Nonhormone Therapy for Metastatic Castration-Resistant Prostate Cancer: Chemotherapy, Bone-Targeted Treatments, and Others

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OVERVIEW

There is no doubt that more therapeutic progress has been achieved during the last 3 years for patients with metastatic castration-resistant prostate cancer (mCRPC) than during the previous 30 years. During this limited time frame, not only have six compounds (sipuleucel-T, cabazitaxel, denosumab, abiraterone, radium-223, and enzalutamide, listed in chronologic order) yielded positive results in phase III trials, we have also learned that their mechanisms of action are different, making it quite likely that part of their anticancer activity may be incremental. Most of these agents have already been approved. Further progress may well soon complete this recently enlarged armamentarium, with important trials testing new agents derived from existing families of compounds (new endocrine therapies, new immunotherapies, etc.) and exploring the activity of new families of agents (tyrosine kinase inhibitors such as cabozantinib, inhibitors of chaperone proteins like OGX-O11 and OGX-427). The availability of these agents creates a new major challenge for those who conduct clinical research in mCRPC. Will we be able to personalize therapy based on the biology of the individual’s tumor, as we are already doing in other neoplasms?

Endocrine therapy remains the most commonly used treatment for patients with metastatic prostate cancer; however, abiraterone acetate and enzalutamide now demonstrate improved survival in patients in whom androgen deprivation therapy has failed, and agents with other mechanisms of action also demonstrate clinical activity in randomized trials, including chemotherapeutic agents (cabazitaxel), bone-targeted agents (denosumab), radiopharmaceuticals (radium-223), and immunotherapy (sipuleucel-T). An algorithm summarizing the incorporation of novel agents for the management of advanced prostate cancer (defined as either with metastases or castration-resistant disease, or both) is proposed in Table 1. This report will focus on nonhormone, nonimmunotherapy agents.

TAXANES: STILL A MAJOR ROLE IN mCRPC

Since 2004, docetaxel has been the standard first-line chemotherapy for patients with mCRPC. The most successful phase III trials recently conducted in mCRPC focused on patients experiencing cancer progression after first-line docetaxel chemotherapy. Indeed, improving their outcome was the most critical unmet need, and this stage also provided an opportunity to demonstrate an overall survival improvement more rapidly with an active drug over a shorter time frame. To date, four drugs have afforded an overall survival benefit on top of other clinical improvements for patients whose disease progressed after docetaxel: cabazitaxel, abiraterone, radium-223, and enzalutamide. When available, their use should now be preferred over a rechallenge with docetaxel, which was regarded before 2010 as a reasonable option, without any proof of a gain in survival for patients who were experiencing progression several months after discontinuation of first-line docetaxel.

Cabazitaxel, a “second-generation” taxane with broader preclinical activity than docetaxel, was shown to improve overall survival when added to prednisone compared with mitoxantrone plus prednisone in the TROPIC trial (hazard ratio [HR] 0.72, 95% CI 0.61 to 0.84; median overall survival, 15.1 vs. 12.7 months; p < 0.0001) in 745 patients with mCRPC progressing after treatment with docetaxel. Progression-free survival (PFS) was also improved with cabazitaxel/prednisone (HR 0.75, 95% CI 0.65 to 0.87). The main side effects included hematologic toxicity and diarrhea; consequently, the use of prophylactic granulocyte colony-stimulating factor with the currently recommended dose of 25 mg/m² will be discussed on an individual basis in routine practice. Preliminary data suggested maintained antitumor activity of cabazitaxel in patients in whom both docetaxel and abiraterone failed, with a prostate-specific antigen (PSA)
response rate of approximately 50%. Two ongoing phase III trials aim to optimize the use of cabazitaxel in patients with mCRPC: a front-to-front comparison trial compared with docetaxel in the first-line chemotherapy setting (FIRSTANA, NCT01308567), and a trial aimed at defining the optimal dose (20 or 25 mg/m²) in the second-line setting (PROSELICA, NCT01308580). Another large phase III trial (PEACE 2) testing cabazitaxel in patients with localized prostate cancer and very high-risk features of relapse is also scheduled to begin its accrual in 2013.

So far, the development of nontaxane chemotherapy has ended with failures, with the development of epothilones almost at a standstill and only modestly improved progression-free survival being reported for satraplatin in the post-docetaxel setting in a phase II trial. Although platin-based combinations retain activity at this stage of the disease, regardless of whether a neuroendocrine phenotype is present, more efforts should be made to identify patients with mCRPC who could benefit from these approaches, and programs searching for those with a BRCA-ness phenotype are ongoing.

**TABLE 1. A Proposed Evidence-Based Treatment Algorithm for Patients with Advanced Prostate Cancer.**

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Standard Treatment</th>
<th>Alternative Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-metastatic CRPC</td>
<td>None (continuing ADT)</td>
<td>Endocrine manipulations denosumab*</td>
</tr>
<tr>
<td>Metastases, hormone-naive</td>
<td>ADT</td>
<td>CAB: ADT + AR inhibitor</td>
</tr>
<tr>
<td>Metastatic CRPC</td>
<td>Bone metastases from CRPC</td>
<td>Denosumab*</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic CRPC</td>
<td>Zoledronic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abiraterone*</td>
</tr>
<tr>
<td>Symptomatic CRPC</td>
<td>Docetaxel</td>
<td>Docetaxel + estramustine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alpharadin* (patients with bone metastases, unfit for docetaxel)</td>
</tr>
<tr>
<td>CRPC progressing after docetaxel</td>
<td>Cabazitaxel*</td>
<td>Docetaxel rechallenge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abiraterone*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alpharadin*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enzalutamide*</td>
</tr>
<tr>
<td>CRPC progressing after docetaxel and novel drugs with an overall survival benefit</td>
<td>None (ADT)</td>
<td>Clinical trial</td>
</tr>
</tbody>
</table>

* Agents recently incorporated in the CRPC armamentarium based on positive phase III data

Abbreviations: CRPC, castration-resistant prostate cancer; ADT, androgen deprivation therapy (= castration); CAB, complete androgen blockade; AR, androgen receptor.

**TARGETING THE BONE MICROENVIRONMENT WITH OSTEOCLAST INHIBITORS IN mCRPC: NOW AN ESTABLISHED STANDARD**

In the 2000s, zoledronic acid was the only drug capable of demonstrating an improvement in time to skeletal-related events (SRE) over a placebo in patients with bone metastases from mCRPC, without any demonstrated improvement in overall survival.

RANKL is a key protein secreted by osteoblasts that promotes osteoclast differentiation and bone resorption. Evidence of increased RANKL expression and decreased osteoprotegerin (a RANKL natural inhibitor) was provided in preclinical models of bone metastases from mCRPC. Denosumab is a RANKL inhibitor that was originally developed in a proof-of-concept randomized phase II trial in patients with localized prostate cancer and very high-risk features of relapse and is also scheduled to begin its accrual in 2013.

So far, the development of nontaxane chemotherapy has ended with failures, with the development of epothilones almost at a standstill and only modestly improved progression-free survival being reported for satraplatin in the post-docetaxel setting in a phase III trial, although platin-based combinations retain activity at this stage of the disease, regardless of whether a neuroendocrine phenotype is present. More efforts should be made to identify patients with mCRPC who could benefit from these approaches, and programs searching for those with a BRCA-ness phenotype are ongoing.

**KEY POINTS**

- Besides endocrine therapy, taxanes, immunotherapy (sipuleucel-T), and bone-targeted agents (zoledronic acid, denosumab, and radium-223) have reported positive phase III trials in metastatic castration-resistant prostate cancer.
- New promising drugs are currently being developed, including tyrosine kinase inhibitors (cabozantinib), immunotherapies (ipilimumab, rilimogene galvacirepvec), and oligonucleotide antisense (OGX-011 and OGX-427).
- Personalizing treatment based on the individual cancer biology is becoming a priority.

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denosumab is now approved for use in mCRPC in Europe and the United States.

A second large study, the “147” phase III trial, enrolled 1,432 men with nonmetastatic CRPC and at least one of the following factors associated with a high risk for bone metastases: PSA of 8.0 μg/L or higher, or PSA doubling time of 10.0 months or shorter. Patients were randomly assigned to denosumab (120 mg SC) or a placebo every 4 weeks. The trial was considered statistically positive because denosumab increased the primary endpoint of bone-metastasis–free survival by 15% (29.5 vs. 25.2 months; HR 0.85, 95% CI 0.73 to 0.98; \( p = 0.028 \)), although the risk/benefit ratio of denosumab in this setting is being challenged because this difference may be regarded as modest. There was no overall survival difference, and long-term exposure to denosumab is associated with an increased risk of osteonecrosis of the jaw.

### Radiopharmaceuticals: They Finally Made It!

Bone-targeting radiopharmaceuticals have a high affinity to bone enabling the delivery of radiation preferentially to areas of high bone turnover after IV injection. Whether they also improve overall survival is unclear, and even higher efficacy was reported in patients with chemosensitive mCRPC.

Radium-223 (also called alphadin) is a calcium-mimetic radiopharmaceutical with high bone affinity. As an alpha emitter, it has two theoretical advantages over beta-emitters: (1) only a few “hits” are required to induce double-strand breaks in cancer cells, and (2) the first cell layer can stop its penetration in the bone marrow, thus preventing hematologic toxicity. Radium-223 was first studied in a proof-of-concept randomized phase II trial, with favorable results compared with a placebo in patients with bone metastases from mCRPC.\(^\text{10}\) The ALSYMPCA phase III trial was then conducted in 922 patients (approximately 60% of whom had been pretreated with docetaxel, and 40% had been considered unfit for docetaxel) who were randomly assigned in a 2:1 fashion between radium-223 (50 kBq/Kg for 4 weeks for 6 cycles) and a placebo. The updated analysis showed improved overall survival (HR 0.695, 95% CI 0.581 to 0.832; \( p = 0.00007 \)) with a median duration of 14.9 and 11.3 months, respectively. A similar trend toward better overall survival in favor of the radium-223 arm was found in various subgroups (according to the use of bisphosphonates, prior docetaxel, and the performance status). Patients with baseline elevated serum alkaline phosphatase tend to reap an even stronger overall survival benefit. Time to the first SRE was also improved (HR 0.658, 95% CI 0.522 to 0.830; \( p = 0.00037 \)) with a median duration of 15.6 compared with 9.8 months. Overall, tolerance was good, with 25% experiencing diarrhea compared with 15% in the radium-223 arm (the drug is excreted by the small bowel), but there were no excess grade 3 to 4 events.\(^\text{11}\)

An expanded access program for radium-223 is ongoing.

### More to Come?

### More to Come with Bone Targeting?

C-Met is a tyrosine kinase expressed by osteoblasts and osteoclasts, and overexpressed by prostate cancer cells. Cabozantinib (XL-184), a c-Met and vascular endothelial growth factor receptor-2 inhibitor, was tested in patients with mCRPC. Impressively results from a phase II study that enrolled 171 patients were recently reported, notably including a partial or complete improvement in the bone scan in 68% and pain improvement in 67% of the patients.\(^\text{25}\)

Median PFS was 23.9 weeks (95% CI 10.7 to 62.4 weeks) with cabozantinib and 5.9 weeks (95% CI 5.4 to 6.6 weeks) with a placebo (HR 0.12; \( p < 0.001 \)). Toxicity is as expected for a tyrosine kinase inhibitor, including fatigue, hypertension, and palmar-plantar syndrome, and constitutes a challenge for the original 100 mg/day dose for further development.

Two phase III trials were recently initiated: one with pain as the primary endpoint (COMET-2, NCT01522443) and a global phase III trial with overall survival as the primary endpoint in patients with mCRPC in whom docetaxel and abiraterone failed (COMET-1, NCT01605227). The exact mechanism of action of cabozantinib in patients with mCRPC remains to be elucidated, since another c-Met inhibitor, rilotumumab, failed to demonstrate efficacy in a randomized phase II trial.\(^\text{26}\)

Another potential target for therapy in mCRPC is Src, which is expressed by osteoclasts and by some prostate cancer cells. Dasatinib, a Src inhibitor, was tested in patients with mCRPC as a single agent and combined with chemotherapy.\(^\text{27}\) The results of a large phase III trial testing docetaxel with and without dasatinib (NCT00744497) was very recently reported to be negative.

### More to Come: Novel Drugs with Original Targets?

Many potential targets for mCRPC have been identified in the recent past, and numerous trials testing inhibitors are ongoing (which cannot all be presented in detail in this article). Among them, original technologies include antisense oligonucleotides like OGX-011 (which targets clusterin, a chaperone protein) and OGX-427 (which targets heat-shock protein 27). OGX-011 was tested in a randomized phase II trial in combination with docetaxel. A better overall survival duration was reported in the combination arm (median, 23.8 and 16.9 months, respectively).\(^\text{28}\) Two phase III trials are ongoing to confirm these results in combination with chemotherapy: one in the first-line setting (SYNERGY, testing docetaxel with or without custirsen, NCT01188187), the other in the second-line setting (AFFINITY, testing cabazitaxel with and without custirsen, NCT01578655). OGX-427 was tested in a randomized phase II trial compared with prednisone with, respectively, 71% and 40% of patients alive and free of progression at 12 weeks, and activity also reported in terms of PSA response, RECIST criteria, and circulating tumor cell conversion.\(^\text{29}\)

Tasquinimod targets S100A9; its antiangiogenic and immune-modulation properties are still incompletely understood. This oral compound was tested in a randomized
phase II trial in 201 asymptomatic patients with mCRPC: the primary endpoint, PFS, was significantly improved (7.6 vs. 3.3 months; p = 0.0042). A confirmatory phase III trial is ongoing in the same setting. A proof-of-concept “switch maintenance” randomized study is also ongoing with tasquinimod in patients with disease response or stabilization on first-line docetaxel chemotherapy (NCT01732549).

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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