

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Systemic Therapeutic Strategies for Prostate Cancer

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H&O In which clinical settings are systemic treatments for prostate cancer considered?

WN Androgen-deprivation therapy can be given as an adjuvant to external beam radiation for high-risk localized prostate cancer (clinical stage T2c-T4, Gleason score of 8–10, or serum prostate-specific antigen [PSA] level >20 ng/mL) or for locally advanced prostate cancer. Otherwise, men who are candidates for systemic treatments tend to have progressive androgen-dependent prostate cancer with or without detectable cancer metastases (but with a rising serum PSA level after adequate local prostate cancer treatment) or androgen-independent prostate cancer (AIPC) with or without detectable metastases and with or without significant cancer symptoms. Each of these different disease states tends to present different treatment challenges.

H&O What are the most common strategies for the systemic treatment of progressive androgen-dependent prostate cancer?

WN The most straightforward treatment for advanced androgen-dependent prostate cancer, and the first successful systemic therapy for the disease, is the removal of the major source of androgens, the testes, which of course results in a reduction in serum testosterone. However, nonsurgical approaches for reducing serum testosterone are now much more often used. Currently the most common strategy features the use of luteinizing hormone-releasing hormone (LHRH) analogs (eg, goserelin [Zoladex, AstraZeneca] and leuprolide acetate). These agents initially stimulate luteinizing-hormone (LH) release by the pituitary gland, causing a rise in serum testosterone,

but upon chronic exposure subsequently suppress LH and testosterone production. Other therapeutic approaches available include the newly introduced LHRH antagonists (eg, abarelix [Plenaxis, Praecis Pharmaceuticals]), which do not provoke an initial stimulation of testosterone production (only a decrease), and pharmacological doses of estrogens, which also cause reductions in serum testosterone levels.

H&O Are estrogens still used in the treatment of androgen-dependent prostate cancer?

WN Estrogens, which have been available for many years for the treatment of these patients, act centrally and peripherally to suppress testosterone production. In the 1960s and 1970s, diethylstilbestrol (DES) was frequently used for prostate cancer treatment. However, because high doses of this agent (5 mg daily) were associated with blood clots and cardiovascular side effects, its use was largely abandoned. Recently, however, interest in estrogens has reemerged. Transdermal estrogen patches, used for hormone replacement therapy in women, may avoid risks for blood clots; estrogens may therefore merit reexamination for the treatment of androgen-dependent prostate cancer.

H&O What about androgen-receptor antagonists?

WN In addition to LHRH analogs and antagonists, castration, and estrogen therapy, androgen-receptor blockers are also widely used in prostate cancer treatment. The most commonly available such agents in the United States are bicalutamide (Casodex, AstraZeneca) and flutamide. These oral antiandrogens have been used both as monotherapy and in conjunction with androgen-deprivation therapy (ie, along with LHRH agonists or castration). A series of clinical trials has suggested that while the administration of androgen-receptor blockers might attenuate the “flare” reaction associated with the initiation of LHRH-agonist treatment, combined therapy does not appear to offer a survival advantage over androgen deprivation alone.

H&O What are the possible explanations for why patients may progress on these therapies?

WN The most common explanation is the emergence of AIPC. However, there are some clinical situations where prostate cancer might be progressing for other reasons. For one, if the patient has been receiving LHRH-agonist therapy for a prolonged period of time, it may be that the serum testosterone is no longer fully suppressed, meaning that the drug is not working appropriately. In this case, another strategy for reducing serum testosterone levels may be effective in treating the prostate cancer. In another well-described phenomenon, patients receiving both an LHRH agonist and an androgen-receptor blocker have a beneficial treatment response to discontinuation of the antiandrogen. In some of these cases, a mutation in the ligand-binding domain of the androgen receptor may have led to the recognition of flutamide or bicalutamide by the receptor not as antagonists but as agonist ligands, thus fueling the growth of the cancer. The antiandrogen withdrawal syndrome may not happen often, but it does occur and is important to consider clinically.

H&O What is understood about the biology of prostate cancer that has progressed on androgen-deprivation therapy?

WN It has become clear that most prostate cancers that are clinically androgen-independent continue to produce the androgen receptor and to use the receptor to fuel PSA production and other cell growth. In some cases, the gene encoding the androgen receptor is amplified, likely increasing the levels of androgen receptor protein in each cancer cell. In such cells, the receptor appears to be more prone to adopting an active conformation. Normally, the receptor undergoes a change in shape when it binds testosterone; this new shape serves as an “on” switch. If large numbers of receptors are present in androgen-independent cancer cells, even though many will not be bound to testosterone because of therapeutically suppressed testosterone levels, a significant fraction of the receptors will still be in a “switched-on” shape. There may be enough receptors in that “on” shape to drive prostate cancer progression.

Another possible mechanism by which androgen receptors drive prostate cancer progression despite low testosterone levels is that polypeptide growth factor–signaling pathways may trigger post-translational modifications, such as phosphorylation, of proteins that interact with androgen receptors, enabling the receptors to more easily stimulate a growth response. As in the case of an increased number of androgen receptors in each cancer cell, the consequences of polypeptide growth factor signaling may be that androgen receptor “switched-on” shapes can be generated with very small amounts of testosterone,

or perhaps even by other ligands, such as other steroid compounds not ordinarily consider androgenic.

H&O What hormonal agents are in development to treat prostate cancer that has progressed despite androgen-deprivation therapy?

WN There are experimental strategies currently being explored, with the aim of either discovering a better androgen-receptor antagonist, inhibiting androgen receptor function, or eradicating the androgen receptor altogether. One approach that has reached preclinical and early clinical studies is the development of analogs of geldanamycin, an agent that disrupts the folding of the androgen receptor protein into the correct shape to trigger cancer cell growth. This folding process is accomplished by a heat shock protein; testosterone binding to the androgen receptor kicks the receptor out of the heat shock protein complex so that it can act to promote cancer cell growth. Geldanamycin and its analog 17-allylamino-17-demethoxygeldanamycin target this pathway, leading to degradation of the androgen receptor by the proteasome, thus markedly decreasing the receptor levels. In animal models this approach appears to be fairly effective at treating both androgen-dependent and androgen-independent prostate cancer.

As for currently available approaches, several are being used and/or explored in clinical trials. For patients on bicalutamide or flutamide, these agents can be stopped in case a mutant receptor is present. Another option is to add one of these agents if it was not previously part of the treatment strategy. High doses of the antifungal agent ketoconazole are also being evaluated. At high doses, the drug blocks the synthesis of androgenic hormone at a precursor stage. The use of high-dose ketoconazole therapy requires coadministration of hydrocortisone as adrenal replacement because the antifungal agent interferes with the synthesis of other hormones as well. Unfortunately, though these second-line hormone manipulations can result in treatment responses, the benefits of these approaches for prostate cancer survival have not yet been established.

H&O Could you discuss the use of chemotherapy in the second-line treatment of AIPC?

WN Just within the last couple of years cytotoxic chemotherapy has been shown to improve the survival of men with metastatic AIPC. When considering the history of cytotoxic chemotherapy for prostate cancer, it is interesting how more generally effective the drugs that target tubulin, such as docetaxel (Taxotere, Sanofi Aventis), paclitaxel, and vinblastine, are compared with other classes of cytotoxic drugs. Two large landmark clinical trials evaluating docetaxel and a docetaxel-based combina-

tion were reported last year. In one of the trials, TAX-327, patients were randomly assigned to receive docetaxel plus prednisone versus the standard of care at the time, which was mitoxantrone plus prednisone. The latter combination had been shown to offer a palliative benefit to patients with symptomatic metastatic AIPC but without a marked prolongation of survival. In TAX-327, docetaxel plus prednisone given every 3 weeks provided a survival advantage over the standard combination. In the other randomized trial, docetaxel plus estramustine (Emcyt®, Pfizer) and prednisone was compared with mitoxantrone and prednisone, and again the docetaxel-based regimen showed a survival advantage.

These 2 studies have led to many questions. First, is the combination of docetaxel plus estramustine more effective than docetaxel alone? The study populations in these trials were reasonably comparable, but it is difficult to discern at this point whether the addition of estramustine, thought to increase response rates, confers a survival advantage. The combination of docetaxel and estramustine does appear to be associated with more side effects, many of which are attributable to the estrogenicity of estramustine. To determine whether docetaxel plus estramustine offers a benefit over docetaxel alone, randomized clinical trials will be needed.

Another key question is when is the optimal time to initiate chemotherapy? Most of the patients in the docetaxel trials had known metastases after androgen-deprivation therapy. Would the agents be more effective if used earlier? Also, what other docetaxel-based regimens might be effective? Ongoing research is exploring several docetaxel-based combinations, adding agents including bevacizumab (Avastin, Genentech), thalidomide, bortezomib (Velcade, Millennium Pharmaceuticals), oblimersen sodium (Genasense, Genta), mammalian target of rapamycin (mTOR) inhibitors, epidermal growth factor receptor kinase inhibitors, KDR (vascular endothelial growth factor receptor 2 kinase) inhibitors, and calcitriol. If any of these combinations offer a survival advantage over docetaxel monotherapy, it would likely become the standard of care for the treatment of AIPC. Several randomized trials evaluating docetaxel-based regimens are in progress. One, anchored at the University of Texas M. D. Anderson Cancer Center, is studying the efficacy of docetaxel with or without imatinib mesylate (Gleevec, Novartis) in 140 patients and is almost completed. The Cancer and Leukemia Group B (CALGB) is conducting a trial of docetaxel with or without bevacizumab, with a planned enrollment of at least 800 patients. A randomized, industry-sponsored trial of docetaxel plus calcitriol that enrolled over 200 patients was reported at the 2005 annual meeting of the American Society of Clinical Oncology. The data showed a slight prolongation of sur-

vival with the combination, but the study was fairly small and follow-up is needed.

H&O How are bony metastases currently managed and what new treatments are on the horizon?

WN Before discussing management, it is important to note that there are at least 2 ways in which prostate cancer affects the bones: through metastases and through osteoporosis, a side effect of androgen-deprivation therapy.

The bisphosphonate zoledronic acid (Zometa, Novartis) has been shown to be effective at reducing skeletal complications in patients with metastatic AIPC, as reported by Saad and colleagues, who conducted a large randomized trial of this agent in this setting. There is also preclinical evidence that combining docetaxel with zoledronic acid increases the rate of prostate cancer cell death. This combination is now being pursued in clinical trials. Other bisphosphonates have not been found to be effective in treating prostate cancer-associated bony metastases; it may be that zoledronic acid is more potent, or may have some activity against both osteoclasts and osteoblasts, each of which contributes to abnormal bone architecture at the sites of prostate cancer metastases.

With regard to osteoporosis in prostate cancer patients maintained on androgen-deprivation therapy, there is not currently a consensus about treatment. Many clinicians monitor bone density during androgen-deprivation therapy and incorporate a bisphosphonate into the treatment regimen if there is a high risk of fracture.

Endothelin-1, a peptide-hormone antagonist of the endothelin A receptor, is currently being explored for the treatment of bone metastases. The endothelin A receptor has been found to be a mediator of osteoblastic bony metastases in preclinical studies. Atrasentan (Xinlay, Abbott), an endothelin A-receptor blocker, has been subjected to a large randomized trial enrolling men with AIPC. The results of this trial, published in the *Journal of Clinical Oncology* and in the *Journal of Urology* in 2003, suggested that atrasentan may have its most dramatic beneficial effects on men with bony metastases. The drug will be evaluated by the Food and Drug Administration's Oncology Drug Advisory Committee soon.

Therapeutic radioisotopes may also be effective for the treatment of bony metastases. Strontium, samarium, and rhenium, each of which has different radiopharmaceutical properties, are all being evaluated for this purpose. It is not clear whether these agents are significantly better than involved-field external beam-radiation therapy using modern techniques, which can shape and target fields more precisely, but studies are underway that should clarify this question.

Combining radiopharmaceuticals with chemotherapy has proven promising but difficult thus far. Radiopharmaceuticals with high-energy particles can irradiate the bone marrow, leading to low blood counts, making it difficult to administer with chemotherapy. Logothetis and his colleagues at the University of Texas M. D. Anderson Cancer Center conducted a study a few years ago in which men with AIPC and bony metastases who had responded well to combination chemotherapy were further treated with doxorubicin plus strontium or with doxorubicin alone. The data showed a survival benefit attributable to the combination. Samarium appears to cause comparatively less bone marrow toxicity, so this agent may prove easier to use in combination with chemotherapy. At this point, radiopharmaceuticals have an established palliative role in for men with bony metastases, but their efficacy in prolonging survival is not yet clear.

H&O What vaccine strategies are being explored for the treatment of AIPC?

WN There are several vaccine immunotherapy approaches for prostate cancer in clinical development, including vaccines against single peptide antigens, such as PSA, vaccines against prostate cancer cells, and dendritic cell vaccines. One prostate cancer cell vaccine, GVAX (Cell Genesys) has progressed to pivotal phase III clinical trials for metastatic AIPC, randomized against treatment with docetaxel. When vaccine preparations are injected intradermally, the vaccine antigens traffic through dendritic cells that engulf the antigens and present them to T cells in order to activate an immune response. Another way to deliver vaccine antigens to dendritic cells is to harvest dendritic cells from the circulation and load them with antigens outside the body. The loaded dendritic cells can then be reintroduced into the body to stimulate an anti cancer immune response. Provenge (Dendreon), a dendritic cell loaded with prostate-specific acid phosphatase peptides, is also in advanced clinical trials for prostate cancer.

There are many natural modulators of immune responses in the body, regulating the aggressiveness of immune responses so as to prevent overreactions leading to autoimmune diseases. Cancer cells may exploit some of these mechanisms to escape detection and/or destruction by the immune system. Several agents are in development that may shift the immune system into a more aggressive reaction. The first of these into clinical trials has been an anti-CTLA4 antibody (Medarex). This antibody is under scrutiny as a single agent in prostate cancer and in combination with prostate cancer vaccines.

H&O What other strategies are being developed?

WN As with many other cancers, growth factor signaling pathways appear to offer opportunities for “targeted” treatments. For prostate cancer, basic molecular biology studies have implicated the phosphatidylinositol 3'-kinase/protein kinase B intracellular signal transduction pathway as a major contributor to cell growth and survival. Because this pathway appears to be corrupted in many prostate cancer cells, agents that target components of this pathway are expected to have great promise as prostate cancer treatments. This strategy is early in its preclinical and clinical development.

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