.2 months) and progression-free survival (4.4 months vs 5.1 months) were similar in the lower and higher dose groups. However, febrile neutropenia, diarrhea, and hematuria were more frequent with the 25 mg/m² dose.

Also in FIRSTANA, grade 3/4 adverse events occurred in 41.2% and 60.1% of patients treated with 20 mg/m² compared with 25 mg/m², respectively.

In September 2017, the US Food and Drug Administration approved the 20 mg/m² dose of cabazitaxel (in combination with prednisone) for the treatment of patients with mCRPC previously treated with a docetaxel-containing regimen.

### 5. Under what circumstances should there be a concern about small cell or neuroendocrine prostate cancer?

**Answer**

A subset of patients with metastatic castration-resistant prostate cancer (mCRPC) can develop neuroendocrine prostate cancer (NEPC) following androgen deprivation therapy (ADT). NEPC is an aggressive variant of prostate cancer with overall survival typically less than 1 year from time of detection.
NEPC tumors retain many of the common prostate cancer genomic alterations as they appear to arise clonally from a prostate adenocarcinoma precursor. However, new molecular alterations occur as well.25 Treatment-emergent NEPC may occur in 30% to 40% of patients with mCRPC, including 10% to 15% with pure small cell histology and about 25% with a phenotype intermediate between adenocarcinoma and small cell.26 The typical presentation of NEPC is in the setting of predominant visceral metastases, ie, liver metastases, bulky lymphadenopathy, low prostate specific antigen (PSA) level despite high volume disease and/or predominantly lytic rather than blastic bone metastases.24

Investigation for NEPC is warranted in patients who have particularly aggressive mCRPC who have failed to respond to typical prostate cancer therapies, with progression in the setting of a low or nonrising PSA.24 By themselves, serum neuroendocrine markers have limited sensitivity, thus metastatic tumor biopsy is needed to make a definitive diagnosis. This is done morphologically or by immunohistochemical staining for neuroendocrine markers like chromogranin A or synaptophysin.

The choice of systemic therapy depends on the clinical context (de novo vs treatment-emergent) and pathologic findings (small cell vs focal neuroendocrine differentiation). Cytotoxic chemotherapy is preferred over androgen pathway inhibitors, such as abiraterone or enzalutamide, when biopsy reveals pure small cell differentiation. For fit patients, carboplatin plus docetaxel is reasonable if the biopsy also reveals concomitant persistent androgen receptor expression. A platinum-etoposide doublet may be preferred in cases with minimal evidence of dependence on AR signaling. Cytotoxic chemotherapy and/or androgen signaling inhibitors can be used if the biopsy reveals high-grade adenocarcinoma with focal neuroendocrine differentiation or intermediate phenotypic features without frank small cell morphology.25,27 Alternatively, a taxane plus carboplatin can be considered for patients who are fit. However, given the relatively poor outcomes and aggressive clinical course, participation in a prospective clinical trial is encouraged.

**Neuroendocrine/Small-Cell Prostate Cancer**

- De novo presentation rare (<1% new diagnoses)
- May arise as a mechanism of resistance to ADT
- Metastatic disease, including unusual sites of metastases
- Low or modestly rising PSA
- Paraneoplastic syndromes (uncommon)
- Elevated CEA or serum neuroendocrine markers (chromogranin, neuron specific enolase) can support the diagnosis
- Tissue IHC expresses chromogranin A and synaptophysin
- Treated like small-cell lung cancer
  - platinum-doublet chemotherapy, eg, cisplatin or carboplatin with etoposide

**Situations to Perform a Metastatic Biopsy**

- Visceral lesions, especially liver metastasis
- Extremely bulky lymph nodes (>5 cm)
- Low PSA in the setting of very high volume disease
- Predominantly lytic rather than blastic bone metastases
Case #1 – Allan

Allan, a 62-year-old man who received sipuleucel-T for metastatic castration-resistant prostate cancer (mCRPC) was found to have progressive disease based on rising prostate specific antigen (PSA) level and imaging. He is experiencing mild pain that is effectively treated with as-needed ibuprofen. Imaging shows metastatic disease involving bone and lymph nodes (3-5 cm) in the pelvis and retroperitoneum. He has a history of chronic active hepatitis B with chronic low-level transaminitis (∼3 times upper limit of normal).

What treatment options should be considered in this situation, given the Allan’s comorbidities?

Answer

In this patient with mCRPC and visceral metastases, treatment options include docetaxel plus prednisone, abiraterone plus prednisone, enzalutamide, or entry into a clinical trial.5

The patient’s abnormal liver function is an important consideration in selecting therapy. This would preclude the use of docetaxel due to concerns about an increased risk of toxicity and death.28 Among the remaining choices, abiraterone plus prednisone and enzalutamide are the most extensively investigated. Elevations (placebo-adjusted) in transaminase levels have been observed in 6% to 7% of chemotherapy-naïve patients with mCRPC treated with abiraterone plus prednisone.29,30 Consequently, enzalutamide would be a better choice than abiraterone plus prednisone as the next step in therapy.
Case #2 – Todd

Todd, a 55-year-old male, initially presented with de novo prostate cancer that had metastasized to the bones diffusely and multiple retroperitoneal lymph nodes. First-line treatment consisted of androgen deprivation therapy (ADT) with 6 cycles of docetaxel chemotherapy. He had a good initial response with an undetectable prostate specific antigen (PSA) level. Unfortunately, soon after completion of docetaxel, his PSA rose rapidly, indicating castration-resistant disease. He was subsequently treated with abiraterone/prednisone for 5 months, but then progressed with a rising PSA, multiple new bone metastases, and new bone pain.

Todd was given cabazitaxel plus prednisone due to his rapid progression after docetaxel for hormone-sensitive disease. His PSA declined slightly over the first 3 cycles but then started to rise slightly to 5.3 ng/mL. Imaging revealed multiple new liver metastases. A metastatic liver biopsy revealed no small cell morphology; immunohistochemistry was negative for chromogranin A and synaptophysin. His biopsy tissue revealed genetic alterations in BRCA2. This was surprising since he had no family history of prostate, breast, or ovarian cancer. Enrollment into a clinical trial investigating poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor was not considered since he was not able to travel. Instead, treatment with docetaxel plus carboplatin was initiated, resulting in decreased size of his liver metastases and improvement of his bone pain.

Discussion

Disease progression is common in men with castration-resistant prostate cancer (CRPC) requiring thoughtful use of sequential therapy based on evolving evidence that includes genomic profiling to identify the molecular subtype. One recent investigation found that approximately 90% of patients with metastatic prostate cancer (mCRPC) harbor clinically actionable molecular mutations, with 23% having DNA repair pathway and 8% harboring germline mutations.31

The most frequent aberrant genes were androgen receptor (62.7%), E26 transformation-specific-fusion (56.7%), TP53 (53.3%), and PTEN (40.7%).

Another recent investigation found that 11.8% of men with mCRPC harbored germline DNA-repair gene mutations, most commonly in the BRCA2 gene (5.3% of men).32 Mutation frequencies did not differ according to family history or age at diagnosis. Family genetic counseling is important when germline alterations are suspected.

PARP inhibitors or other agents that induce double-strand breaks, eg, platinum chemotherapy, may lead to better response in patients having a DNA repair gene abnormality.33-35 A recent phase 2 trial showed that 14 of 16 (88%) evaluable patients with heavily pretreated mCRPC and a DNA repair mutation had a response to the PARP inhibitor olaparib compared with 2 of 33 (6%) patients without a DNA repair mutation.36 The 14 patients with a DNA repair mutation included all 7 with BRCA2 loss (4 with biallelic somatic loss and 3 with germline mutations) and 4 of 5 with ATM mutations.

In summary, preliminary data such as these suggest that there is likely to be clinical benefit with platinum agents and PARP inhibitors; further investigation of patients with DNA repair abnormalities is ongoing.
Furthermore, tumor and germline DNA sequencing should be considered in the management of mCRPC to identify patients who are likely to derive benefit from this approach.

Case #3 – Jeff

Jeff, a 64-year-old male diagnosed with localized, prostate specific antigen (PSA) level 18 ng/mL, Gleason 4+5=9, T1c prostate cancer 4 years ago underwent radical prostatectomy. He had a good initial response with an undetectable PSA level. However, after 1 year, his PSA began to rise and it was followed for 1 year at which time his PSA level reached 10.4 ng/mL, resulting in his being started on androgen deprivation therapy (ADT). Jeff’s PSA did not nadir to undetectable, so rather than going to intermittent ADT, he was kept on therapy. Two years later, his PSA had risen over the last 3 measurements (obtained quarterly) from 0.8 to 1.7 to 5.2 ng/mL.

Discussion
Jeff would be categorized as having M0 or non-metastatic castration-resistant prostate cancer (CRPC). Unfortunately, there currently are no options for treating nonmetastatic CRPC that result in an overall survival (OS) benefit. Treatments that improve OS in CRPC such as sipuleucel-T, abiraterone acetate, and enzalutamide, are approved for metastatic CRPC only. Of note, however, is that a preliminary press release in September 2017 (data not yet released) from the PROSPER trial showed that enzalutamide plus ADT delayed the development of clinically detectable metastases compared to ADT alone in patients with nonmetastatic CRPC whose only sign of underlying disease was a rapidly rising PSA level.37 This preliminary report from PROSPER is encouraging, but is not sufficient to initiate enzalutamide in the nonmetastatic CRPC setting at this time. It is important to consider imaging, at this time, to accurately stage his CRPC. The importance of restaging his disease is emphasized by a recent finding that one-third (32%) of men thought to have nonmetastatic CRPC actually had progressed to metastatic CRPC.38 If the patient were to undergo a CT and bone scan at this time, and metastatic disease were found, then he would be eligible for sipuleucel-T, abiraterone, enzalutamide, or docetaxel.
References


20. de Bono JS, Hardy-Bessard AC, Kim CS, et al. Phase III non-inferiority study of cabazitaxel (C) 20 mg/m² (C20) versus 25 mg/m² (C25) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (D). *J Clin Oncol*. 2016;34(Suppl):Abstr 5008.


