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Current Options and Future Directions in Castrate Resistant Prostate (CRPC)

Suzanne Richter and Srikala S. Sridhar
*Department of Medical Oncology, Princess Margaret Hospital
University of Toronto
Canada*

1. Introduction

Prostate cancer is the most frequently diagnosed malignancy in North America and second leading cause of cancer-related death (Jemal *et al.*, 2010). Despite effective local therapy, prostate cancer often recurs. Standard therapy for recurrent or metastatic prostate cancer remains androgen deprivation therapy (ADT) which is highly effective but not durable (Sharifi *et al.*, 2005). All patients will eventually progress to castrate resistant prostate cancer (CRPC) where there are few treatment options and until recently survival was a dismal 12-18 months (Tannock *et al.*, 1996). In this chapter we will review the current treatment approaches for CRPC, but focus primarily on the newly approved options available in the post-docetaxel setting.

Castrate-resistant prostate cancer (CRPC) is defined as prostate cancer progression despite ADT and may present with either increasing serum prostate-specific antigen (PSA) levels, radiologic progression, and/or the appearance of new metastases (Saad and Hotte, 2010). Over the years, advanced prostate cancer has been referred to as hormone-resistant prostate cancer (HRPC) or androgen-insensitive prostate cancer (AIPC), but the name has changed to CRPC to reflect the fact that intracrine/paracrine androgen production and signaling pathways play an important role in mediating resistance to first line ADT. CRPC presents as a spectrum of diseases ranging from patients with rising PSA alone, without metastases or symptoms to patients with rising PSA, progressive metastatic disease and significant symptoms. In patients who develop CRPC and who are relatively asymptomatic, secondary hormonal treatments may be attempted. To date, no study of secondary hormone treatment has demonstrated survival benefits, but most trials have been small, underpowered and confounded by the use of subsequent treatments. In patients who are progressing on ADT, discontinuation of antiandrogens, introduction of low dose prednisone or ketoconazole to block production of adrenal androgens, can offer transient PSA responses and palliative benefits in 30% to 35% of patients (Storlie *et al.*, 1995; Small *et al.*, 2004; Heng and Chi, 2006).

For CRPC patients with symptoms, rapid PSA progression or visceral disease, docetaxel chemotherapy and prednisone is currently considered standard of care. Docetaxel is a

member of the taxane family of drugs which binds to tubulin and causes microtubule stabilization, leading to cell cycle arrest in the G2/M phase and subsequently cell death (Jordan *et al.*, 1993). Docetaxel is administered every three weeks intravenously at a dose of 75mg/m² with oral prednisone 5 mg twice daily. This is based on two pivotal randomized phase III trials, the TAX 327 trial and the SWOG 9916 trial. TAX 327 randomized more than 1000 patients to receive docetaxel plus prednisone (weekly or every 3 weeks) or mitoxantrone plus prednisone (the previous first-line option). The every 3 week docetaxel arm had a median survival of 18.9 months compared with 16.5 months in the mitoxantrone arm. PSA response rates (defined as $\geq 50\%$ drop in serum PSA level) were 48% in the docetaxel group and 32% in the mitoxantrone arm (Tannock *et al.*, 2004). In the SWOG 9916 study, 770 patients were randomized to receive either docetaxel plus estramustine and prednisone or mitoxantrone plus prednisone. Again the median overall survival was longer (17.5 months vs. 15.6 months, $P=0.02$ by the log-rank test) and PSA response rates were higher (50% vs. 27%, $P<0.001$) with docetaxel compared with mitoxantrone (Petrylak *et al.*, 2004). Given the efficacy of docetaxel as a single agent and potential thromboembolic toxicity from the addition of estramustine, docetaxel alone with daily prednisone became the standard approach. Although in the trial setting, patients received up to 10 cycles of treatment, in routine practice where patients are less fit, an average of 7 cycles is the length of treatment (Chin *et al.*, 2010). Some patients also appear to respond to retreatment with docetaxel, raising the concept of docetaxel refractory vs. docetaxel resistant disease (Chin *et al.*, 2010). Nonetheless, all patients will eventually develop taxane resistance and progress. In the second line setting, mitoxantrone chemotherapy has palliative benefits, but does not offer a survival advantage, underscoring the need for new strategies in the post-docetaxel setting (Tannock *et al.*, 1996).

Much of the research in the post-docetaxel setting has focused on understanding taxane resistance. Several mechanisms have been proposed including alterations in both docetaxel uptake and retention in cells; changes to tubulin affecting binding sites for docetaxel; and changes in the androgen receptor (AR), which may also contribute in part to the anticancer activity of docetaxel (Gan and Kavallaris, 2008; Seruga *et al.*, 2010). Strategies aimed at overcoming taxane resistance may extend the therapeutic benefit of the taxanes in CRPC.

2. Cabazitaxel

Cabazitaxel is a new semi-synthetic derivative of the taxoid 10-deacetylbaaccatin-III, which like docetaxel binds to and stabilizes tubulin. But, unlike docetaxel is a poor substrate for the P-glycoprotein drug efflux pump and may also have enhanced penetration through the blood-brain barrier (Niraula and Tannock, 2011). In a Phase 1 trial of cabazitaxel the dose limiting toxicity at 25 mg/m² every 3 weeks was grade 4 neutropenia, and the common non-hematologic adverse events included low grade diarrhea (52%), nausea (40%) and vomiting (16%). Two patients with CRPC, including one previously treated with docetaxel showed a partial response (Mita *et al.*, 2009).

A phase III multicenter, multinational trial comparing cabazitaxel with mitoxantrone in the second line setting was conducted with a primary endpoint of overall survival (OS) (de Bono, 2010). Cabazitaxel significantly improved median OS compared with mitoxantrone (15.1 months vs 12.7 months, respectively; HR 0.72; 95% CI 0.61-0.84;

$p < 0.0001$). Secondary endpoints including progression free survival (PFS) (2.8 months vs 1.4 months), response rate (14.4% vs 4.4%; $p = 0.005$), and median time to progression (TTP) by tumor assessment (8.8 months vs. 5.4 months; $p < 0.0001$) also favored cabazitaxel. From a toxicity standpoint febrile neutropenia, neutropenia, leukopenia and diarrhea were more common in the cabazitaxel arm. One major concern with cabazitaxel however was a toxic death rate of 5% compared to only 1.9% for mitoxantrone. As cabazitaxel moves out of the controlled clinical trial setting into general use, early and proactive management of the toxicities will be critical. Cabazitaxel was FDA approved in 2010 for patients progressing on or after docetaxel. In the same year, a second drug, Abiraterone was also approved for use in the post-docetaxel setting.

3. Abiraterone

Over the last decade there has been a paradigm shift in the approach to CRPC, where despite castrate testosterone levels, there appears to be continued androgen receptor expression and signaling, suggesting that the androgen receptor axis is still a rational therapeutic target. In CRPC, androgens are mainly produced by the adrenal glands and by the prostate cancer cells themselves. This occurs by the sequential conversion of cholesterol to dihydrotestosterone and testosterone. This conversion is mediated by the CYP17 enzyme, which when inhibited can block androgen production. Ketoconazole, an antifungal agent, was the first generation CYP17 inhibitor that was tested in prostate cancer, with some benefit, but to date no studies have confirmed a survival benefit. On the other hand, abiraterone acetate (abiraterone), an oral, irreversible and more selective inhibitor of CYP17 has shown very encouraging results in the post-docetaxel setting.

In Phase I/II testing of abiraterone, there were no dose limiting toxicities, the main side effects were hypokalemia and lower-limb edema (due to the mineralocorticoid excess from the upstream inhibition of 17 alpha-hydroxylase), and antitumor activity was seen at all dose levels (Ryan *et al.*, 2010). A Phase III double blind, randomized, placebo-controlled trial of abiraterone 1000 mg daily plus prednisone (to avoid the mineralocorticoid related effects) versus prednisone alone, with the primary endpoint of OS was initiated (de Bono *et al.*, 2011). In total, 1,195 post-docetaxel CRPC patients were accrued, and treated until clinical or radiographic disease progression. Of note, biochemical progression alone (rising PSA) was not considered sufficient for discontinuation of the study drug. Interim analysis demonstrated increased median OS in the abiraterone arm, at 14.8 months compared to 10.9 months (HR 0.65, 95% CI 0.54-0.77) for prednisone leading to early termination of the trial. Other key endpoints including PSA response, time to PSA progression and radiographic progression free survival were all significantly improved in the abiraterone arm. Time to skeletal related events (SRE), defined as pathologic fracture, spinal cord compression, or palliative radiation therapy or surgery also favored the abiraterone arm. Mineralocorticoid related adverse events, consisting of hypertension and hypokalemia were more common in the abiraterone arm, but grade 3+ events were infrequent. A second Phase III trial of abiraterone in the pre-docetaxel setting has closed to accrual and results will likely be available in 2012.

Since both abiraterone and cabazitaxel are now approved in the post-docetaxel setting, a key question will be to determine the optimal sequencing of these agents. At this point it

will likely be done on a case by case basis after careful consideration of the rate of disease progression, overall burden of disease, performance status and toxicity profile of either drug.

4. Sipuleucel-T

Aside from cytotoxic therapies and androgen deprivation approaches, immunotherapy has emerged in prostate cancer drug development. Sipuleucel-T (Provenge, Dendreon) is an immunotherapy that can enhance response to the prostate cell tumor antigen, prostatic acid phosphatase. Generation of the immunotherapy involves collection of peripheral blood cells by leukapheresis and subsequent exposure to prostatic acid phosphatase and granulocyte macrophage colony stimulating growth factor. The cells are then reintroduced into the patient. Sipuleucel-T is an autologous dendritic cell vaccine which enhances prostatic acid phosphatase related T cell response.

Encouraging phase I/II trial results led to the pivotal randomized, double-blind, placebo-controlled, multicenter trial (Study 9902B) known as the IMPACT trial (Immunotherapy for Prostate Adenocarcinoma Treatment), with a primary endpoint of overall survival (Kantoff *et al.*, 2010). All patients underwent three leukapheresis procedures (Weeks 0, 2, and 4), followed 3 days later by either sipuleucel-T or the non-activated control. Eligible CRPC patients had metastatic disease in soft tissue and/or bone with evidence of radiologic or biochemical disease progression. Patients with moderate to severe prostate cancer-related pain and/or use of narcotics were excluded. Tumor expression of prostatic acid phosphatase of 25% or more was required. Five hundred twelve patients were randomized (2:1) to sipuleucel-T (n=341) or control (n=171). The sipuleucel-T arm had a 4.1 months improvement in median overall survival (25.8 mos versus 21.7 mo, p= 0.032, HR 0.775, 95% CI 0.61, 0.98). There was no difference in time-to-progression. Common adverse events (AE) for sipuleucel-T were mild or moderate and included chills, fatigue, fever, back pain, nausea, joint ache and headache. Serious adverse reactions (SAE) more common with sipuleucel-T were acute infusion reactions and stroke. Similar survival and tolerability results were seen in two additional trials, which ultimately led to approval by the US Food and Drug Administration in 2010 (Small *et al.*, 2006; Higano *et al.*, 2009). Priced at \$31,000 per treatment, Sipuleucel-T is one of the most expensive treatments ever, and as such may not be as widely available as either abiraterone or cabazitaxel.

5. Zoledronic acid

Over the last 10 years, there has also been growing interest in the issue of bone health in prostate cancer as it is known that both androgen deprivation therapy, and bony metastases can promote bone destruction. Zoledronic acid, is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. In a randomized placebo controlled clinical trial in men with CRPC and bone metastases, zoledronic acid reduced skeletal related events and decreased bone pain leading to its approval by the FDA in 2002 (Saad *et al.*, 2002). Bone resorption is a process that is dependent on RANK Ligand, a protein that acts as the primary mediator of osteoclast formation, function and survival. Preclinical models have demonstrated that inhibiting RANK Ligand significantly improves cortical and trabecular bone density, volume and strength. Studies with a novel bone targeting agent

known as Denosumab have been encouraging, and offers another agent to address the bone complications of prostate cancer.

6. Denosumab

Denosumab is a fully humanized monoclonal antibody against the RANK ligand. RANK plays a major role in osteoclast activation. In the phase III trial of 1901 CRPC patients with one or more metastases, compared to zoledronic acid, denosumab delayed time to skeletal related events by approximately 3 months with a 2.3% incidence of osteonecrosis of the jaw compared to 1.3% in the zoledronic acid arm. Notably, there was no difference in overall survival (Fizazi *et al.*, 2011). This phase III study garnered FDA approval for Denosumab for the prevention of skeletal related events (SRE) in CRPC patients with bone metastases. Denosumab is also being evaluated for its ability to delay the development of bone metastases in CRPC patients. A third role for denosumab may be in protecting against ADT related osteoporosis. In this study, 912 patients on ADT received denosumab 60 mg subcutaneously every 6 months. At 24 months followup, denosumab was associated with increased bone mineral density at all sites and a reduction in the incidence of new vertebral fractures (Smith *et al.*, 2009). Denosumab also offers the benefit of being subcutaneously administered, and this might be an advantage for patients who are not otherwise requiring intravenous treatments.

7. Summary

There has been a significant increase in the number of treatment options available to men with CRPC. These advancements have included therapies with new taxane derivatives, drugs targeting the androgen axis, immunotherapy and bone targeting agents. Cabazitaxel, abiraterone and sipuleucel-T all show survival benefits, while Denosumab appears to reduce the risk of new bone metastases and skeletal related events in CRPC patient with bone metastases. But, with these new options comes new questions, such as, what is the optimal sequencing of these agents. As sequencing strategies become increasingly common, comparison of survival against historic data in addition to comparison of outcomes between newer agents and their associated trials will become increasingly difficult to analyze. Whether results in the post docetaxel setting will be replicated in the chemo-naïve prostate cancer population awaits further definition. Also it is unclear if any of these agents will work better in combination with each other or with other molecular targeted therapies, although to date the latter have been disappointing in prostate cancer. What is very exciting however, is the fact that through drug development new information has become available enhancing our understanding of tumor progression in prostate cancer. Future areas of exploration include the use of newer agents in the prechemotherapy and neoadjuvant setting, using objective biologic endpoints such as pathologic response and radiographic response over short treatment intervals. Defining new endpoints may assist in circumventing the eventual difficulty in proceeding with large trials of heterogeneous patients in whom a placebo controlled trial design may not be feasible. Lastly, as the understanding of the molecular drivers of disease progression become increasingly understood, molecular markers that may serve as surrogate clinical trial endpoints may emerge, further enhancing a flourishing field.

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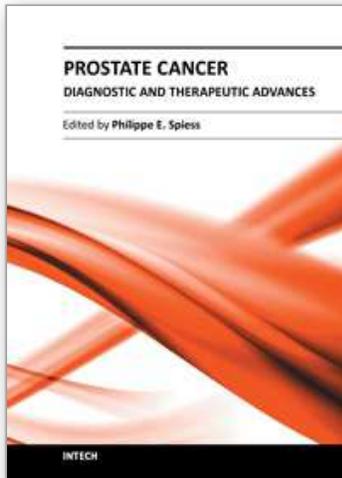
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In this book entitled "Prostate Cancer - Diagnostic and Therapeutic Advances", we highlight many of the significant advances made in our treatment armamentarium of prostate cancer. The book is subdivided into four sections termed: 1) novel diagnostic approaches, 2) surgical treatments options, 3) radiation therapy and its potential sequelae, and 4) medical management and its treatment complications. After reading the present book, readers will be very familiar with the major clinical advances made in our multifaceted treatment approach to prostate cancer over the past decade. This book is a tribute to our pioneering urologists and allied healthcare professionals who have continually pushed forward our traditional therapeutic envelope.

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