Castrate-resistant prostate cancer

Major breakthroughs have led to novel treatment paradigms

Peter Black, MD, FACS, FRCSC

Castrate-resistant prostate cancer (CRPC) represents the end stage of the most common cancer in men. If a patient presents with metastatic disease or fails local definitive therapy, androgen deprivation therapy (ADT) is implemented. Usually, this is given in the form of a luteinizing hormone-releasing hormone (LHRH) agonist injected as a 1- or 3-month depot, although surgical castration remains an option, and a LHRH antagonist has now also entered the market.1 Each method leads to cessation of testosterone production in the testicles and castrate levels of testosterone in the serum. The androgen receptor in the prostate cancer cells is itself unaffected. Small amounts of androgens are still synthesized in the adrenal glands and we also know now that the prostate itself is capable of steroidogenesis and androgen production. Blockade of the effects of androgen from these secondary sites can be achieved with the addition of non-steroidal antiandrogens such as bicalutamide or flutamide. These agents block the androgen receptor.

Regardless of the form of ADT, all prostate cancer eventually becomes refractory to this therapy: the prostate-specific antigen (PSA) rises and the patient eventually demonstrates clinical progression. This has traditionally been referred to as androgen-independent prostate cancer, but more recent discoveries have revealed that androgens still play a very active role in progression of these cancers. The androgen receptor is frequently found to be amplified, overexpressed, alternately spliced or mutated. The newer term is therefore CRPC, as the disease is resistant to our methods for castration, but ultimately still dependent on androgen regulation. CRPC typically leads to the patient’s death within 18 to 36 months.

CURRENT STANDARD OF CARE

If the PSA rises in a surgically or medically castrate patient, an antiandrogen is often added and approximately one-third of patients experience a transient PSA response (weeks to months). When the PSA starts to rise again, the antiandrogen is discontinued because we know that these agents can act as partial agonists and actually drive prostate cancer growth. Sometimes, this antiandrogen withdrawal will again lead to a transient decline in the PSA.

Not long ago, the only treatment options beyond the hormone manipulations described were further secondary hormone treatments, including low-dose estrogen therapy or ketoconazole. Ketoconazole is a weak and nonspecific inhibitor of cytochrome P450 17A1 (CYP17), an important enzyme in steroidogenesis. Overall, the results were only temporary and were associated with significant adverse effects.

Mitoxantrone was the first chemotherapeutic agent proven efficacious in prostate cancer. It was associated with decreased pain and improved quality of life, but not prolonged survival in men with CRPC.2 Mitoxantrone was supplanted by docetaxel, which was the first cytotoxic agent to demonstrate a survival advantage in men with CRPC.3 Docetaxel has become the standard of care. Typically, patients are observed until they begin to show symptoms of disease progression and then are started on chemotherapy.

A RAPIDLY EXPANDING FIELD WITH MULTIPLE NOVEL AGENTS

Over the past several years, a number of major breakthroughs have been achieved in the management of CRPC and we are currently on the verge of an embarrassment of riches for treatment of this disease. These breakthroughs have included completely novel treatment paradigms, such as the first vaccine therapy to be proven successful in any type of solid cancer. A major discovery driving further development of new agents has been the realization that CRPC is still regulated by androgens. A significant focus of treatment has also been the management

### TABLE 1. New therapies for castrate-resistant prostate cancer: mechanisms of action and stage of clinical development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Stage of development</th>
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<tbody>
<tr>
<td>Denosumab</td>
<td>Monoclonal antibody targeting RANK-ligand</td>
<td>Approved in metastatic patients</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Bisphosphonate (inhibits bone turnover)</td>
<td>Approved in metastatic patients</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>Autologous dendritic cell vaccine</td>
<td>Approved in asymptomatic and minimally symptomatic patients prior to chemotherapy</td>
</tr>
<tr>
<td>Cabazitoxel</td>
<td>Microtubule stabilization</td>
<td>Approved post-docetaxel, Phase III trial pre-docetaxel ongoing</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>CYP17 inhibitor (blocks steroidogenesis)</td>
<td>Approved post-chemotherapy, Phase III trial pre-chemotherapy complete but not reported</td>
</tr>
<tr>
<td>MDV3100</td>
<td>Androgen receptor inhibitor</td>
<td>Phase III trial complete but not reported (post-chemotherapy), second Phase III trial ongoing (pre-chemotherapy)</td>
</tr>
<tr>
<td>OGX-011</td>
<td>Antisense oligonucleotide targeting clusterin</td>
<td>Ongoing Phase III trials</td>
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of bone health and the prevention of complications related to osteoporosis and bone metastasis. The new agents include not only targeted therapies, but also a new cytotoxic agent.

THE FIRST SUCCESSFUL VACCINE THERAPY
Sipuleucel-T is a form of cellular immunotherapy. Dendritic cells from the prostate cancer patient are isolated by leukapheresis and exposed to a prostate antigen. This antigen is a recombinant protein consisting of prostatic acid phosphatase fused with granulocyte macrophage colony stimulating factor (GM-CSF). The activated dendritic cells are transfused back into the patient and the treatment is repeated after 2 and 4 weeks for a total of 3 cycles.

Sipuleucel-T was approved for treatment in the US and Europe in 2010. In men with asymptomatic or minimally symptomatic metastatic CRPC without visceral metastases, an overall survival (OS) advantage was noted from 21.7 months in the placebo group to 25.8 months in the treatment group (p=0.03). The main side effect of sipuleucel-T was a transfusion reaction, observed in 54% of patients. The principal barrier to introduction of this treatment option, especially in Canada, is the extraordinary cost. In the US, the current cost for 3 cycles of vaccination is approximately $90,000.

In the context of immunotherapy for prostate cancer, another new agent is also in late-stage clinical evaluation. Ipilimumab is a monoclonal antibody targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which is an inducible receptor expressed by T cells that is relevant for self-tolerance. Early-phase trials demonstrate efficacy and Phase III trials are underway. A second vaccine agent, Prostvac, is also under clinical evaluation.

THE ANDROGEN RECEPTOR REVISITED
With the recognition that CRPC is driven by autocrine and paracrine androgen stimulation with active signaling through the androgen receptor, research efforts have focused on further targeting of this pathway. The first drug to be successful all the way to clinical implementation has been abiraterone. This is a CYP17 inhibitor that blocks all androgen synthesis. In this regard, it is similar to ketoconazole, but more potent and more selective, with fewer adverse effects. A Phase III trial comparing abiraterone with placebo in men who failed prior docetaxel chemotherapy showed a 4-month improvement in (14.8 months vs 10.9 months). The main side effect of sipuleucel-T was a transfusion reaction, observed in 54% of patients. The principal barrier to introduction of this treatment option, especially in Canada, is the extraordinary cost. In the US, the current cost for 3 cycles of vaccination is approximately $90,000.

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APPROACHING THE FINISH LINE
At the top of the list of promising new targeted agents in late-stage development with novel mechanisms of action is OGX-011. This is a second-generation antisense oligonucleotide that specifically inhibits clusterin. Clusterin is a cell survival chaperone protein that is activated in prostate cancer in androgen and chemotherapy resistance. Targeting clusterin sensitizes the prostate cancer to docetaxel and it is therefore given in combination with docetaxel. A Phase II trial in chemotherapy-naïve patients showed a remarkable improvement in OS from 16.0 to 23.8 months. Two large Phase III trials are underway.

NEAR MISSSES
One of the biggest stories in the last 2 years in the development of new agents for CRPC is the failure of atrasentan and zibotentan, both endothelin receptor antagonists. Atrasentan failed first in 2 Phase III trials evaluating progression-free survival (PFS) as the primary endpoint. A third trial targeted particularly at patients with bone metastases was recently reported and also showed no benefit. Zibotentan was evaluated aggressively in 3 parallel Phase III trials. It had been successful

FIGURE 1. Clinical scenarios in CRPC
![Clinical scenarios in CRPC diagram]

The different clinical contexts that define a patient’s disease status are outlined.

Novel treatments that have been tested in clinical trials for each scenario are indicated; those still in clinical trials are in parentheses.
in a Phase II trial and was thought to be more potent than atrasantan because it inhibits both type A and B endothelin receptors. Unfortunately, the first 2 Phase III trials in asymptomatic metastatic and non-metastatic settings failed to show an OS advantage. The third Phase III trial in men with symptomatic metastatic disease is still ongoing. Although treatment was well tolerated in all settings, targeting the endothelin receptor no longer appears to be worthwhile.

**TARGETING THE BONE**

Since CRPC spreads with a significant predilection to bone, bone health and so-called “skeletal-related events” (SREs) are a very important issue in patients with prostate cancer. SREs include the requirement of radiation or surgery of bone, bone fractures and spinal cord compression. In patients with CRPC and bone metastasis, zoledronic acid was shown to decrease SREs vs placebo (33% vs 44%; p=0.02). The time to first SRE increased from 321 days to 488 days (p=0.009).17 The challenges with zoledronic acid therapy are the need for IV infusion every 3 or 4 weeks as well as toxicities that include renal failure, which requires monitoring renal function, and osteonecrosis of the jaw.

Denosumab has followed zoledronic acid and has also been approved for treatment of patients with CRPC and bone metastasis. Denosumab is a monoclonal antibody that targets the RANK ligand, which has been shown to be a key regulator of osteoclast activation. Denosumab was compared head-to-head with zoledronic acid and was found to decrease the rate of SREs as well as increase the time to first SRE.18 Denosumab has the advantage of easy subcutaneous injection, although it shares the complication of osteonecrosis of the jaw.

A Phase III trial evaluating denosumab for the prevention of bone metastasis in patients with non-metastatic CRPC was recently reported in abstract form. This study reports a delay in the time to first bone metastasis of 4.2 months vs placebo. Further followup is necessary to see if there will be a prolongation of survival.

**NOT TO FORGET THE CYTOTOXICS**

Parallel to these developments in targeted therapy, a new cytotoxic agent has also been developed that has shown clear efficacy against CRPC. Cabazitaxel was approved by the FDA in 2010 for second-line chemotherapy after docetaxel. A Phase III trial showed superiority of cabazitaxel vs mitoxantrone.19 There was a 30% reduction in the risk of death and an improvement in OS from 12.7 to 15.1 months. The only troublesome complication with the cabazitaxel was an almost 82% rate of neutropenia. The dose used in the Phase III trial was higher than the recommended dose from the Phase I trial and a further trial is planned to evaluate lower dosing with the hope of decreasing toxicity. A Phase III trial is also planned to test cabazitaxel as a first-line chemotherapy. Prior to cabazitaxel, mitoxantrone was the only cytotoxic agent with some evidence of efficacy in the post-docetaxel setting.

**MAKING SENSE OF NOVEL OPTIONS IN CRPC**

With new agents to treat patients with CRPC, we must now define how best to sequence these drugs and determine which patients are likely to benefit most from each agent. The trials with the various new agents have shown that our endpoint definitions are difficult to assess. For example, the typical definitions of PFS appear to be irrelevant with the vaccine treatment even though a clear difference in OS was determined. Similarly, some of the trials show no benefit on parameters defined by PSA, yet continue to show a survival advantage. Novel biomarkers for assessing risk and response are urgently needed in order to design personalized treatment algorithms that would facilitate optimal delivery of care at the lowest possible expense.

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16. A Phase III trial of ZD4054 (Zibotentan) (Endothelin A Antagonist) in Hormone Resistant Prostate Cancer With Bone Metastases (ENTHUSE M1)."