Overview: Prostate cancer is the most common nonskin malignant neoplasm in men worldwide. In the United States, 241,740 new diagnoses of prostate cancer and 28,170 prostate cancer deaths have been estimated for 2012, representing 28% of new cancer cases and 10% of male cancer deaths. Although metastatic prostate cancer remains an incurable disease, substantial advances have been made in therapeutic options available for men in the past several years. Development of novel agents that modulate the androgen receptor pathway, growth factor signaling pathways, and immune function and bone targeting pathways has been the focus of therapeutic strategies because of its significance in the biology of prostate cancer progression. Several of the agents have gained U.S. Food and Drug Administration (FDA) approval, whereas many are in late-stage clinical trials. With the growth of available treatment options, a major challenge as we move forward will be to determine the best sequence and/or combination of therapy that will result in maximum clinical efficacy with minimum toxicity. Highlighted in this publication are several of the exciting advances in prostate cancer therapy for patients with metastatic, castrate-resistant prostate cancer.

Androgens are the key regulators of cell growth and proliferation in prostate cancer. Androgen deprivation therapy is initially a highly effective therapy because of the induction of apoptosis. Persistent androgen receptor (AR) activation is an important mediator of disease progression in castrate-resistant prostate cancer (CRPC). There are multiple mechanisms by which this activation happens, including AR overexpression, AR mutations that increase androgen sensitivity to or activation by other steroids, increased local androgen production by prostate cells via expression of steroidogenic enzymes, AR activation via crosstalk of signal transduction pathways (epidermal growth factor, insulin-like growth factor, interleukin 6), modulated expression of coactivators or corepressors of AR, and proteolytic processing of AR to an androgen-independent isoform. Preclinical research has validated these concepts and thus has served as the basis for the translation of novel, potent AR-targeted therapies for patients with prostate cancer who experience relapse after initial androgen inhibition. Several clinical studies have demonstrated that CRPC cells continue to be under the influence of androgen signaling as evidenced by the high number of AR expression. As a result, these newer agents tend to be more specific targets of enzymes downstream in the hormonal cascade.

Abliraterone

Abliraterone acetate is more potent than ketoconazole and a selective inhibitor of the C17α-hydroxylase and the C17, 20-lyase function of CYP17A. In a phase II trial, 47 men with metastatic CRPC deemed refractory to docetaxel-based chemotherapy were given oral abiraterone at 1,000 mg/d. The results were prostate-specific antigen (PSA) decreases of 30% or higher, 50% or higher, and 90% or higher seen in 32 of 47 patients (68%), 24 of 47 patients (51%), and 7 of 47 patients (15%), respectively. These results, coupled with a favorable safety profile, have laid the foundation for the development of two randomized, double-blind, placebo-controlled, phase III clinical trials. Recently, in the first of the phase III trials, 1,195 patients with metastatic CRPC previously treated with docetaxel who were given abiraterone plus prednisone showed improved overall survival compared with those given placebo plus prednisone (median overall survival time, 14.8 vs. 10.9 months; hazard ratio [HR], 0.65; p < 0.0001). All secondary end points, including time to PSA progression (10.2 vs. 6.6 months; p < 0.001), progression-free survival (5.6 vs. 3.6 months; p < 0.001), and PSA response rate (29% vs. 6%, p < 0.001), favored abiraterone. Common adverse effects with this agent include hypokalemia, hypertension, and pedal edema. The effects are explained by a syndrome of mineralocorticoid excess. On the basis of these results, the FDA granted approval in April 2011 of abiraterone for the treatment of patients with metastatic CRPC whose disease had progressed regardless of their docetaxel-based chemotherapy. The second of the phase III trials is investigating abiraterone in asymptomatic or mildly symptomatic men with metastatic CRPC who had not received prior chemotherapy. This trial has completed accrual, with final results pending (NCT00887198).

The clinical trial of abiraterone compared with placebo in the postdocetaxel population is also important because considerable progress has been made in the area of circulating tumor cells. Evaluation of circulating tumor cells was embedded in the phase III trial as a potential surrogate endpoint for overall survival. At the 2011 Annual Meeting of the American Society of Clinical Oncology, results from this phase III trial confirmed that pretreatment circulating tumor cells and lactate dehydrogenase, alone and in combination, served as prognostic biomarkers. Interestingly, PSA did not. This important trial will set the foundation for future trials that incorporate biomarkers as surrogate endpoints.

TAK-700

TAK-700 is a novel, selective CYP450c17 inhibitor similar to abiraterone in its mechanism of reducing testosterone and dehydroepiandrosterone levels. In a phase I/II study of this compound in asymptomatic patients with metastatic CRPC, the drug was tolerated well at various doses, and there was a 50% decrease in 12 of 15 patients who were treated with 300 mg or more twice daily for 3 months or longer. No dose-limiting toxicity was seen, and the most common adverse events were fatigue (62%), nausea (38%), constipation (35%), and vomiting (30%). The preliminary phase I/II study results have led to a phase II, ongoing evaluation of TAK-
700 at a dose of 400 mg twice daily with prednisone in patients with metastatic CRPC. There are now two phase III, multicenter, randomized, double-blind trials that are evaluating TAK-700 plus prednisone compared with placebo plus prednisone in patients with metastatic CRPC. One trial is evaluating chemotherapy-naive patients (primary endpoints: overall survival and radiographic progression-free survival) (NCT01193244), whereas the other focuses on chemotherapy-naive patients (primary endpoint: overall survival) (NCT01193257). Both trials are actively recruiting, with a target accrual of 1,000 to 1,400 patients, and results are expected to be available by 2013–2014. Accrual to the postdocetaxel chemotherapy protocol may be more challenging in the future because of the FDA approval of abiraterone and the positive phase III results of MDV3100.

Studies evaluating combination therapy of abiraterone or TAK-700 with docetaxel chemotherapy are underway (NCT01400555 and NCT01084655, respectively). These results are eagerly awaited because each of these agents may be more challenging in the future because of the FDA approval of abiraterone and the positive phase III results of MDV3100.

Another hormonally driven strategy is to target the AR directly. MDV3100 is an oral AR antagonist that directly inhibits AR by irreversibly binding to the receptor. This interaction impairs AR nuclear translocation, DNA binding, and recruitment of coactivators. Preclinical studies have demonstrated that MDV3100 is a more potent binder to the AR receptor than bicalutamide, thus leading to complete suppression of the AR pathway. In a phase I/II study, MDV3100 showed antitumor activity in patients with metastatic CRPC. In this trial, 56% of 140 patients demonstrated decreases in serum PSA of 50% or more, and 61 of the 109 patients had stabilized bone disease after treatment. The AFFIRM trial is a randomized, double blind, placebo-controlled, multinational trial of 1,199 men assigned to 160 mg/d of MDV3100 (800 patients) or placebo (399 patients). MDV3100 was associated with a median overall survival of 18.4 months compared with 13.6 months for patients assigned to placebo (HR, 0.631). Median progression-free survival also favored MDV3100 (8.3 vs. 2.9 months). Approximately 30% of patients assigned to MDV3100 had complete or partial response compared with 1.3% in the placebo group. The drug also was associated with a PSA reduction of at least 50% from baseline in 54% of the MDV3100 group compared with 1.5% of the placebo group and at least a 90% reduction from baseline in 25% of the MDV3100 group compared with 1% of the placebo group. Median time to PSA progression was 8.3 months in the experimental group compared with 3 months in the placebo group. MDV3100 was well tolerated. The most common adverse events that occurred more frequently in the MDV3100 group (>2%) than in the placebo group included fatigue, diarrhea, and hot flushes. Five of 800 patients treated with MDV3100 in the study reported seizures compared with no seizures among the placebo arm. The 0.6% seizure rate attributed to MDV3100 is below the approximate 1.5% rate seen in an earlier study of the drug using higher doses.

The PREVAIL trial is a phase III trial evaluating patients with chemotherapy-naive CRPC treated with 160 mg/d of MDV3100 with standard of care compared with placebo with standard of care (NCT01212991). With a target accrual goal of 1,700 patients nearly complete, the study has the primary endpoints of overall survival and progression-free survival and secondary endpoints of time to initiation of cytotoxic chemotherapy and time to first skeletal-related event (SRE). ARN-509 is a second-generation antiandrogen that is currently undergoing clinical evaluation. ARN-509 inhibits both AR nuclear translocation and AR binding to androgen response elements in DNA. The compound also does not exhibit agonist activity in prostate cancer cells that overexpress AR. In a recent study, ARN-509 was optimized for inhibition of AR transcriptional activity and prostate cancer cell proliferation, pharmacokinetics, and in vivo efficacy. In a clinically valid murine xenograft model of human CRPC, ARN-509 showed greater efficacy than MDV3100. Maximal therapeutic response in this model was achieved at 30 mg/kg daily of ARN-509, whereas the same response required 100 mg/kg daily of MDV3100 and higher steady-state plasma concentrations. Thus, ARN-509 appears to have a higher therapeutic index than current AR antagonists. ARN-509 seems to be a promising therapy in both castration-sensitive and castration-resistant forms of prostate cancer. Currently, it is in phase II clinical trials (NCT01171898).

Agents such as abiraterone, TAK-700, and MDV3100 are appealing options even during clinical trials because patients are often inclined to consider treatment with pills rather than systemic chemotherapy. Furthermore, there is a familiarity of androgen modulators as therapy because patients undergoing treatment with luteinizing hormone-releasing hormone or gonadotropin-releasing hormone agents have most likely been treated with antiandrogens, such as flutamide and nilutamide, in the past. Finally,
agents modulating the androgen signaling axis frequently result in PSA reduction, another familiar signal of treatment effect. However, a major challenge now is how to best position these oral agents to maximize efficacy. MDV3100 has shown success in patients in whom docetaxel-based chemotherapy has failed, which is in the same patient group as those who benefited from abiraterone. Therefore, with two highly active oral agents, there will be concerns regarding which agent should be initially administered in patients in whom chemotherapy has failed. The treatment landscape will also be affected when the results of the clinical trials conducted in patients before chemotherapy are available. The sequencing and/or role of combination therapy is important and practical and must be further explored in future clinical trials.

Cell Signaling Pathways

Angiogenesis, the process of new blood vessel formation, is a crucial step in the propagation of malignant tumor growth and metastasis. Among the multiple proangiogenic factors that promote the process of vessel formation, vascular endothelial growth factor (VEGF) is one of the most important. Bevacizumab is a humanized monoclonal antibody directed against VEGF-A and causes potent inhibition of VEGF receptor (VEGFR) signaling and angiogenesis. Bevacizumab is approved for use in combination with chemotherapy for patients with metastatic colorectal, breast, and lung cancers. In prostate cancer, bevacizumab has been evaluated in several clinical trials, including the Cancer and Leukemia Group B (CALGB) phase II trial of bevacizumab in combination with docetaxel and estramustine in 79 patients with metastatic CRPC. A PSA decrease of more than 50% from baseline occurred in 81% of patients, the median time to progression was 9 months, and overall survival was 21 months. These favorable trials led to a recent phase III randomized placebo-controlled trial of docetaxel, prednisone, and bevacizumab compared with docetaxel and prednisone in 1,050 patients with chemotherapy-naive metastatic CRPC. The primary endpoint, was 20.7 months for bevacizumab compared with 17.1 months for zoledronic acid. The median time to first on-study SRE, the primary endpoint, was 20.7 months for bevacizumab vs. 17.1 months for zoledronic acid.22 The median time to first osteonecrosis of the jaw was similar in the two groups (2.3% vs. 3.1%). No differences were found in PSA time, overall disease progression, or overall survival. The two treatment groups had a similar frequency of serious toxicities; the cumulative incidence of osteonecrosis of the jaw was similar in the two groups (23% for denosumab vs. 13% for zoledronic acid). These results, combined with two other pivotal phase III trials of the same, led to the FDA approval of denosumab for prevention of skeletal complications in patients with bone metastases from solid tumors, except multiple myeloma.

Bone Targeting

Until recently, the only standard of care was to administer vitamin D, calcium, and a bisphosphonate, such as zoledronic acid, to help minimize bone resorption, which leads to reduction of SREs. Denosumab, a humanized monoclonal antibody with specificity for the RANK ligand, was shown to be superior to zoledronic acid in a study of 1,901 men with CRPC. Denosumab delayed or prevented SREs more effectively than zoledronic acid. The median time to first on-study SRE, the primary endpoint, was 20.7 months for denosumab compared with 17.1 months for zoledronic acid (HR, 0.82; 95% CI, 0.71 to 0.95; p = 0.0002). No differences were found in PSA time, overall disease progression, or overall survival. The two treatment groups had a similar frequency of serious toxicities; the cumulative incidence of osteonecrosis of the jaw was similar in the two groups (23% for denosumab vs. 13% for zoledronic acid). These results, combined with two other pivotal phase III trials of the same, led to the FDA approval of denosumab for prevention of skeletal complications in patients with bone metastases from solid tumors, except multiple myeloma. Denosumab was also found to improve bone metastasis–free survival (29.5 months) compared with placebo in men with M0 CRPC disease (25.2 months). However, no survival benefits were seen with denosumab in the phase III trial that was reported at the European Multidisciplinary Cancer Congress and the European Society for Medical Oncology Meeting 2011. In September 2011, denosumab received FDA approval for its indication to increase bone mass in patients at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. Fortunately, for men with CRPC, there are now two FDA-approved agents to
help improve and strengthen metastatic bones. Zoledronic acid is administered via intravenous infusion and requires monitoring of renal function. Denosumab is administered via subcutaneous injection and requires monitoring of calcium and other electrolytes. Both agents have a role in the treatment of prostate cancer.

Another agent that targets the osteoclasts, osteoblasts, and bone microenvironment is dasatinib. Dasatinib is an oral tyrosine kinase inhibitor with activity against Src kinases. A phase I/II trial evaluating dasatinib alone and in combination with docetaxel chemotherapy in CRPC reported activity with bone turnover markers with mild PSA response. Current, a phase III trial with an estimated enrollment of 1,500 patients comparing docetaxel and dasatinib with docetaxel and placebo is under way (NCT00744497).

A new drug that targets bone signaling pathways leading to actual overall survival is radium-223 chloride. Radium-223 chloride is an intravenously administered radiopharmaceutical that targets bone metastasis with high-energy, short-range α-particles. At the European Multidisciplinary Cancer Congress and the European Society for Medical Oncology Meeting 2011, results from a trial of nearly 1,000 patients with CRPC with 2:1 randomization to either radium-223 chloride or placebo revealed a superior median overall survival of 14 months in the radium-223 chloride arm compared with the 11.2 months in the placebo arm. This 30% reduction in the risk of death (HR, 0.695, p = 0.00185) in overall survival is important because the typical treatment of bone targeting agents results in mediating symptom relief and not necessarily affecting survival. The study results were promising enough that the data safety and monitoring committee for this study halted the accrual. The adverse effects include hematologic effects, such as anemia, and mild gastrointestinal toxicities. Next steps in the development of radium-223 chloride are eagerly awaited.

Cytotoxic Therapy

In 2004, our current stand-of-care chemotherapy, docetaxel, in combination with prednisone had shown efficacy in patients with CRPC. An overall survival benefit of almost 3 months and a PSA response of more than 50% were seen in almost one-half of patients compared with mitoxantrone and prednisone. In March 2010, the efficacy results of a new taxane, cabazitaxel, for use in docetaxel-treated patients with CRPC were presented. This large, multicenter study showed an overall survival benefit of 3 months when compared with mitoxantrone. On the basis of these results, the FDA-approved cabazitaxel as a second-line therapy for prostate cancer. As expected, clinical trials conducted in 2011 are primarily combination therapy evaluating cabazitaxel with chemotherapy, such as docetaxel (NCT01308567), abiraterone (NCT01522536), and tasquinimod (NCT01513733). Clinical trials evaluating optimal sequencing of cabazitaxel and abiraterone and other future agents must be efficiently designed to quickly meet its objectives.

Conclusion

In the last several years, notable advances have been made in the field of prostate cancer. Treatments emerging from our knowledge of the cell biology, androgen regulation, immunology, and chemoresistance of prostate cancer have led to the development of mechanism-based drug discovery. This in turn has led to various clinical trials based on a sound biologic rationale. Several phase III trials testing rational drug combinations in prostate cancer are ongoing. However, clinical trials to determine optimal sequence of therapy are yet to be conducted.

The role of immunotherapy, including the 2010 FDA-approved sipuleucel-T, is also an important part of the treatment paradigm and one that would benefit from biomarker identification. Sipuleucel-T is the first therapeutic cancer vaccine to gain FDA approval for patients with metastatic CRPC. The landmark phase III study of sipuleucel-T showed an overall survival benefit of 4.1 months; however, tumor response rates were minimal. The study validated the efficacy of immunotherapy in prostate cancer and has led to an investigation of additional clinical trials of sipuleucel-T in prostate cancer. Additional promising agents in phase III clinical trials include anti-CTLA-4 (NCT01057810) and ProstVAC-V/F (NCT01322490).

Multiple new drugs have recently been approved for the treatment of prostate cancer, but they all have not been able to demonstrate cure of the disease. In addition to targeting the different mechanisms of action discussed in this publication, multiple other molecular targets also promise to provide the next generation of advances. We must continue to maintain a close collaboration between basic and clinical science so that our knowledge of the molecular physiology can lead to strategic development of further viable drug targets.

Authors’ Disclosures of Potential Conflicts of Interest

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*No relevant relationships to disclose.

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