ABSTRACT

Prostate cancer (PCA) is the most common non-skin cancer diagnosed in North America, and it affects 1 in 6 men. Patients with recurrent or metastatic PCA will inevitably develop castration-resistant disease after an initial period of hormone responsiveness. The standard first-line treatment for men with castration-resistant PCA (CRPC) is docetaxel, but further treatment options are limited. This review summarizes the research being conducted in CRPC, with specific regard to immunotherapy and to novel targeted therapies directed against the androgen axis, vascular endothelial growth factor, chaperone proteins, the phosphoinositide 3 kinase/Akt/phosphatase and tensin homolog/mammalian target of rapamycin pathway, and endothelin-1.

KEY WORDS

Castration-resistant prostate cancer, novel therapy, targeted therapy

1. INTRODUCTION

Men with recurrent or metastatic prostate cancer (PCA) will, invariably, develop castration resistance after an initial period of hormone responsiveness. Historically, the treatment arsenal for men with castration-resistant PCA (CRPC) has been limited to those interventions that afford some modicum of symptomatic benefit. Treatments approved for use in symptomatic men with CRPC include mitoxantrone (1), radioactive isotopes (2), and the bisphosphonate zoledronic acid (3). Docetaxel is the only approved systemic agent that has been shown to improve overall survival (OS: median improvement: 2.4 months over mitoxantrone) (4,5). Recently, cabazitaxel, a novel taxane, was reported to have a median OS benefit of 2.4 months over mitoxantrone and prednisone in patients progressing after docetaxel, although regulatory approval is still pending (6). Given the fact that PCA is the most commonly diagnosed non-skin cancer in North America (7) and given the paucity of treatment options that afford an OS benefit, significant preclinical and clinical research is being conducted in an effort to change the situation.

Clinicians are now poised for significant potential change when it comes to the management of CRPC. An increase in the understanding of the biologic underpinnings of cancer in general, and of PCA specifically, has led to rational drug development, and the resulting drugs are currently being tested in both early- and late-phase clinical trials. Novel therapies that target androgen receptor signalling, the vascular endothelial growth factor pathway, apoptosis, chaperone proteins, the insulin-like growth factor pathway, and the phosphoinositide 3 kinase (PI3K)/Akt/phosphatase and tensin homolog (PTEN)/mammalian target of rapamycin (mTOR) pathway have been developed and are being evaluated. Beyond that, therapeutics focused on bone targeting, novel cytotoxic chemotherapies, and drug combinations are also under investigation.

This article focuses on some of the current concepts behind targeted therapy for CRPC, with a focus on novel agents that are currently in late-phase clinical trials or that target unique pathways.

2. DISCUSSION

2.1 Androgen Receptor Signalling

For many patients with recurrent or metastatic disease, hormonal therapy has the ability to induce long-term disease control, but the development of castration-resistant disease is inevitable. When CRPC develops, either (or both of) rising prostate-specific antigen (PSA) and radiologic progression is seen despite castrate levels of testosterone (8,9). Historically, this circumstance was termed “hormone refractory disease.” It has long been observed, however, that men who progress after first-line hormonal maneuvers will often have a PSA and clinical response to second-line hormonal treatments, and thus the term “hormone refractory” is no longer appropriate.

Clinical response to second-line hormonal maneuvers was initially thought to be solely related to extragonadal androgen production, but additional...
mechanisms potentially underlie such responses. Several studies have demonstrated amplification and increased expression of the androgen receptor (AR) in CRPC tissue \(^{10-12}\), and in vitro and in vivo studies have also shown that, for the evolution of CRPC, increased expression of the AR is necessary \(^{11}\). Prostate cancer cells also possess the biochemical machinery to synthesize androgens by an autocrine/paracrine mechanism \(^{13-16}\). Finally, AR splice variants lacking the ligand binding domain have been observed to be constitutively active, independent of the presence of ligand \(^{17}\). Over the last several years, an area of active research has been the development of more potent inhibitors of extragonadal androgen production and of small-molecule antagonists of the AR \(^{18}\).

Abiraterone acetate (AA) is an orally administered inhibitor of the cytochrome P450 enzyme, CYP17A1. The CYP17A1 enzyme has dual functions both as a 17α-hydroxylase and a C\(_{17,20}\)-lase, both functions being necessary for the conversion of cholesterol precursors into androgen. A phase I clinical trial has demonstrated a high degree of tolerance \(^{19}\), and the reported toxicities were, as anticipated, related to mineralocorticoid excess (hypertension, hypokalemia, edema) and were easily controlled with co-administration of low doses of prednisone. Patient populations who were chemotherapy-naïve and those that had progressed post docetaxel were subsequently evaluated in several phase II clinical trials of AA.

In one such trial, 27 patients with CRPC who had never received chemotherapy received AA, and a PSA decline of more than 50% was observed in 85% of those patients \(^{20}\). Another phase II trial evaluated AA in 47 patients who were previously treated with docetaxel \(^{21}\). Declines in PSA of more than 50% were observed in 51% of the patients, and partial radiologic responses were observed in 6 of 35 patients (17%) with measurable disease. Responses were durable, with 17 patients remaining on therapy for more than 6 months, and treatment continued for a median duration of 167 days. Another phase II trial evaluated AA in patients who were heavilypretreated \(^{22}\). Patients who had previously been exposed to high doses of ketoconazole (a less-specific inhibitor of CYP450 enzyme) appeared to be less responsive to abiraterone: as compared with 55% of patients who had not received prior ketoconazole, 30% of those who did experienced a greater-than-50% PSA decline.

A multicentric randomized double-blind placebo-controlled phase III trial evaluating abiraterone in patients with metastatic CRPC and with progression after docetaxel chemotherapy has completed accrual (see NCT00638690 at www.ClinicalTrials.gov). The trial randomized 1158 patients 2:1 in favour of AA. The primary endpoint is overall survival. A second phase III trial with AA has also completed accrual. Approximately 1000 minimally symptomatic chemotherapy-naïve patients were randomized to AA or placebo (see NCT00887198 at www.ClinicalTrials.gov) with primary endpoints of OS and progression-free survival.

Another novel anti-androgen under development is MDV3100. Compared with bicalutamide, this drug is a more potent AR antagonist, and it possesses no agonistic activity. In PCA models and clinically, it is often observed that bicalutamide can have agonistic effects on the AR \(^{11}\) as a result of nuclear translocation, DNA binding, and co-activator recruitment. In contrast, when MDV3100 binds the AR, nuclear translocation is inefficient, and DNA binding is completely inhibited. A first-in-humans phase II dose-escalation study was recently reported. At 12 weeks, 57% of chemotherapy-naïve patients and 45% of pretreated patients had a 50% or better PSA decline. Dose-limiting toxicities included seizures, but these were not observed at lower doses that were still associated with clinical activity \(^{23}\). A phase III trial is currently recruiting patients with CRPC who have progressed after docetaxel and is randomizing patients 2:1 in favour of MDV3100, with a planned accrual of 1200 patients and a primary endpoint of OS (see NCT00974311 at www.ClinicalTrials.gov).

### 2.2 Vascular Endothelial Growth Factor and Its Receptor

Growth beyond a few millimetres and the ability to metastasize depend on a malignant tumour’s ability to recruit new vasculature through angiogenesis. The vascular endothelial growth factor (VEGF) pathway is a well-characterized mediator of angiogenesis, and many agents have been developed that target the VEGF pathway and receptor. Elevated levels of VEGF-R2 are seen in human PCAs \(^{24}\), and increased plasma levels of VEGF have been associated with poor prognosis and disease progression \(^{25}\).

Bevacizumab is a monoclonal antibody directed against VEGFα that causes potent inhibition of VEGF receptor (VEGF-R) signalling and angiogenesis. Bevacizumab has been evaluated and approved for use in renal, colorectal, breast, and lung cancer. In PCA, bevacizumab has been trialed in combination with docetaxel with encouraging early-phase results \(^{26}\); however, a recent press release from Roche has stated that the Cancer and Leukemia Group B (CALGB) randomized placebo-controlled phase III trial of docetaxel with or without bevacizumab has failed to meet its primary endpoint of improved OS (see NCT00110214 at www.ClinicalTrials.gov).

Afiribcept (“VEGF trap”) is a recombinantly-produced fusion protein consisting of human VEGFR extracellular domains fused to the Fc portion of human immunoglobulin G1. By binding to and inactivating the circulating factors VEGF and VEGF, afiribcept prevents them from binding to VEGFR1 and 2 \(^{27}\). Phase I studies have shown that the combination of afiribcept and docetaxel is safe \(^{28}\), and a phase III placebo-controlled trial assessing the effect
of docetaxel with or without aflibercept is underway (see NCT00519285 at www.ClinicalTrials.gov).

Sunitinib is an orally administered multi-targeted tyrosine kinase inhibitor of VEGFR, platelet-derived growth factor receptor, and Kit. A phase II trial of sunitinib given after patients had progressed on docetaxel showed a PSA decline of 50% or more in 12% of patients and of 30% or more in 21%. Despite the activity, 53% of patients discontinued treatment secondary to toxicities, and 2 treatment-related deaths occurred. A phase III trial of sunitinib as second-line treatment after docetaxel is currently accruing (see NCT00676650 at www.ClinicalTrials.gov).

2.3 Chaperone Proteins

A number of chaperone proteins have been identified as being of interest in CRPC, including clusterin. Clusterin exists as both an intracellular truncated form that is proapoptotic and as a cytoplasmic and secretory form that is antiapoptotic. In cancer, clusterin has been largely defined in its role of inhibiting apoptosis. After therapeutic stress, clusterin is activated and functions as a cytoprotective chaperone, similar to an adenosine triphosphate–independent small heat shock protein. It is transcriptionally activated by heat shock factor 1. Bax is a critical proapoptotic member of the Bel2 family, and clusterin has been shown to inhibit activated Bax, thereby inhibiting apoptosis. Clusterin has also been associated with activation of the PI3K/Akt pathway through the megalin cell-surface receptor. In cancer models, forced overexpression of clusterin confers resistance to radiation, hormone therapies, and chemotherapy. Further, inhibition of clusterin enhances apoptotic death from those same treatment modalities. In preclinical models of PCA, clusterin has been associated with androgen-independent progression. In clinical samples, increased expression of clusterin is associated with increasing Gleason grade and castration-resistant disease. Taken together, these findings make clusterin an attractive target in the treatment of CRPC.

The phosphorothioate antisense molecule OGX-011 inhibits translation of clusterin messenger RNA, thereby decreasing secretory clusterin expression in vitro and in vivo. In phase I trials, it has been demonstrated that OGX-011 can inhibit expression of clusterin in PCA tissue and that the compound can be delivered safely with chemotherapy. A randomized phase II trial of OGX-011 (given with either mitoxantrone or docetaxel) in patients who had progressed either on or within 3 months of treatment with docetaxel was reported at the 2008 American Society of Clinical Oncology (ASCO) annual meeting. In 27% of patients who received mitoxantrone with OGX-011, a PSA decline of 50% or more was observed, and the median OS in that group was 11.4 months. In the group that received docetaxel with OGX-011, 40% experienced a 50% or greater drop in PSA, and median OS was 14.7 months. A second randomized phase II trial was presented at the 2009 ASCO annual meeting. In that study, 82 chemotherapy-naïve patients with metastatic CRPC were randomized to receive first-line docetaxel either with or without OGX-011. Although there was no difference in PSA decline between groups, fewer patients had progression as best response, and the group receiving OGX-011 with docetaxel experienced a longer time to progression. Mature results from that study demonstrated a median OS of 16.9 months in the docetaxel-alone group as compared with 27.5 months in the docetaxel with OGX-011 group. A phase III trial expected to commence later in 2010 will compare docetaxel and OGX-011 with docetaxel alone in patients with chemotherapy-naïve metastatic CRPC. The primary endpoint will be OS.

2.4 PI3K/Akt/mTOR

Several cell-surface receptors that activate the downstream PI3K/Akt/mTOR signal transduction pathway to regulate survival, growth, proliferation, and angiogenesis—epidermal growth factor receptor, platelet-derived growth factor, insulin-like growth factor receptor (IGF-R), insulin receptor, and interleukin 6 receptors—have been implicated in cancer progression. In PCA, activation of the PI3K/Akt/mTOR pathway has been associated with ligand-independent activation of the AR and with androgen-independent progression of PCA. The tumour-suppressor gene PTEN, frequently deleted in PCA, normally serves to negatively regulate the PI3K/Akt survival pathway. A number of approaches to targeting this pathway are in early-phase clinical development in PCA. These approaches include activity against cell-surface receptors [for example, monoclonal antibodies to IGF1R (see NCT00313781 at www.ClinicalTrials.gov)] or PI3K, Akt, and mTOR (see NCT00110188, NCT00629525, NCT00574769, NCT0085566, NCT00703625, and NCT00703170 at www.ClinicalTrials.gov) either as single agents or in combination with other agents.

2.5 Endothelin 1

Prostate cancer has a propensity to metastasize to bone, and so targeting the pathways that mediate bone progression is a rational approach. Endothelins (ETs) are 21-amino-acid peptides that are elevated in men with metastatic PCA and that are known mediators of the osteoblastic response of bone to metastatic disease. Endothelin 1 preferentially binds to endothelin A (ETA), and ETA signalling has been associated with proliferation, antiapoptotic effects, and pain. Atrasentan is an orally bioavailable competitive inhibitor of ETA. Biologic effects were observed in early-phase studies, however, two phase III trials have failed to demonstrate an improvement in time to progression despite evidence of decreased bone turnover.
of atrasentan in combination with docetaxel continues. Phase I/II studies of this combination have resulted in high rates of febrile neutropenia (16%–25%) and a shorter-than-expected median OS 52. Nevertheless, the Southwest Oncology Group is conducting a phase III trial comparing docetaxel–prednisone with docetaxel–prednisone–atrasentan in 930 patients with metastatic CRPC; the primary endpoint is OS (see NCT00134056 at www.ClinicalTrials.gov).

A more specific inhibitor of ETA, ZD4054, is currently in testing. A 3-arm randomized phase II trial assessing 2 doses of AD4054 as compared with placebo showed no difference in the primary endpoint of progression, but did demonstrate an OS benefit of more than 6 months in favour of the treatment arms 53. Consequently, 3 phase III trials are currently underway: ZD4054 versus placebo in CRPC with no metastases (see NCT00626548 at www.ClinicalTrials.gov), in CRPC with bone metastases that have no or minimal associated symptoms (see NCT00544229 at www.ClinicalTrials.gov), and in patients receiving docetaxel (see NCT00617669 at www.ClinicalTrials.gov).

2.6 Immunotherapy

Another rapidly evolving area in the treatment of CRPC is immunotherapy, wherein the goal is to harness the body’s own immune system to elicit an antitumour effect. To properly immunize a patient with a tumour-specific antigen, inducing an antitumour effect, antigen-presenting cells [APCs (such as dendritic cells)] must process and present the antigens to T cells.

Sipuleucel-T is dendritic cell–based vaccine designed to stimulate T-cell immunity against prostatic acid phosphatase (PAP), which is expressed in benign and malignant prostate epithelia alike. Vaccine preparation requires patients to undergo a 1.5–2.0 blood-volume mononuclear cell leucapheresis. The APCs are extracted and cultured with a fusion protein that consists of PAP linked to granulocyte–macrophage colony–stimulating factor (GM-CSF). As a result, the APCs are activated, and upon re-introduction to the patient, they load and process the PAP antigen for presentation to the T cell.

Phase I and II trials have demonstrated that this approach is feasible, and sipuleucel-T testing in phase III trials produced evidence of antitumour activity 54. Two small, identical design randomized phase III trials (double-blind and placebo-controlled) have evaluated sipuleucel-T in men with metastatic CRPC. The primary endpoint of PFS was not statistically different between the treatment groups, but OS was statistically improved in the treatment group (as compared with placebo), showing a median OS benefit of 4.5 months 55. The data from these trials were compiled and evaluated together, with the result that the OS benefit was maintained, with a 33% reduction in the risk of death in the treatment group 56. Updated results from a larger 500-patient phase III trial were reported at the 2010 ASCO genitourinary symposium. That trial was designed with OS as the primary endpoint, and it demonstrated a 4.1-month survival advantage for the patients treated with sipuleucel-T 57. Those results provide a “proof of principle” demonstration of clinical benefit and the viability of an active immunotherapy approach to cancer.

Other vaccine approaches have been less successful. The GVAX (GM-CSF gene-modified tumour) vaccine uses whole cells as an antigen source to provoke an immune response to multiple antigens. Phase I/II trials demonstrated safety 58, but two phase III studies in men with CRPC both closed early. The first study randomized 408 patients to docetaxel with GVAX or to GVAX alone, and it was closed by the independent data monitoring committee after an imbalance of deaths was observed in the immunotherapy arm (see NCT00133224 at www.ClinicalTrials.gov). A second trial accrued 626 asymptomatic patients and randomized them to receive GVAX or docetaxel (see NCT00089856 at www.ClinicalTrials.gov); that trial also closed early after interim analysis determined that the study was unlikely to meet its primary endpoint.

3. SUMMARY

Knowledge of the mechanisms driving the development and progression of CRPC has increased exponentially in the last several years, resulting in highly rational drug design based on sound preclinical evidence. Significant inroads are therefore being made in the treatment of a disease that, to date, has had only one intervention that affords a survival benefit. Positive results from the AA and MDV3100 trials are hoped for, and some success has already been seen with novel cytotoxics and immunotherapy. However, those successes bring attendant issues of availability and cost to the health care system that will have to be addressed in the coming months and years.

4. REFERENCES


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