Emerging novel therapies in the treatment of castrate-resistant prostate cancer

Alym Abdulla, MD; Anil Kapoor, MD, FRCSC

Abstract

The treatment options for patients with castration-resistant prostate cancer (CRPC), until very recently, only included docetaxel. In the past 10 months, newly Federal Drug Administration (FDA) approved agents in the United States have shown survival benefit for patients with CRPC. This review takes a closer look at these newer agents: sipuleucel-T (immune therapy) and cabazitaxel (cytotoxic therapy). We also review the evidence supporting the FDA's approval of denosumab (bone-targeted therapy) as a treatment option for men with CRPC and bony metastases. Newer agents currently being investigated in phase III clinical trials for their potential role in metastatic CRPC are also reviewed. These agents include abiraterone (hormonal therapy), TAK-700 (hormonal therapy), MDV3100 (hormonal therapy), ipilimumab (immune therapy), zibotentan (endothelin-A receptor antagonist) and dasatinib (tyrosine kinase inhibitor). As ongoing studies using all the aforementioned agents continue to evolve, our understanding of how and where these agents fit into the treatment paradigm for patients with CRPC will become clearer.

Cite as: *Can Urol Assoc J* 2011;5(2):120-33; DOI:10.5489/cuaj.10160

Résumé

Les options thérapeutiques des patients atteints d'un cancer de la prostate résistant à la castration (CPRC), jusqu'à tout récemment, ne comprenaient que le docetaxel. Au cours des 10 derniers mois, de nouveaux agents approuvés par la Food and Drug Administration (FDA) des États-Unis ont montré un avantage lié à la survie chez les patients atteints d'un CPRC. Nous examinons ici plus étroitement ces nouveaux agents : le sipuleucel-T (immunothérapie) et le cabazitaxel (traitement cytotoxique). Nous passons aussi en revue les données étayant l'approbation par la FDA du dénosumab (traitement ciblant les cellules osseuses) comme option thérapeutique chez les hommes atteints d'un cancer de la prostate résistant à la castration avec métastases osseuses. Les nouveaux agents en cours d'études cliniques de phase III en raison de leur rôle potentiel dans le traitement du CPRC métastatique sont aussi examinés. Ces agents incluent l'abiraterone (hormonothérapie), le TAK-700 (hormonothérapie), le MDV3100 (hormonothérapie), l'ipilimumab (immunothérapie), le zibotentan (antagoniste des récepteurs de l'endothéline-A) et le dasatinib (inhibiteur de la tyrosine-kinase). À mesure que les études en cours sur ces agents continuent de progresser, notre compréhension du rôle et de l'usage de ces agents dans le paradigme thérapeutique des patients atteints de CPRC s'approfondira.

Introduction

Prostate cancer is the second most common malignancy diagnosed in Canadian men. It is expected that in 2010, over 24 000 Canadian men were diagnosed with the disease and over 4000 died because of advanced metastatic disease. On average, 470 Canadian men were diagnosed with prostate cancer on a weekly basis and 80 Canadian men died of the disease each week in 2010.¹ As these numbers continue to grow in the coming years, an increasing number of patients will present with advanced metastatic disease. The current standard of care for biochemical recurrence or hormone sensitive metastatic prostate cancer is androgen deprivation therapy via medical or surgical castration. In many cases, progression of the metastatic process occurs within 12 to 24 months of initial androgen deprivation.²⁻⁴ In a certain number of patients with non-metastatic prostate cancer and biochemical recurrence, follow-up hormone therapy can be instituted after initial androgen deprivation, however results are far from promising with the currently available treatments.²⁻⁴ Once prostate cancer progresses in the face of castrate levels of androgens, it is termed castrate-resistant prostate cancer (CRPC).

At this stage of the disease process, many patients have rising prostate-specific antigen (PSA) levels despite castrate levels of androgens (1.73 nmol/L or 50 ng/dL). Other common clinical manifestations include bone or lymph node metastases and increasing amounts of pain secondary to bony and soft-tissue metastases.^{4,5} Treatment options at this stage of the disease are a continued area of interest. As of April 2010, only 1 approved chemotherapeutic agent, docetaxel, showed promising results in improving survival in patients with metastatic CRPC. Today, not only are hormonal and cytotoxic treatment modalities available to patients with metastatic CRPC, but also more novel treatments in the areas of immune and targeted therapies. In the United States, the FDA's recent approval of sipuleucel-T, cabazitaxel and denosumab, along with the promising results seen in clinical trials with hormonal therapies (such as abiraterone, TAK-700 and MDV3100) and the potential seen with endothelin-receptor antagonists and tyrosine kinase inhibitors, we are marking the beginning of a new era in the treatment of metastatic CRPC.⁶

Current treatment paradigm

Prior to April 2010, the established treatment regimen for those with CRPC involved docetaxel-based chemotherapy (Fig. 1). Docetaxel is a cytotoxic agent that falls into a class of drugs known as taxanes. Taxanes block microtubule activity during cell division, eventually impairing a cancer cell's ability to replicate. Treatment with docetaxel in these patients was based on 2 studies in 2004 which showed improved survival with the use of docetaxel. The first was the TAX-327 trial, in which 1006 patients were divided into 3 groups: one group received docetaxel every 3 weeks (Q3W), the other group received docetaxel weekly and the final group received mitoxantrone; all 3 groups also received daily doses of low-dose prednisone. This study showed that the docetaxel Q3W extended overall survival, was associated with higher rates of PSA response (i.e., 50% reduction in PSA from baseline) and showed superiority in pain control when compared to the established treatment of mitoxantrone. Patients who received docetaxel weekly experienced similar responses to docetaxel Q3W group, but there was no significant difference in overall survival between the 2 docetaxel treatment arms.^{7,8}

The second trial was the Southwest Oncology Group (SWOG) 99-16 trial. In this trial, 770 men received either a combination of docetaxel Q3W, estramustine and dexamethasone, or a treatment regimen that included mitoxantrone and prednisone. The findings of this trial were similar to that of TAX-327 in that patients in the docetaxel arm

showed an increase in overall survival compared with the mitoxantrone arm (17.5 vs. 15.6 months, $p = 0.02$).⁹ The results of these two trials solidified docetaxel therapy (intravenous docetaxel 75 mg/m² Q3W in addition to oral prednisone 5 mg twice daily) as the standard for patients with metastatic CRPC.

Another issue in CRPC is skeletal-related complications associated with the treatment and disease process. First, bone loss associated with hormonal therapy is well-documented and has been shown to increase the risk of fracture.¹⁰⁻¹² Second, about 80% to 90% of patients with metastatic CRPC will develop bony metastases. These compounding factors increase bone fragility and place these patients at increased risk for developing pathological fractures, spinal cord compression and bone pain, all of which have a significant detrimental effect on quality of life.¹³ The current treatment of choice for patients with CRPC and bony metastases is zoledronic acid (4 mg intravenous Q3W), the only bisphosphonate approved for treating men with bony metastases in prostate cancer. This treatment has been recommended on the basis of a trial by Saad and colleagues,¹⁴ which compared zoledronic acid to placebo in men with metastatic CRPC. This randomized, placebo-controlled trial showed that men in the zoledronic acid arm had fewer skeletal-related events than those receiving the placebo (38% vs. 49%; 95% confidence interval [CI], -20.2% to -1.3%; $p = 0.028$). Zoledronic acid also increased the median time to the first skeletal-related event (488 days vs. 321 days, $p = 0.01$). Lastly, there was a 36% reduction (risk ratio = 0.64, 95% CI,

Fig. 1. Treatment paradigm. Overview of the treatment principles for the different stages of prostate cancer, prior to April 2010. Adapted by permission from Macmillan Publishers Ltd. Drake CG. Prostate cancer as a model for tumour immunotherapy. *Nat Rev Immunol* 2010;10:580-93.

0.485-0.845; $p = 0.002$) in the rate of skeletal-related events in those treated with zoledronic acid. Although no duration of treatment was specified in the study, the safety and efficacy of this treatment were established within 24 months.¹⁴

Before initiating zoledronic acid therapy in patients who meet the criteria, physicians should ensure adequate renal function (treatment is not recommended for patients with a baseline creatinine clearance <30 mL/min) and should counsel patients on the increased risk of osteonecrosis of the jaw while receiving bisphosphonate therapy.¹⁵ Patients with pre-existing dental problems are typically those at highest risk for osteonecrosis of the jaw; it is recommended that these patients maintain good oral care, undergo a baseline dental assessment prior to initiating therapy and avoid invasive dental surgery while on bisphosphonate therapy to reduce their risk of osteonecrosis of the jaw.¹⁶⁻¹⁸ Lastly, zoledronic acid has been used safely with different chemotherapeutic agents in clinical trials and no increases in adverse events related to bisphosphonate therapy were reported when used concurrently with cytotoxic chemotherapies.^{14,19}

Although the established treatment plan offers an overall survival benefit in patients with metastatic CRPC, there is typically a finite amount of time before the prostate cancer cells develop resistance to the docetaxel-based therapy. This resistance is thought to be due in large part to the adenosine triphosphate-dependent drug efflux pump P-glycoprotein 1. Docetaxel has been thought to have a high affinity for this efflux pump, which is found in increasing numbers on prostate cancer cells as the disease progresses.²⁰⁻²² The approval of sipuleucel-T and cabazitaxel in the United States is perhaps just the tip of the iceberg in the evolution of new treatments for those with metastatic CRPC.

Recently approved treatment modalities

Immune therapy

Sipuleucel-T

Sipuleucel-T (Provenge, Dendreon, Rockville, MD) is a recently approved (April 2010) immune therapy for patients with asymptomatic or minimally symptomatic metastatic CRPC in the United States; it has not yet been approved for use in Canada.⁶ This drug falls into an emerging class of novel cancer treatments known as active cellular immunotherapies. Sipuleucel-T is a prostate cancer vaccine that is autologous in nature. This therapy uses the patient's own antigen-presenting cells (APCs) – dendritic cells and macrophages – pulsed ex vivo with a recombinant fusion protein (PA2024) consisting of granulocyte macrophage colony-stimulating factor (GM-CSF) and prostatic acid phosphatase (PAP). The rationale behind this therapy lies in the fact PAP is expressed in 95% of prostate cancers,⁶ and by creating the right cytotoxic milieu ex vivo, the patient's dendritic cells act as potent APCs that are responsible for the uptake, processing, and presentation of antigens on their cell surface. These dendritic cells, which now express PA2024 as antigens on their cell surface, are infused back into the patient and are then capable of sensitizing naïve T-cells to develop reactivity towards PA2024, specifically the PAP peptide portion. The overall outcome is to prime a patient's native T-cells to recognize and kill prostate cancer cells in an antigen-dependent manner (Fig. 2).²³

Although this drug has only recently been made available in the United States, it had been an active area of research for quite some time. Two randomized, placebo-controlled, phase III trials were carried out (D9901²⁴ and D9902A²⁵). The identical study designs of these trials allowed for an inte-

Fig. 2. Steps in creating the Sipuleucel-T IV treatment infusion. Leukaphoresis of 1-2 blood volumes (8-14L) with isolation of peripheral blood mononuclear cells (PBMCs) via centrifugation. Isolated PBMCs are then washed and incubated with PA2024 (fusion protein of full length PAP linked via its COOH terminus to the NH₂ terminus of full length GM-CSF) for 36-44 hours. After incubation, the cells are washed and suspended in lactated Ringer's solution for infusion. The process is done a total of 3 times for three separate infusions over a 4 week span (0, 2 and 4 weeks). Reprinted by permission from Macmillan Publishers Ltd: Drake, CG. Prostate cancer as a model for tumour immunotherapy. *Nat Rev Immunol* 2010;10:580-93.

grated analysis of the data. In the combined analysis, a total of 225 patients with asymptomatic metastatic CRPC were randomized to sipuleucel-T ($n = 147$) or placebo ($n = 78$), given as 3 intravenous infusions over a 4-week span (0, 2 and 4 weeks). Patients in the study were followed for survival until death or a prespecified cutoff of 36 months after randomization. The primary endpoint of this trial was time to disease progression, with a secondary endpoint being overall survival. In the final analysis, the study did not show a statistically significant improvement in its primary endpoint. However, the unified analysis did show that sipuleucel-T offered a survival advantage to those with asymptomatic metastatic CRPC. Sipuleucel-T demonstrated a 33% reduction in the risk of death (hazard ratio [HR] 1.50; 95% CI, 1.10-2.05; $p = 0.011$) compared to the placebo arm. The treatment arm had a median survival of 23.2 months, while the placebo arm had a median survival of 18.9 months.^{24,25}

The promising results of the integrated analysis of these trials were further confirmed in a landmark study known as the IMPACT (IMmunotherapy for Prostate AdenoCarcinoma Treatment) trial.²⁶ In this double-blind, placebo-controlled, multicentre, phase III trial, 512 patients with asymptomatic or minimally symptomatic metastatic CRPC were randomly assigned in a 2:1 ratio to either the treatment arm (341 patients receiving sipuleucel-T) or the placebo arm (171 patients receiving the placebo). Patients in each arm received 3 intravenous infusions over a 4-week period (0, 2 and 4 weeks). The primary endpoint of this study, unlike the previous trials, was overall survival. Time to objective disease progression (monitored by computed tomography [CT] scans and blood chemical analysis at weeks 6, 14, 26, 34 and every 12 weeks thereafter, and by bone scanning at weeks 6, 10, 14, 18, 22, 26, 34 and every 12 weeks thereafter) was analyzed as a secondary endpoint. In the final analysis, the sipuleucel-T arm demonstrated a 22% reduction in the risk of death (HR 0.78; 95% CI, 0.61-0.98; $p = 0.03$) compared to the placebo arm. The treatment arm had a median survival of 25.8 months, while the placebo arm had a median survival of 21.7 months. Further, the sipuleucel-T group showed a 3-year survival of 32.1% compared to 23.0% in the placebo group. Like the trials before it, the IMPACT trial did not show a statistically significant difference in the outcome of time to objective disease progression. Lastly, the IMPACT trial substantiated the safety profile of sipuleucel-T that was seen in the other phase III trials before it. Adverse events included chills, pyrexia, headache, influenza-like illness, myalgia, hypertension and hyperhidrosis. These events were mild and transient, usually occurring within 1 day of infusion and resolving within 24 to 48 hours.²⁶

The IMPACT trial did meet its primary outcome in showing a statistically significant difference in overall survival, but its inability to show a significant difference in the secondary outcome of time to objective disease progression is

somewhat of a difficult concept to grasp. Clinicians may wonder how a therapy can improve overall survival, but fail to correlate with time to progression. This is a concept that has been seen before in previous immunotherapy trials,^{27,28} but a clear explanation has yet to be elucidated. One possible explanation is that there is some type of delay in the activation of the immune system. These therapies may require time to prime one's immune system before its biological effects are seen at the tissue level. This theory is supported by the fact that those patients receiving bone marrow transplantation in the treatment of lymphoma typically do not show an objective response until upwards of 6 months post-transplantation.²⁹ This is an important concept pertaining to immunotherapies in treating cancer, as tumour progression will undoubtedly occur in these patients as the immune system is being activated. Despite this delay, the research shows that overall survival is improved when using these types of therapies.

At present, there are a number of clinical trials underway involving sipuleucel-T. The NeoACT (NEOadjuvant Active Cellular ImmunoTherapy) phase II trial is currently recruiting patients in the United States.³⁰ In this trial, patients with localized prostate cancer will undergo neoadjuvant treatment with sipuleucel-T prior to radical prostatectomy. The primary outcome of this trial is to assess the immune response within prostate tissue following neoadjuvant treatment with sipuleucel-T. To accomplish this, researchers will compare prostatectomy tissue specimen with that of tissue obtained at the time of core biopsy prior to immunotherapy. Furthermore, following radical prostatectomy subjects will be randomized to receive either a booster of sipuleucel-T or no further treatment.³⁰

Another promising study currently ongoing, but no longer recruiting patients, is the PROTECT (Provenge for the Treatment of Hormone Sensitive Prostate Cancer) phase IIIB clinical trial for patients with hormone-sensitive prostate cancer.³¹ This is a prospective, double-blind, placebo-controlled trial in which about 175 men who have previously undergone radical prostatectomy and whose only sign of disease recurrence is a rise in serum PSA are randomized in a 2:1 ratio to receive sipuleucel-T or placebo, after a run-in treatment of luteal phase hormone therapy for 3 months to ensure a PSA of ≤ 1 ng/mL. The 2 primary objectives of this trial are to compare the time to biochemical failure (defined as PSA ≥ 3 ng/mL) between sipuleucel-T and placebo and to assess the safety of sipuleucel-T. Secondary outcomes of this trial are to compare time to distant failure (defined as distant metastatic disease as confirmed by bone scan, CT scan and/or any other relevant imaging modality), PSA doubling time and survival between the 2 treatment groups. After confirmed distant failure, patients will be followed for safety and survival for the remainder of their lives. The total time of the study for each participant is estimated to be 10 to 13 years.³¹

Although the sipuleucel-T treatment is quite promising, it does not come without its costs. At present, Canadian patients are required to travel to centres in the United States to gain access to this specialized immune therapy. It is estimated that Canadian patients will have to pay approximately \$93 000USD for the complete treatment of sipuleucel-T.³²

Cytotoxic therapy

Cabazitaxel

Cabazitaxel (Jevtana, sanofi-aventis, Bridgewater, NJ) is another chemotherapeutic agent now available, to be used in combination with prednisone to treat metastatic CRPC in patients previously treated with a docetaxel-containing treatment regimen. Although this drug has been approved (June 2010) by the FDA in the United States, it has not yet been approved for use in Canada.⁶ Like docetaxel, cabazitaxel falls into the class of drugs known as taxanes (Fig. 3).³³ This drug inhibits microtubule depolymerization and cell division by binding to and stabilizing tubulin. Like docetaxel, cabazitaxel causes cell division to arrest in the G2/M phase, thus preventing tumour cells to replicate. The superiority of this drug compared to docetaxel lies in the fact that it has very low affinity for the adenosine triphosphate-dependent drug efflux pump P-glycoprotein 1.²⁰⁻²²

The landmark phase III trial that resulted in the FDA's approval of cabazitaxel is known as the Treatment of Hormone-Refractory Metastatic Prostate Cancer Previously Treated With a Taxotere-Containing Regimen (TROPIC) trial.³⁴ In this double-blind, placebo-controlled, multicentre, phase III trial, 755 patients with metastatic CRPC previously treated with a docetaxel-containing regimen were randomized to either cabazitaxel 25 mg/m² intravenous Q3W plus oral prednisone 10 mg daily or mitoxantrone 12 mg/m² intravenous Q3W plus oral prednisone 10 mg daily. The primary

endpoint of the study was overall survival, while secondary endpoints included PSA response, progression-free survival, response rate according the Response Evaluation Criteria In Solid Tumors (RECIST) criteria and pain response. In the final analysis, the study showed an improvement in overall survival in the group treated with cabazitaxel. Median overall survival in the cabazitaxel arm was 15.1 months compared to 12.7 months in the mitoxantrone arm (HR 0.70; 95% CI, 0.59-0.83; $p < 0.0001$). In terms of secondary endpoints, median progression-free survival (composite of tumour, PSA or pain progression, or death) was 2.8 months versus 1.4 months, in the cabazitaxel and mitoxantrone groups, respectively (HR 0.74; 95% CI, 0.64-0.86; $p < 0.0001$). In comparing the remainder of the secondary endpoints, the response rates for tumour assessments by RECIST, PSA response, and PSA progression were also statistically significantly in favour of the cabazitaxel group.^{6,32,34}

An area of concern with respect to this trial was the incidence of neutropenia. This trial showed that 81.7% of the patients treated with cabazitaxel experienced grade 3 out of 4 neutropenia compared to 58.0% in the mitoxantrone arm. Furthermore, the incidence of febrile neutropenia was also higher in the cabazitaxel arm at 7.5% compared to 1.3% in those treated with mitoxantrone. In total, 18 treatment-related deaths (5% of patients) were reported in the cabazitaxel group compared to 7 such deaths (or 2% of patients) in those treated with mitoxantrone.³⁴ These findings may limit the use of cabazitaxel in combination therapy with other cytotoxic agents, as it could put patients at further risk of adverse events. A possible explanation for the increased incidence of neutropenia is that many of these patients were already treated with docetaxel and the cumulative effects of these chemotherapeutic agents may have been more toxic in such patients.³² Furthermore, the patients in this trial tended to have poor prognosis disease. Visceral metastases was seen in 25% of patients, while about 50% of patients enrolled had

Fig. 3. Comparing the molecular structures of cabazitaxel (left) and docetaxel (right). The addition of two methyl groups to cabazitaxel is thought to play a critical role in overcoming docetaxel resistance in metastatic castration-resistant prostate cancer.

measurable disease. This combination of disease burden, infiltration of bone marrow and previous treatment with chemotherapy agents may help explain the high rates of neutropenia and febrile neutropenia in the cabazitaxel arm of this trial. The dose of cabazitaxel used in this study has also been raised as a possible mitigating factor for the high rates of neutropenia. The dose of cabazitaxel in phase I trials was set at 20 mg/m² while the dose in the TROPIC trial was set at 25 mg/m². Some researchers have proposed a dose-reduction for future trials to 20 mg/m² to reduce myelotoxicity, however this may also decrease the benefit from cabazitaxel in these patients. Future studies are needed to evaluate the safety as well as degree of inferiority in using the 20 mg/m² dose compared to the 25 mg/m² dose.³⁴

A trial that is currently being planned as a means to reduce this cumulative toxic effect includes a study comparing cabazitaxel and docetaxel as first-line treatment in chemotherapy-naïve patients with metastatic CRPC. Other ideas include combining cabazitaxel with growth factors, such as the Granulocyte/macrophage colony stimulating factor (GM-CSF), to reduce the incidence of neutropenia in patients previously treated with docetaxel-based chemotherapy.²⁹ For the time being, it appears that the favoured treatment dose in future clinical trials will be the 25 mg/m² of cabazitaxel.^{6,34}

Bone-targeted therapy

Denosumab (XGEVA)

The current guidelines by both the European Association of Urology and the International Consultation on Urological Diseases recommend that bisphosphonates be used to preserve bone health and to prevent skeletal complications in men with bony metastases from CRPC, whether or not they are symptomatic. Another treatment that will compete with bisphosphonates in this patient population is the RANK-ligand (RANK-L) inhibitor denosumab (XGEVA, Amgen, Thousand Oaks, CA).¹⁵ RANK-L is normally synthesized by osteoblasts and acts by binding the RANK-receptor which is found on the surface of osteoclasts. The ligand-receptor interaction causes the activation of survival and proliferation pathways in osteoclasts that triggers bone resorption. This activation of bone resorption is thought to play a critical role in skeletal-related events, such as pain, pathological fractures and spinal cord compression. This pathway of bone resorption is counteracted by osteoprotegerin, a soluble protein that can bind RANK-L thus preventing its interaction with the RANK-receptor. Research has shown that prostate cancer cells interact with osteoblasts and increase the production of RANK-L, which in turn increases osteoclast activation and subsequent bone resorption. The rationale in using a RANK-L inhibitor, such as denosumab, is to inhibit

the effects of RANK-L by preventing its interaction with the RANK-receptor. Denosumab is a fully human monoclonal antibody directed against RANK-L.³⁵

In November 2010, the FDA approved the use of denosumab to prevent skeletal-related events in cancer patients with solid tumours and bony metastases.³⁶ This decision was made primarily on the results of a randomized phase III trial of denosumab versus zoledronic acid in patients with bone metastases from CRPC. In this study by Fizazi and colleagues,³⁷ which was presented in abstract form at ASCO 2010, 1901 patients with CRPC and at least 1 site of bony metastases, but no prior use of intravenous bisphosphonate therapy, received either subcutaneous denosumab (120 mg) and intravenous placebo (n = 950) or intravenous zoledronic acid (4 mg) and subcutaneous placebo (n = 951). All participants were also encouraged to take supplemental calcium and vitamin D. The primary endpoint was time to first on-study SRE, defined as pathological fracture, radiation or surgery to bone or spinal cord compression. In this study, denosumab significantly delayed the time to first on-study SRE compared to zoledronic acid (HR 0.82; 95% CI, 0.71-0.95; *p* = 0.008). Patients receiving denosumab had a median time of first on-study SRE of 20.7 months compared to 17.1 months in those receiving zoledronic acid, a difference of 3.6 months or an overall risk reduction of 18%. Furthermore, an SRE was sustained in 36% of patients in the denosumab group compared to 41% in the zoledronic acid group (*p* = 0.0002). Of note, overall survival (HR 1.03; 95% CI, 0.91-1.17; *p* = 0.65) and time to cancer progression (HR 1.06; 95% CI, 0.95-1.18; *p* = 0.30) were similar between the 2 treatment arms.³⁷

In terms of adverse events, the overall rates for both groups were quite similar. Each group reported an overall adverse event rate of 97%, while serious adverse event rates were 63% in the denosumab group versus 60% in the zoledronic acid group. Hypocalcaemia was reported in 13% of patients in the denosumab arm compared to 6% in the zoledronic acid arm. Lastly, osteonecrosis of the jaw was reported in 22 patients (2.3%) in the denosumab group versus 12 patients (1.3%) in the zoledronic acid group (*p* = 0.09).³⁷ That said, study investigators noted that a large majority of patients who experienced osteonecrosis of the jaw had risk factors and less than 10% of these patients required bone resections.³⁸

These promising results, along with the FDA's approval of denosumab, have created another treatment option for patients with CRPC and bony metastases. This will not come without cost. At present, the estimated cost for a monthly treatment of denosumab is \$1650USD³⁶ compared to the monthly cost of zoledronic acid which averages about \$450USD.³⁹ Although a treatment option is available to compete with zoledronic acid, cost may play a role in terms of which treatments are offered to which patients. Further studies are already underway assessing the use of

denosumab on prolonging bone metastases-free survival in patients with metastatic CRPC.⁴⁰

Emerging treatment modalities

Hormonal therapy

Abiraterone

Abiraterone is a hormonal therapy currently under investigation. This may be somewhat surprising, as it is a bit counterintuitive to be using a hormonal-based treatment for CRPC. That said several clinical studies have demonstrated that hormone refractory prostate cancer cells continue to be under the influence of androgen signalling as evidenced by the high number of androgen receptors they continue to express.⁴¹⁻⁴³ As a result, these newer agents tend to be more specific targets of enzymes downstream in the hormonal cascade. Being a more selective hormonal therapy, abiraterone functions as an inhibitor of the cytochrome P450 (CYP) 17A1. This drug is similar to ketoconazole in terms of its mechanism of action, but it is a more potent and selective inhibitor of the 17- α -hydroxylase and the C17,20-lyase function of CYP17A1. Ultimately, this drug irreversibly inhibits the enzyme responsible for the biochemical conversion of cholesterol to testosterone.⁴⁴

Phase II trials have shown that abiraterone may have some potential in treating patients with metastatic CRPC, in particular those who have become refractory to docetaxel-based therapy. A total of 47 men with metastatic CRPC deemed refractory to docetaxel-based chemotherapy were given oral abiraterone 1000 mg daily. The primary endpoint of the study was achievement of PSA decline of $\geq 50\%$ in at least 7 of 35 patients. The results were quite promising; PSA declines of $\geq 30\%$, $\geq 50\%$ and $\geq 90\%$ were seen in 68% (32 of 47), 51% (24 of 47) and 15% (7 of 47) of patients, respectively.⁴⁵ These results, along with a more favourable safety profile compared to docetaxel-based therapy, have laid the foundation for the development of 2 randomized, double-blind, placebo-controlled, phase III clinical trials comparing abiraterone and prednisone versus placebo and prednisone in both docetaxel-pre-treated patients and in chemotherapy-naïve patients. These trials are currently ongoing and initial results pertaining to the primary endpoint of overall survival in the trial looking at abiraterone in patients pre-treated with docetaxel were recently released in Europe.^{46,47}

Preliminary results of the phase III trial in docetaxel pre-treated patients were recently released (October 11, 2010) at the European Society for Medical Oncology (ESMO) Congress with promising results. This trial enrolled 1195 men with metastatic CRPC who were deemed refractory to docetaxel-based therapy. Of these patients, 787 patients

were randomized to the group that received oral abiraterone 1000 mg daily plus oral prednisone 5 mg twice daily. The remaining 398 patients were assigned to receive placebo plus the same dose of prednisone. Preliminary results show that treatment with abiraterone in this patient population led to a 35% reduction in the risk of death (HR 0.65; 95% CI, 0.54-0.77; $p < 0.0001$) and this translated into an increase in median survival of about 36%. Patients who received abiraterone and steroids achieved a median survival of 14.8 months compared to placebo and steroids which achieved a median survival of 10.9 months. In addition to the primary endpoint of overall survival, the preliminary data also revealed statistically significant difference in the time to disease progression; in patients receiving abiraterone, it was 10.2 months compared to 6.6 months in the placebo arm ($p < 0.0001$).⁴⁸ Although these results have only been published to date in abstract form, they lay the foundation for what appears to be the imminent approval of a third drug in less than a 12-month period that will benefit patients suffering from metastatic CRPC. These results, along with the fact that abiraterone was generally well tolerated in this phase III study, have oncologists on the brink of what appears to be a practice-changing treatment for patients with metastatic CRPC. An FDA application for the drug's approval has already been submitted by Centocor Ortho Biotech Incorporated, the company responsible for manufacturing abiraterone in the United States.⁴⁹

TAK-700

TAK-700, like abiraterone, is another oral, selective inhibitor of the C17,20-lyase enzyme that reduces testosterone and DHEA levels.⁵⁰ Drecier and colleagues⁵¹ have studied the effects of TAK-700 by conducting an open-label, dose-escalating phase I/II study to assess the safety and tolerability of this new compound in patients with metastatic CRPC. In this study, 26 patients received TAK-700 at 5 dose levels: 100 mg (3 patients), 200 mg (3 patients), 300 mg (3 patients), 400 mg (7 patients) or 600 mg (5 patients) BID; a further 5 patients received TAK-700 400 mg BID plus prednisone 5 mg BID. No dose-limiting toxicity was seen. The most common treatment-related adverse event was fatigue, seen in 16 patients (62%), which included 3 patients with grade 3 or greater events at the 600 mg BID dose. Other common treatment-related adverse events included nausea (38%), constipation (35%) and vomiting (30%). In terms of efficacy, this study showed decreases in median testosterone from 4.9 to 0.6 ng/dL and in dehydroepiandrosterone sulphate (DHEA)-sulphate from 53.8 to <0.1 μ g/dL at the 400 mg BID dose. Furthermore, doses at or above 300 mg BID for at least 3 cycles produced a 50% or greater decrease in PSA in 11 of 14 patients (70%) and 4 of these patients (29%) had $\geq 90\%$ PSA decrease. This study also showed a

blunting of the cortisol response after Adrenocorticotrophic hormone (ACTH) stimulation in 2 of 7 patients at the 400 mg BID dose, and in 5 of 5 patients at the 600 mg BID dose.⁵¹ These preliminary phase I/II results have led to the continued phase II evaluation of this drug in men with metastatic CRPC at a dose of 400mg BID along with oral prednisone. This trial is ongoing.⁵²

These encouraging results have led to the development of 2 randomized, double-blind, multicentre, phase III clinical trials. One study will examine TAK-700 plus prednisone compared to placebo plus prednisone in patients with chemotherapy-naïve metastatic CRPC,⁵³ while the other study will evaluate TAK-700 plus prednisone compared to placebo plus prednisone in men with metastatic CRPC that has progressed following taxane-based therapy.⁵⁴ Both of these trials are currently recruiting patients, and will have primary endpoints of overall survival and radiographic progression-free survival in the chemotherapy-naïve study, while the latter study will solely look at overall survival as its primary endpoint. Each study is expected to enrol 1000 to 1400 patients and results are expected to be available in 2013-2014.^{53,54}

MDV3100

Another promising hormonal therapy currently under investigation in phase III clinical trials is MDV3100, an oral androgen-receptor (AR) antagonist with a higher affinity for the AR than bicalutamide. It prevents the binding of androgen to the AR, thus preventing nuclear translocation of the AR-complex. It also prevents the binding of the AR-complex to DNA; as such, its effects are superior to agents, such as bicalutamide. Ultimately, when the AR-complex is unable to bind to DNA in prostate cancer cells, the necessary genes for cancer growth and replication cannot be expressed. This triple action of AR blockade, prevention of nuclear translocation of the AR-complex and inhibition of DNA binding is thought to induce apoptosis in resistant prostate cancer cell lines.^{55,56}

The initial phase I/II clinical trial by Scher and colleagues⁵⁵ evaluated the safety and efficacy of this drug in 140 patients with CRPC. In this study, 46% of the patients were chemotherapy-naïve, while 54% of patients had received previous chemotherapy. In terms of hormonal therapy, all patients enrolled in the study received at least 1 form of hormonal manipulation, while some had received upwards of 4 prior to study enrolment. With respect to metastases, 78% of the patients had evidence of bony metastases, 54% had lymph node metastases and 5% had their disease classified as M0. Doses ranged from 30 to 600 mg/day. The key findings of this study were that PSA responses (>50% reduction in PSA from baseline) were recorded more frequently (62%) in chemotherapy-naïve patients than in those

pre-treated with chemotherapy (51%), while stable disease was reported in 74% of patients with measurable soft tissue lesions and in 62% of patients with bone lesions. The PSA decreases in patients were dose-dependent from doses of 30 mg to 150 mg/day, while a plateau was seen in these dose-dependent effects from doses ranging from 150 mg to 240 mg/day. No additional anti-tumour benefits were seen in doses greater than 150 mg/day. These results, along with a favourable safety profile (fatigue being most common side-effect and usually seen in doses >240 mg/day) have prompted the creation of two phase III clinical trials studying the use of MDV3100: AFFIRM (A study evaluating the efficacy and safety of Investigational dRug MDV3100 in men with advanced prostate cancer)⁵⁷ and PREVAIL.⁵⁸

AFFIRM and PREVAIL are randomized, double-blind, placebo-controlled, multicentre, phase III clinical trials. The AFFIRM trial will study the use of oral MDV3100 160 mg/day or placebo in patients with metastatic CRPC already treated with standard docetaxel therapy. This study has an accrual target of about 1200 patients and will have overall survival as its primary endpoint. First results are expected to be released in 2012.⁵⁷ The PREVAIL trial, launched in September 2010 and currently recruiting patients, will study the use of oral MDV3100 160 mg/day plus standard care or placebo plus standard care in patients with prostate cancer who are progressing despite androgen deprivation therapy and are chemotherapy-naïve. This study is expected to enrol 1700 patients and will have 2 co-primary endpoints: overall and progression-free survival. Secondary endpoints will include time to first SRE and time to initiation of cytotoxic chemotherapy.^{58,59}

Immune therapy

Ipilimumab

Ipilimumab is an immune therapy that is being investigated as a promising treatment for patients with metastatic CRPC. Already approved for treating melanoma, this drug is a human monoclonal antibody that binds to CTLA-4 (cytotoxic T lymphocyte-associated antigen 4), a molecule on helper T-cells that is believed to play a critical role in regulating natural immune responses.⁶⁰ CTLA-4 is an inhibitory molecule on helper T-cells that induces T-cell down-regulation. Ipilimumab is designed to block the activity of CTLA-4 by binding the antigen and blocking its activity. This inhibition of CTLA-4 prevents T-cell down-regulation, thereby sustaining an active immune response in T-cell attack on cancer cells.⁶⁰

In terms of its use in metastatic CRPC, a phase II experience explored the use of ipilimumab alone and in combination with radiotherapy. In this study, 45 patients with metastatic CRPC were divided into 3 groups. One group received ipilimumab alone (16 patients), another group of

patients who were chemotherapy-naïve received a combination of ipilimumab and radiotherapy (15 patients), while the last group also received the combination treatment, but it was a group that consisted of patients with prior exposure to chemotherapy (14 patients). The dose of ipilimumab was 10 mg/kg Q3W for a total of 4 doses and those who received radiation received up to 800 cGy delivered to 3 involved bony sites. The endpoints of the study were to confirm safety and look at initial assessment of activity. A total of 26 adverse immune-related events were reported in 17 (38%) patients and these included diarrhoea/colitis (12), rash/pruritis (6), hepatitis (4) and endocrinopathy (4), all of which resolved with immunosuppression. In terms of PSA declines, 10 of 45 patients (22%; 95% CI, 10-34%) had confirmed PSA declines $\geq 50\%$; 5 of these patients with were from the 16 patients who received ipilimumab alone. Median time to PSA decline was 5.7 weeks (range 3 to 21) and median duration of response was 23 weeks (3 to 84+).⁶¹ The results of this study prompted the initiation of a number of other trials to evaluate the use of ipilimumab in the setting of metastatic CRPC. One such study is a randomized phase II clinical trial comparing 4 monthly doses of ipilimumab as a single agent or used in combination with a single dose of docetaxel in patients with CRPC.⁶² The study itself is now complete, but the results have yet to be published.

Other trials on the horizon and currently recruiting patients include 2 double-blind, randomized, phase III clinical trials: one comparing ipilimumab versus placebo following radiotherapy in subjects with CRPC that have received prior treatment with docetaxel,⁶³ and the other comparing the efficacy of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naïve CRPC.⁶⁴

Targeted therapy

Zibotentan

Zibotentan is a targeted therapy that is currently being investigated in phase III clinical trials. It falls into a class of drugs known as endothelin-receptor antagonists. The endothelin pathway is thought to play a key role in the regulation, growth and proliferation of many tumours including, breast, lung, ovary and prostate.

Endothelin-1 (ET-1) is a peptide produced by tumour cells, that when bound to the endothelin-A receptor (ET_A) can promote various biologic processes including tumour angiogenesis, tumour invasion, inhibition of apoptosis and formation of osteogenic metastasis. Furthermore, stimulation of the receptor has also been known to cause an osteoblastic response, fuelling tumour cell growth and triggering acute and neuropathic pain pathways.^{65,66} Conversely, ET-1 effects at the endothelin-B receptor (ET_B) are quite the opposite.

ET-1 binding to the ET_B on prostate cancer cells activates a signal cascade that actually increases the rate of apoptosis and helps increase the rate of clearance of ET-1 by cells. By increasing the clearance of ET-1, there is less peptide around to bind the ET_A and less activation of its anti-apoptotic signal cascade⁶⁵⁻⁶⁸ (Fig. 4).

Zibotentan is a drug that specifically targets the ET_A and competes with ET-1 to bind the receptor. More specifically, this drug is an antagonist specific to the ET_A receptor that works by competitive inhibition. When the ET_A is occupied by an antagonist, there is thought to be increased likelihood of ET-1 binding the ET_B thus creating a pro-apoptotic environment in which cancer cells may become more sensitive to destruction by established chemotherapeutic agents.⁶⁵⁻⁶⁸

Currently, the use of zibotentan has been studied in a population of 312 asymptomatic or minimally symptomatic patients with metastatic CRPC. In this randomized, double-blind, placebo-controlled, multicentre trial, patients were randomized to receive oral, once daily zibotentan 15 mg or 10 mg or placebo. Patients enrolled in the study had documented evidence of bony metastases, were surgically or medically castrated with rising PSA levels and could not have undergone prior cytotoxic chemotherapy or received anti-androgens within 4 weeks (flutamide) or 6 weeks (bicalutamide, nilutamide) of randomization. The primary endpoint of this study was the time to disease progression, while the secondary endpoints included overall survival and tolerability.⁶⁹

Although the study did not meet its primary endpoint, there was a benefit seen in overall survival. Those in the 10 mg and 15 mg dose groups of zibotentan had an overall survival of 24.5 and 23.5 months, respectively, compared with 17.3 months in the placebo arm. Overall, the drug was well-tolerated. Most patients experienced at least 1 adverse event (91%, 93% and 87% in the 15 mg, 10 mg and placebo groups respectively). The most common adverse events were peripheral oedema, nasal congestion and headache, all of which are in keeping with ET_A blockade.³⁸ These promising findings of improved overall survival and tolerability have paved the way for the ENTHUSE (ENdoTHelin A USE) phase III clinical program. This clinical program consists of 3 randomized, double-blind, placebo-controlled trials, across 400 centres worldwide, enrolling more than 3000 patients with CRPC. In each trial, zibotentan will be administered in a 10 mg dose, as no added benefit to survival was seen with the 15 mg dose.⁶⁹

The ENTHUSE M0 (also known as study 15) trial⁷⁰ will include 1500 patients with CRPC and a rising PSA but no evidence of metastatic spread. The study will run for 5 years and will randomize patients 1:1 to zibotentan or placebo. This trial will have 2 primary endpoints: overall survival and progression-free survival, defined as the time to appearance of metastases. Secondary endpoints will include health-related quality of life, safety/tolerability and PSA levels.⁷⁰

The second part of the program, referred to as the ENTHUSE M1c (also known as study 33) trial,⁷¹ will include 1044 patients with documented metastatic CRPC suitable for chemotherapy. These patients will be randomized in a 1:1 ratio to receive either zibotentan in combination with docetaxel or placebo with docetaxel, and they are expected to be followed for 36 months. This trial will look at overall survival as its primary endpoint, and secondary endpoints will be progression-free survival, PSA levels, safety/tolerability and treatment effect on skeletal events.⁷¹

The final part of the program, which ended in August 2010, is referred to as the (Endothelin A Antagonist) in Hormone Resistant Prostate Cancer With Bone Metastases (ENTHUSE M1) trial; it is also known as study 14.⁷² This study enrolled 594 patients with CRPC, who have documented bony metastases and a rising serum PSA despite medical or surgical castration. These patients were randomized in a 1:1 ratio to receive either zibotentan 10 mg or placebo added to standard of care treatment. With overall survival as the primary endpoint, this trial also looked at progression-free survival, safety/tolerability, skeletal events, bone metastases, PSA levels and health-related quality of life as secondary endpoints over the 30-month period of the trial.⁷² Unfortunately, a recent press release (September 27, 2010) by AstraZeneca revealed that the results of this part of the ENTHUSE program did not meet its primary endpoint.⁷³ Based on the findings of this study, AstraZeneca plans no regulatory submissions for zibotentan at this time. The pharmaceutical company will continue with its other 2 trials within the ENTHUSE clinical program and will publish the full results of the ENTHUSE M1 trial, including secondary endpoints, in 2011.⁷³ At this point, it is difficult to say whether or not zibotentan will become an available option in the treatment of metastatic CRPC. At present, it appears that it may be some time before zibotentan is considered a key player.

Dasatinib

Another area of active research is the use of tyrosine kinase inhibitors. There is strong evidence that SRC family kinases (SFK) play an important role in prostate cancer.^{74,75} In particular, research has shown that there is SFK over-expression in prostate cancer cell lines and tissues, and that following

SRC inhibition there is evidence of reduced cancer cell proliferation, invasion and migration.^{74,76-79} During advanced stages of prostate cancer, it is thought that SRC may be involved in androgen-independent growth pathways. Studies have shown that prostate cancer cells exhibiting low androgen receptor activity, exhibit high SRC activity and are sensitive to SRC blockade.⁸⁰ Furthermore, experimental models also suggest that SRC inhibition decreases bone turnover as evidenced by decreases in urinary N-telopeptide and bone-specific alkaline phosphatase.⁶

Dasatinib is an oral tyrosine kinase inhibitor with potent activity against SFKs, as well as against BCR-ABL, platelet-derived growth factor receptor, and c-KIT. Currently used to treat chronic myelogenous leukemia and acute lymphoblastic leukemia, dasatinib has shown tremendous potential in clinical trials in patients with metastatic CRPC.⁸¹ A phase II trial, investigating dasatinib in chemotherapy-naïve patients with CRPC enrolled 47 patients; 25 patients received a dose of 100 mg twice daily and 22 received a twice daily dosing of 70 mg with no established reduction or escalation protocol. Of the 47 patients, 41 (87%) patients had documented bone disease. At 12 weeks, 43% of patients (20/47) did not show progression of disease, while at 24 weeks 19% of patients (9/47) did not show progression of disease as deter-

Fig. 4. The effects of endothelin-1. The proposed mechanisms by which endothelin pathway can affect the growth, progression and spread of prostate cancer.

Fig. 5. The modified treatment paradigm for prostate cancer. Adapted by permission from Macmillan Publishers Ltd. Drake CG. Prostate cancer as a model for tumour immunotherapy. *Nat Rev Immunol* 2010;10:580-93.

mined by RECIST criteria. In terms of PSA response, only 3 patients showed $\geq 50\%$ declines in PSA. Furthermore, bone turnover markers in eligible patients also showed favourable results. Of 41 evaluable patients, 21 (51%) patients achieved $\geq 40\%$ reduction in urinary N-telopeptide by week 12, with 33 (80%) achieving some level of reduction at any point during the study. In terms of bone alkaline phosphatase levels, of 40 evaluable patients, 24 (60%) showed a reduction at the 12-week mark during the study.⁸¹

Overall, dasatinib was well-tolerated, but an area of concern was the development of pleural effusions while taking dasatinib. To address this issue, an amendment in dosing was made from 100 mg to 70 mg twice daily. However, upon completion of the study, analysis showed no significant difference between the 2 cohorts and pleural effusions (any

grade) were reported in 51% of the overall population. Aside from pleural effusion, the most common adverse events were diarrhoea (62%), nausea (47%) and fatigue (45%).⁸¹

Another phase II trial investigated the combination of dasatinib 100 mg daily plus docetaxel 75 mg/m² every 21 days in 31 chemotherapy-naïve men with metastatic CRPC.⁸² Of those enrolled, 21 patients had measurable disease by RECIST criteria and 16 of these patients did not show progression after more than 21 weeks. Furthermore, 30 of 31 patients had a best response of improved (32%) or stable disease (65%) after 6 weeks or more, which was objectively evidenced by bone scan. The dose of dasatinib at 100 mg daily was chosen in this trial for 2 reasons. First, dasatinib 100 mg once daily in the treatment of hematologic malignancies provides responses similar to those in patients tak-

ing the approved 70 mg twice daily dose, with reduced side effects. Second, because of the concerning number of pleural effusions noted in the study using dasatinib at 100 mg twice daily dosing, it was felt that a reduced dose may also help reduce the incidence of pleural effusions. In the study combining the use of dasatinib 100 mg daily and docetaxel, the incidence of pleural effusions in the entire population study was 7%. This is much less than the 51% reported in the higher dosing trials previously addressed.⁸²

These phase II studies have paved the way for a clinical trial currently recruiting patients to assess dasatinib's effect in metastatic CRPC.⁸³ This is a randomized, double-blind, phase III trial comparing docetaxel combined with dasatinib (100 mg daily) to docetaxel combined with placebo in chemotherapy-naïve patients with CRPC. The primary endpoint of this trial is overall survival and secondary endpoints will include rate of change in urinary N-telopeptide, time to first SRE, rate of change in pain intensity, time to PSA progression and safety and tolerability of combination therapy. Results of this study are expected to be made available in 2013.⁸³

Conclusion

There has been a large focus in the recent past to develop new treatments for patients with CRPC. Our improved understanding of tumour biology and our continued appreciation for what the immune system can do has helped pave the way for a new era in the treatment of cancer. In April 2010, a revolutionary step was taken in the treatment of not just prostate cancer, but also in the treatment of all solid tumours. Sipuleucel-T is the first immune-based therapy approved for the treatment of solid tumours and has opened the door to uncharted areas of cancer treatment. Our ability to understand resistance-mediated mechanisms in tumour biology has also led to the creation of cabazitaxel as an alternative to those who fail to show a response to docetaxel-based chemotherapy regimens. Furthermore, the recent FDA approval of denosumab for men with CRPC and accompanying bony metastases has provided another treatment option alongside zoledronic acid for these patients.

Our advanced understanding of androgen signalling in metastatic CRPC has led to the evolution of promising hormonal therapies: abiraterone, TAK-700 and MDV3100. The encouraging results revealed at the European Society for Medical Oncology concerning abiraterone and the recent creation of the AFFIRM and PREVAIL trials looking at MDV3100, we are expanding the arsenal available for treating patients with CRPC. The potential addition of treatments like ipilimumab and dasatinib will only expand the treatment options for patients battling prostate cancer. As the treatments available for patients increase and we continue to build our armamentarium in combating this disease, we

will provide more answers for patients with metastatic CRPC. That said, this will also raise more questions, in particular from clinicians and researchers with respect to how to alter the current treatment paradigm for patients with metastatic CRPC (Fig. 5).²³ In the coming years, as the results of studies currently underway with the newly approved therapies become available, our understanding of where these treatments fall into place should become clearer.

Lastly, in working under a publicly funded health care system in Canada, there will also be questions left to be answered by politicians and policy-makers. The astronomical cost for the complete sipuleucel-T therapy^{32,84} compared to the more affordable cost of cabazitaxel (\$5000USD per cycle)⁸⁵ could surely influence what treatment modalities are made available to Canadians battling metastatic CRPC. At present, Canadians are able to access such drugs as cabazitaxel and abiraterone by having their physician file an application for special access through Health Canada's Special Access Program⁸⁶ or to gain early access, patients may enrol in clinical trials using these therapies at specific clinical academic centres in Canada.^{87,88} In terms of sipuleucel-T, accessibility for Canadian patients is limited to patients who can afford the cost of treatment and who are able to travel to the United States for therapy. Currently, access to sipuleucel-T via clinical trials for Canadian patients is limited.

McMaster Institute of Urology, Division of Urology, Department of Surgery McMaster University, Hamilton, ON

Competing interests: None declared.

This paper has been peer-reviewed.

References

1. Canadian Cancer Society. Prostate cancer statistics. <http://www.cancer.ca>. Accessed March 3, 2011.
2. Hamberg P, Verhagen PC, de Wit R. When to start cytotoxic therapy in asymptomatic patients with hormone refractory prostate cancer? *Eur J Cancer* 2008;44:1193-7.
3. Sternberg CN. Systemic chemotherapy and new experimental approaches in the treatment of metastatic prostate cancer. *Ann Oncol* 2008;19:vii91-5.
4. Galsky MD, Vogelzang NJ. Docetaxel-based combination therapy for castration-resistant prostate cancer. *Ann Oncol* 2010;10:1093-102.
5. Halabi S, Small EJ, Kantoff PW, et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. *J Clin Oncol* 2003;21:1232-7.
6. Di Lorenzo G, Buonerba C, Autorino R, et al. Castration-resistant prostate cancer current and emerging treatment strategies. *Drugs* 2010;70:983-1000.
7. Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: update survival in the TAX 327 study. *J Clin Oncol* 2008;26:242-5.
8. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502-12.
9. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513-20.
10. Diamond TH, Higano CS, Smith MR, et al. Osteoporosis in men with prostate carcinoma receiving androgen deprivation therapy: recommendations for diagnosis and therapies. *Cancer* 2004;100:892-9.

11. Preston DM, Torrens JI, Harding P, et al. Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss. *Prostate Cancer Prostatic Dis* 2002;5:304-10.
12. Shahinian VB, Kuo YF, Freeman JL, et al. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005;352:154-64.
13. Weinfurt KP, Li Y, Castel LD, et al. The significance of skeletal related events for the health-related quality of life of patients with metastatic prostate cancer. *Ann Oncol* 2005;16:579-84.
14. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst* 2004;96:879-82.
15. Saad F, Hotte SJ. Guidelines for the management of castrate-resistant prostate cancer. *Can Urol Assoc J* 2010;6:380-4.
16. Sarin J, DeRossi SS, Akintoye SO. Updates on bisphosphonates and potential pathobiology of bisphosphonate-induced jaw osteonecrosis. *Oral Dis* 2008;14:277-85.
17. Pazianas M, Miller P, Blumentals WA, et al. A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics. *Clin Ther* 2007; 29:1548-58.
18. Migliorati CA, Siegel MA, Elting LS. Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. *Lancet Oncol* 2006;7:508-14.
19. Ullen A, Lennartsson L, Harmanberg U, et al. Additive/synergistic antitumoral effects on prostate cancer cells in vitro following treatment with a combination of docetaxel and zoledronic acid. *Acta Oncol* 2005;44:644-50.
20. Attard G, Greystoke A, Kaye S, De Bono J. Update on tubulin-binding agents. *Pathol Biol (Paris)* 2006;54:72-84.
21. Pivot X, Koralewski P, Hidalgo JL, et al. A multicentre phase II study of XRP6258 administered as a 1-h i.v. infusion every 3 weeks in taxane-resistant metastatic breast cancer patients. *Ann Oncol* 2008;19:1547-52.
22. Mita AC, Denis LJ, Rowinsky EK, et al. Phase I and pharmacokinetic study of XRP6258, a novel taxane, administered as a 1-hour infusion every 3 weeks in patients with advanced solid tumours. *Clin Cancer Res* 2009;15:723-30.
23. Drake CG. Prostate cancer as a model for tumour immunotherapy. *Nat Rev Imm* 2010;10:580-93.
24. Small EJ, Schellhammer PF, Higano CS. Placebo controlled phase III of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J Clin Oncol* 2006;24:3089-94.
25. Higano CS, Schellhammer PF, Small EJ, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer* 2009;115:3670-9.
26. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411-22.
27. Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J Clin Oncol* 2006;24:3089-94.
28. Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. *J Clin Oncol* 2010;28:1099-105.
29. Vogelzang NJ, Petrylak DP, Kelly G, et al. Prostate Cancer: CCO Independent Conference Coverage of the 2010 Genitourinary Cancers Symposium. Clinical Care Options, LLC.
30. Sipuleucel-T as Neoadjuvant Treatment in Prostate Cancer (NeoACT) [Clinical Trials.gov identifier NCT00715104]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
31. Provenge (TM) for the Treatment of Hormone Sensitive Prostate Cancer (PROTECT) [Clinical Trials.gov identifier NCT00779402]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
32. Longo DL. New therapies for castration-resistant prostate cancer. *N Engl J Med* 2010;363:479-81.
33. Jevtana. sanofi-aventis, Bridgewater, NJ. www.jevtana.com. Accessed March 4, 2011.
34. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomized open-label trial. *Lancet* 2010;376:1147-54.
35. Dougall WC, Chaisson M. The RANK/RANKL/OPG triad in cancer-induced bone diseases. *Cancer Metastasis Rev* 2006;25:541-9.
36. Chustecka Z. Denosumab approved for cancer patients with bone metastasis. <http://www.medscape.com/viewarticle/732891>. Accessed February 9, 2011.
37. Fizazi K, Carducci M, Smith M, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with castration resistant prostate cancer [abstract LBA4507]. *J Clin Oncol* 2010;28:18s.
38. Goodman A. Denosumab superior to zoledronic acid in delaying time to skeletal events in castrate-resistant prostate cancer. <http://www.ascp.org/articles/august-2010/denosumab-superior-to-zoledronic-acid-in-delaying-time-to-skeletal-events-in-castrate-resistant-prostate-cancer>. Accessed February 9, 2011.
39. Reed SD, Radeva JI, Glendenning AG, et al. Cost-effectiveness of zoledronic acid for the prevention of skeletal complications in patients with prostate cancer. *J Urol* 2004;4:1537-42.
40. Study on Prolonging Bone Metastasis-Free Survival in Men With Hormone Refractory Prostate Cancer [Clinical Trials.gov identifier NCT00286091]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
41. Small EJ, Halabi S, Dawson NA, et al. Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB 9583). *J Clin Oncol* 2004;22:1025-33.
42. Scher HI, Sawyers CL. Biology of progressive, castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signalling axis. *J Clin Oncol* 2005;23:8253-61.
43. Taplin ME, Regan MM, Ko YJ, et al. Phase II study of androgen synthesis inhibition with ketoconazole, hydrocortisone, and dutasteride in asymptomatic castration-resistant prostate cancer. *Clin Cancer Res* 2009;15:7099-105.
44. Yap TA, Carden CP, Attard G, et al. Targeting CYP17: established and novel approaches in prostate cancer. *Curr Opin Pharmacol* 2008;4:449-57.
45. Danila DC, Morris MJ, de Bono JS, et al. Phase II multicentre study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. *J Clin Oncol* 2010;28:1496-501.
46. Abiraterone acetate in castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy [Clinical Trials.gov identifier NCT00638690]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: <http://clinicaltrials.gov> [accessed February 9, 2011].
47. Abiraterone acetate in asymptomatic or mildly symptomatic patients with castration-resistant prostate cancer [Clinical Trials.gov identifier NCT00887198]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
48. De Bono J. Abiraterone acetate plus low dose prednisone improves overall survival in patients with metastatic castration-resistant prostate cancer who have progressed after docetaxel-based chemotherapy: Results of COU-AA-301, a randomized double-blind placebo-controlled phase III study. ESMO 2010;P:135.
49. Centocor Ortho Biotech Inc. Centocor Ortho Biotech Inc. Announces NDA Submission for Abiraterone Acetate for the Treatment of Metastatic Advanced Prostate Cancer. http://www.centocororthobiotech.com/cobi/viewDocumentByTitleAlias.html?title=PR_122010. Accessed February 9, 2011.
50. Molina A, Belldegrin A. Novel therapeutic strategies for castration resistant prostate cancer: inhibition of persistent androgen production and androgen receptor mediated signalling. *J Urol* 2011;185:787-94.
51. Drecier R, Angus DB, MacVicar GR, et al. Safety, pharmacokinetics, and efficacy of TAK-700 in castration-resistant metastatic prostate cancer: a phase I/II open label study. *Genitourin Cancer Symp Proc* 2010;89:abstract 103.
52. Safety Study of TAK-700 in Subjects With Prostate Cancer. [Clinical Trials.gov identifier NCT00569153]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
53. Study Comparing Orteronel Plus Prednisone in Patients With Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer [Clinical Trials.gov identifier NCT01193244]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
54. Study Comparing Orteronel Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer [Clinical Trials.gov identifier NCT01193257]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
55. Scher H, Beer TM, Higano CS, et al. Antitumor activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Lancet* 2010;375:1437-46.
56. Miller K. Experts comments and summary RE: Antitumor activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Eur Urol* 2010;58:462-6.
57. AFFIRM: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients with Progressive Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy [Clinical Trials.gov identifier NCT00974311]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
58. PREVAIL: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naive Patients with Progressive Metastatic Prostate Cancer Who Have Failed Androgen Deprivation Therapy [Clinical Trials.gov identifier NCT01212991]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
59. Medivation. Medivation and Astellas Announce Initiation of a Second Phase 3 Clinical Trial of MDV3100 in Advanced Prostate Cancer. <http://investors.medivation.com/releasedetail.cfm?ReleaseID=512202>. Accessed February 9, 2011.
60. Lassi K, Dawson NA. Update on castrate-resistant prostate cancer: 2010. *Curr Opin Oncol* 2010;22:263-7.
61. Slovin SF, Beer TM, Higano CS, et al. Initial phase II experience of ipilimumab alone and in combination with radiotherapy in patients with metastatic castration-resistant prostate cancer abstract 5138. *J Clin Oncol* 2009;27:15s.
62. Comparison Study of MDX-010 (CTLA-4) Alone and Combined With Docetaxel in the Treatment of Patients With Hormone Refractory Prostate Cancer [Clinical Trials.gov identifier NCT00050596]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.

63. Study of Immunotherapy to Treat Advanced Prostate Cancer [Clinical Trials.gov identifier NCT00861614]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
64. Phase 3 Study of Immunotherapy to Treat Advanced Prostate Cancer [Clinical Trials.gov identifier NCT01057810]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
65. Nelson J, Bagnato A, Battistini B, et al. The endothelin axis: emerging role in cancer. *Nat Rev Cancer* 2003;3:110-6.
66. Fizazi K, Miller K. Specific endothelin-A receptor antagonism for the treatment of advanced prostate cancer. *BJU Int* 2009;104:1423-6.
67. Warren R, Liu G. ZD4054: A specific endothelin A receptor antagonist with promising activity in the metastatic castration-resistant prostate cancer. *Expert Opin Investig Drugs* 2008;17:1237-45.
68. Gowcott JW. Preclinical anticancer activity of the specific endothelin A receptor antagonist ZD4054. *Anticancer Drugs* 2009;20:83-8.
69. James ND, Caty A, Borre M, et al. Safety and efficacy of the specific endothelin-A receptor antagonist ZD4054 in patients with hormone-resistant prostate cancer and bone metastases who were pain free or mildly symptomatic: a double-blind, placebo-controlled, randomised, phase 2 trial. *Eur Urol* 2009;55:1112-23.
70. Phase III trial of ZD4054 (endothelin A antagonist) in non-metastatic hormone resistant prostate cancer (ENTHUSEMO) [Clinical Trials.gov identifier NCT00626548]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
71. Phase III trial of ZD4054 (endothelin A antagonist) and docetaxel in metastatic hormone resistant prostate cancer with bone metastases (ENTHUSEM1c) [Clinical Trials.gov identifier NCT00617669]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
72. Phase III trial of ZD4054 (endothelin A antagonist) in hormone resistant prostate cancer with bone metastases (ENTHUSEM1) [Clinical Trials.gov identifier NCT00554229]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
73. AstraZeneca Global. Results of Zibotentan Phase III trial in castration resistant prostate cancer. <http://www.astrazeneca.com/Media/Press-releases/Article/Results-of-Zibotentan-Phase-III-trial-in-castration-resistant-pr>. Accessed March 4, 2011.
74. Fizazi K. The role of Src in prostate cancer. *Ann Oncol* 2007;18:1765-73.
75. Thomas X, Olteanu N, Charrin C, et al. Acute lymphoblastic leukemia in the elderly: the Edouard Herriot Hospital experience. *Am J Hematol* 2001;67:73-83.
76. Chang YM, Kung HJ, Evans CP. Non-receptor tyrosine kinases in prostate cancer. *Neoplasia* 2007;9:90-100.
77. Edwards J, Krishna NS, Witten CJ, et al. Gene amplifications associated with the development of hormone-resistant prostate cancer. *Clin Cancer Res* 2003;9:5271-81.
78. Summy JM, Gallick GE. Src family kinases in tumour progression and metastasis. *Cancer Metastasis Rev* 2003;22:337-58.
79. Posadas EM, Al-Ahmadie H, Robinson VL, et al. FYN is overexpressed in human prostate cancer. *BJU Int* 2009;103:171-7.
80. Mendiratta P, Mostaghel E, Guinney J, et al. Genomic strategy for targeting therapy in castration-resistant prostate cancer. *J Clin Oncol* 2009;27:2022-9.
81. Yu EY, Wilding G, Posadas E, et al. Phase II study of dasatinib in patients with metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2009;23:7421-8.
82. Araujo J, Gallick G, Trudel G, et al. Dasatinib and docetaxel combination treatment for patients with castration-resistant progressive prostate cancer: a phase 1.2 study (CA 180-086) [abstract 5061] *J Clin Oncol* 2009;27:15s.
83. Randomized Study Comparing Docetaxel Plus Dasatinib to Docetaxel Plus Placebo in Castration-Resistant Prostate Cancer [Clinical Trials.gov identifier NCT00744497]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
84. Morris E. Newest FDA approval of targeted cancer therapy: sipuleucel-T for advanced prostate cancer. <http://www.examiner.com/health-news-in-boston/newest-fda-approval-of-targeted-cancer-therapy-sipuleucel-t-for-advanced-prostate-cancer>. Accessed February 9, 2011.
85. Hayes E. With Jevtana approved for advanced prostate cancer, Sanofi could see expansion to first-line use. http://www.oncologystat.com/news/With_Jevtana_Approved_for_Advanced_Prostate_Cancer_Sanofi_Could_See_Expansion_to_First_Line_Use.html. Accessed February 9, 2011.
86. Health Canada. Drugs and Health Products. http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapfs_pasfd_2002-eng.php. Accessed February 9, 2011.
87. Study of Abiraterone Acetate in Patients with Advanced Prostate Cancer [Clinical Trials.gov identifier NCT01217697]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.
88. Early Access to Cabazitaxel in Patients with Metastatic Hormone Refractory Prostate Cancer Previously Treated with a Docetaxel-containing Regimen [Clinical Trials.gov identifier NCT01254279]. US National Institutes of Health. <http://clinicaltrials.gov>. Accessed February 9, 2011.

Correspondence: Dr. Anil Kapoor, Associate Professor of Surgery (Urology) and Chair, Genitourinary Oncology Program, Juravinski Cancer Centre, McMaster University, St. Joseph's Hospital, 50 Charlton Ave. E., Hamilton ON L8N 4A6; akapoor@mcmaster.ca