Overview: Although metastatic castration-resistant prostate cancer (mCRPC) remains the second leading cause of cancer-related deaths for men in the United States, effective treatment options have been limited. Recently, the therapeutic armamentarium for mCRPC has expanded. Sipuleucel-T, abiraterone, and cabazitaxel have all shown improvements in overall survival in phase III trials, and several other agents are currently being explored. Advances have also occurred in the management of skeletal metastases. Denosumab was shown in a phase III trial to delay the time to a skeletal-related event relative to zoledronic acid for men with mCRPC who have osseous metastases. With these recent advances come additional challenges for oncologists, including how to choose and sequence therapies appropriately for individual patients.

Metastatic Castration-Resistant Prostate Cancer 2011: Exciting Advances, New Challenges

By Gary R. MacVicar, MD

Immunotherapy

Immunotherapy stimulates the immune system to generate an attack on a tumor while overcoming tumor-induced tolerance and avoiding autoimmune reactions. The typically slow-growing nature of prostate cancer, the identification of tumor-specific antigen targets, and preclinical data demonstrating the feasibility of eliciting an antitumor immune response support developing immune-based strategies. Several immunotherapies are in various stages of investigation with encouraging results.

Antigen-presenting Cell Vaccines

Sipuleucel-T is a first-in-class, personalized immunotherapy developed for use in mCRPC. This therapy requires isolation of mononuclear cells from patients by leukopheresis, exposure of collected cells to a fusion protein of prostatic acid phosphatase (PAP) and granulocyte macrophage colony-stimulating factor (GM-CSF), and reinfusion of treated cells into patients. This process is repeated every two weeks, three times. In initial randomized trials, the primary end point of progression-free survival (PFS) was not met, but sipuleucel-T yielded an improvement in OS in a combined analysis. A larger phase III study, the IMPACT trial, was subsequently conducted with OS as the primary end point. The median survival was 25.8 months in sipuleucel-T arm compared with 21.7 months in the placebo arm (p = 0.03), resulting in FDA approval as treatment in asymptomatic or minimally symptomatic men with mCRPC. These exciting results are the first to demonstrate a survival advantage with an immune-based therapy in mCRPC.

Nevertheless, as with earlier sipuleucel-T studies, no difference in either prostate-specific antigen (PSA) response rate or time to progression (TTP) was noted between the two arms despite an OS benefit. Although the reasons for this are not clear, one explanation is that the results are spurious, falling into the 5% chance that a false-positive trial result occurs despite no real difference between arms. Statistics aside, OS results of the IMPACT trial and the earlier studies are similar, suggesting reproducibility. Another possibility is that the placebo arm is not a true control. No evidence supports this, but the potential exists that leukopheresis and depletion of mononuclear cells may have had a detrimental effect on survival among the placebo group. A more plausible explanation is that the treatment arm indeed experienced an improvement in survival, but our current clinical metrics of progression are inadequate. Immune responses to vaccines require time to develop, and the lack of differences in progression could result from delayed antitumor responses occurring after PSA or radiologic progression. Oncologists are now challenged to determine response to sipuleucel-T and timing of subsequent therapy without a reliable readout of efficacy. Additionally, oncologists are faced with choosing the most appropriate effective treatment for patients: immunotherapy or chemotherapy. Currently, we can be guided only by eligibility criteria for the IMPACT trial. Only asymptomatic or minimally symptomatic men who are without visceral disease should be considered for sipuleucel-T, whereas symptomatic men should proceed with chemotherapy. Subsequent therapy should be considered as concern for progression arises clinically.

Virus-based Vaccines

PROSTVAC-VF is a pox viral vaccine consisting of fowlpox and vaccinia vectors, which encode PSA along with a triad of costimulatory molecules: ICAM-1, B7.1, and LFA-3. In a randomized phase II trial, chemotherapy-naive men with mCRPC received either PROSTVAC-VF and GM-CSF or...
control empty vector and GM-CSF placebo. The study failed to meet the primary end point of PFS, but 3 years post-study the OS was improved with PROSTVAC-VF (25.1 vs. 16.6 months; p = 0.0061). These results are provocative given they mirror early findings with sipuleucel-T. The Eastern Cooperative Oncology Group recently activated a phase II study in which men with mCRPC are randomly assigned to 3 months of PROSTVAC vaccinations followed by docetaxel and prednisone or to immediate chemotherapy with OS as its primary end point. This study is important because it will address relevant sequencing questions and may determine whether chemotherapy is additive to immunotherapy.

**Immune Check Points**

Inhibition of immune check points, a series of molecules that limit immune response, is another immunotherapy under investigation. Cancer immunologists have hypothesized that patients have tumor-specific T-cells capable of mediating an antitumor response that are restrained by expression of cytotoxic T-lymphocyte antigen-4 (CTLA4), a cell surface receptor that, when engaged by ligands on antigen-presenting cells, results in inhibition of T-cells. Ipilimumab is a humanized, monoclonal anti-CTLA4 antibody which binds to the CTLA4 receptor on T-cells, blocking CTLA4 and in turn, activating T-cell antitumor activity. Early studies with ipilimumab have demonstrated a PSA response rate of 22%, but 24% of patients experienced grade 3 or greater immune-related adverse events. Randomized, placebo-controlled phase III studies with ipilimumab in the pre- and postdocetaxel settings are ongoing. If this treatment is proven effective, further study with immune check point inhibitors will be warranted, perhaps in combination with other immunotherapy or with chemotherapy.

**Monoclonal Antibodies**

Bone metastases occur in more than 80% of mCRPC patients and can result in substantial morbidity. Complex signaling interactions among prostate cancer cells, osteoclasts, and osteoblasts occur within the microenvironment of bone metastases. Bisphosphonates inhibit the differentiation and maturation of osteoclasts and have a direct apoptotic effect, interrupting these processes. Zoledronic acid has been shown to reduce the risk of skeletal-related events (SREs) and delay the time to a first SRE in men with mCRPC and bone metastases, resulting in FDA approval. Growth factors secreted by tumor cells into the bone microenvironment induce stromal cells and osteoblasts to secrete receptor activator of nuclear factor kappa-B ligand (RANKL), a key factor of osteoclast formation and activation. Preclinical models suggest that inhibition of RANKL has favorable effects on animal models of bone metastases. Denosumab, a fully human monoclonal antibody to RANKL, was compared with zoledronic acid in a phase III study, and denosumab resulted in a 3.6-month improvement in the time to a first SRE compared with zoledronic acid (p = 0.008). However, rates of hypocalcemia, osteonecrosis of the jaw, and renal toxicity did not differ between the two arms. The FDA has since approved denosumab for the prevention of SREs in patients with bone metastases resulting from solid tumors. Of note, phase III studies evaluating the ability of these agents to delay the development of bone metastases are ongoing. Positive results will be important, suggesting that early use alters the progression of prostate cancer and has a further impact on disease-associated morbidity and quality of life.

**Novel Hormonal Therapies**

Evidence suggests that mCRPC continues to be androgen driven, in part as a result of reactivation of androgen receptor (AR) function. Multiple mechanisms of restoring AR function have been proposed, including local production of androgens. Despite androgen deprivation therapy, sufficient concentrations of dihydrotestosterone persist within tumor cells to promote AR signaling. Further, tumor cells may convert adrenal androgens to testosterone or synthesize androgens from cholesterol or progesterone. Thus, in some men with mCRPC, intracrine mechanisms rather than endocrine mechanisms may be driving disease progression. Indeed, a portion of “hormone-refractory” patients remain sensitive to further hormonal manipulations such as antiandrogen withdrawal or ketoconazole. Encouraging results have been demonstrated with novel hormonal therapies.

**CYP17A Inhibition**

Abiraterone is an oral inhibitor of CYP17A, an enzyme that catalyzes both 17 alpha-hydroxylase and C17,20-lyase reactions in the synthesis of androgens. By targeting CYP17A, abiraterone decreases androgen production in the adrenal glands, prostate, and tumor tissues. In phase I and II studies of abiraterone in chemotherapy-naive men with mCRPC, PSA response rates of 55% to 67% and a partial response (PR) rate of 37.5% were reported. In phase II studies in men previously treated with docetaxel, PSA responses rates were 36% to 51%, and PR rates were 18% to 27%. Notably, several men responded to abiraterone despite prior treatment with ketoconazole, which inhibits multiple CYP enzymes. These findings led to two phase III trials in which men who were either chemotherapy naive or who had experienced disease progression despite docetaxel were ran-
domly assigned to abiraterone and prednisone or to placebo and prednisone. In the postdocetaxel study, median OS with abiraterone was 14.8 months compared with 10.9 months with placebo (p < 0.0001). This result is remarkable because it refutes the notion that men with mCRPC are hormone refractory and validates preclinical data that prostate cancer remains driven by androgens. The trial in chemotherapy-naive men with mCRPC has completed accrual, and results are pending. TAK-700, a 17,20-lyase inhibitor, showed a PSA response rate of 52% in a phase I/II study in chemotherapy-naive men with mCRPC, and phase III studies are planned with TAK-700, both pre- and postdocetaxel. Results with these agents in the prechemotherapy setting are eagerly awaited because if positive, they will likely be used primarily in chemotherapy-naive men. And if so, questions as to whether they should be continued with chemotherapy, as is done with LHRH agonists, will arise. Of note, a phase I/II study evaluating the safety and efficacy of docetaxel in combination with TAK-700 is already underway.

Androgen Receptor Inhibition

New inhibitors of the AR are also in development. MDV3100 is an oral compound demonstrated in preclinical models to have higher affinity for the AR than bicalutamide and to have activity in bicalutamide-resistant models. The drug also impairs nuclear translocation of the AR, inhibits receptor binding to DNA and coactivators, and induces apoptosis. In a phase II/I study of men with mCRPC, PSA responses were observed in 62% of chemotherapy-naive patients and in 51% postdocetaxel patients. A phase III study of MDV3100 in men previously treated with docetaxel recently closed to accrual, and a trial for chemotherapy-naive men is ongoing. Another novel AR antagonist, ARN-509, is early in development and being evaluated in an ongoing phase I/I study. If either of these AR inhibitors extends survival in the phase III setting, further possibilities will arise as to whether they should be combined with abiraterone or whether cross-resistance between agents exists.

Cell Signaling Inhibition

With improved understanding of the molecular biology of prostate cancer, agents targeting signaling pathways and biologic processes are being evaluated in mCRPC, either as single agents or in combination with docetaxel and prednisone. Although phase III trials with novel agents are ongoing, none to date have been adopted into standard practice.

Antiangiogenesis

Vascular endothelial growth factor (VEGF) has been postulated to be important in mCRPC, and retrospective analyses have correlated increased serum VEGF levels with shortened survival. Cancer and Leukemia Group B 90401, a phase III study that randomly assigned men with mCRPC to docetaxel and prednisone with or without bevacizumab, generated negative results and did not show an improvement in OS with the addition of bevacizumab. Additionally, a phase III trial of the oral tyrosine kinase inhibitor sunitinib in men with mCRPC who had experienced progression despite treatment with docetaxel was terminated after an interim analysis revealed that the drug was unlikely to improve OS. Although these results are disappointing, important work with additional antiangiogenic drugs continues. On the basis of early results with aflibercept, a recombinant decoy fusion protein of VEGF receptors 1 and 2 and the Fc fragment of immunoglobulin G1, and lenalidomide, a second-generation immunomodulatory drug with antiangiogenic properties, phase III trials are ongoing with these agents in combination with docetaxel. Further, correlative analyses from at least some of these studies will be insightful, potentially identifying subpopulations of men who are most likely to benefit from an antiangiogenic approach.

Endothelin-A Receptor Antagonists

Endothelin-1 (ET-1) is involved in the osteoblastic bone remodeling response typical of prostate cancer, and tumor-derived ET-1 drives osteoblast proliferation and new bone formation. In turn, osteoblasts generate other growth factors that stimulate tumor production. ET-A receptor antagonists atrasentan and zibotentan inhibit the biologic effects of ET-1. A placebo-controlled phase III study of atrasentan in men with chemotherapy-naive mCRPC did not meet its primary end point of time to progression, perhaps as a result of early discontinuation for men who displayed bone scan progression without concurrent clinical progression. The Southwest Oncology Group recently completed accrual to a phase III trial of docetaxel and prednisone with or without atrasentan, and results are pending. Zibotentan, another ET-A receptor antagonist evaluated in prostate cancer, did not meet its primary end point of time to progression in a randomized, placebo controlled phase II study in men with chemotherapy-naive mCRPC, but an improvement in OS with zibotentan was noted, generating enthusiasm for this agent. Although a phase III study of zibotentan in chemotherapy-naive men did not meet its primary end point of OS, phase III studies in nonmetastatic CRPC and in combination with docetaxel as front-line therapy for men with mCRPC are ongoing.

Additional Strategies

Other molecularly targeted therapies are also in various stages of clinical development. These include drugs that target VEGF, epidermal growth factor receptor, platelet-derived growth factor receptor, insulin-like growth factor, phosphoinositide 3-kinase/Akt/mammalian target of rapamycin, hedgehog, and Src kinase pathways as well as histone deacetylase inhibitors and agents that affect apoptosis. Clusterin is an antiapoptotic protein that is activated after therapeutic stress, and custisirens is an antisense oligonucleotide designed to inhibit clusterin expression by binding to its translation initiation site. On the basis of promising early results when administered in combination with docetaxel, a phase III study of docetaxel retreatment with or without custisirens is open to accrual. Dasatinib has also been combined with docetaxel with encouraging early results. This oral tyrosine kinase inhibitor blocks Src, a tyrosine kinase believed to be integral to tumor cell proliferation and migration and to osteoclast activity, and is now in phase III testing with docetaxel as front-line therapy for mCRPC. The large number of targeted agents in clinical trials is exciting (Table 1), and should any of the phase III studies yield positive results, they will likely alter our standard of care.
than in the mitoxantrone arm (15.1 vs. 12.7 months, \( p < 0.0001 \)). However, grade 3 or higher febrile neutropenia and diarrhea, as well as treatment-related deaths, primarily related to infectious complications and renal failure, were more frequent with cabazitaxel. Patients receiving cabazitaxel should be monitored closely for toxicity, particularly for neutropenia and diarrhea, and appropriate supportive care should be provided. With two cytotoxic agents with proven efficacy, a phase III trial comparing docetaxel with cabazitaxel as front-line therapy is planned. However, if abiraterone receives FDA approval, two agents will be available for postdocetaxel mCRPC with no trial data to direct choice of therapy. With the toxicity profile of cabazitaxel, oncologists may prefer to use abiraterone, particularly in frail men with mCRPC. However, disease will likely develop resistance to and progress during treatment with the new hormonal agent at some point, at which point men will require further chemotherapy.

**Conclusion**

With three innovative therapies proven to positively affect OS in men with mCRPC in a short span of time, remarkable advances have occurred during the previous year. In addition to important gains to patients, findings have challenged oncologists’ conceptual understanding of prostate cancer. Immunotherapy and novel hormonal agents have underlined for the first time the importance of immune surveillance and the continued disease dependence on AR activity in men with mCRPC. However, these gains are modest. Several questions remain, and many challenges lie ahead. Certainly additional investigations must determine how to maximize gains thus far, including how to sequence or combine agents. However, critical to progress is to learn from early immunotherapy studies and understand that PSA response and PFS may not be one-size-fits-all measures of efficacy for our next generation of cancer treatments. Time must be devoted to developing other signals of clinical benefit, as well as to conducting correlative studies which may assist in targeting appropriate therapies to specific patient populations.
subpopulations and aid in fostering sophisticated clinical decision making. Further, trial design must also be given careful consideration going forward, realizing that without the randomized design of the early sipuleucel-T, PROSTVAC, and zibotentan trials, a signal for a potential OS benefit might have been missed. These advances for mCRPC are exciting for a field that has had few effective options for so long. Now we must accept these challenges, and continue to move this field forward to ultimately improve these survival results for the sake of our patients.

Author’s Disclosures of Potential Conflicts of Interest

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