New Treatments for Castration-Resistant Prostate Cancer

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Most of us were taught in medical school that prostate cancer was exquisitely dependent on circulating androgens and that castration, whether surgical or medical, resulted in significant decrease in tumor mass, associated pain in the setting of metastatic disease, and reduction in acid phosphates and prostate-specific antigen (PSA).

However, we were told, the cancer would inevitably adapt to the androgen-deprived milieu and progress. So-called *androgen-independent (androgen-resistant) prostate cancer* (now more often referred to as *castration-resistant prostate cancer* [CRPC]) was the reason that prostate cancer represents the second most common cause of cancer mortality.

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We should have questioned this concept more vigorously. Certainly there were clues that the role of androgens in prostate cancer was not "all or none." We know, for example, that once a man had progressed to the so-called androgen-independent state, cessation of castration (made possible with diethylstilbestrol but more completely with the advent of luteinizing hormone-releasing hormone agonists) most often resulted in more rapid tumor progression. Even before this we had learned from pioneering studies by Willett Whitmore at Memorial Sloan-Kettering Cancer Center that giving testosterone to men previously castrated in an attempt to improve cytotoxic chemotherapeutic response was disastrous, with severe exacerbation of the tumor and patient death.

Recently many of these concepts have been disproved. There is evidence to suggest that although castration removes the gonadal testosterone in prostate cancer, androgens originating from other sources, including the adrenal gland and, intriguingly, the prostate cancer itself, may continue to act as a ligand and result in androgen receptor signaling. Recent studies have demonstrated high levels of androgens in CRPC tumor, with ongoing androgen receptor stimulation. This intracrine effect results in the tumor being better able to survive and progress in the castrate setting.

Two companies are conducting clinical trials of agents that affect the intratumor androgen effect, and salient findings were presented at the 44th Annual Meeting of the American Society of Clinical Oncology held in Chicago, IL. Cougar Biotechnology (Los Angeles, CA) is developing abiraterone. This novel molecule affects

CRPC by targeting an enzyme that catalyzes 2 key steroid reactions involving 17α-hydroxylase and C(17,20)-lyase—critical enzymes in the testosterone synthesis pathway. This is the same target of ketoconazole.

De Bono and associates[1] described a phase I/II investigation with abiraterone in chemotherapy-naive CRPC patients and a phase II trial in men who progressed while receiving docetaxel. In the phase I study, daily oral doses of 250 to 2000 mg abiraterone were well tolerated. Toxicity owing to increased mineralocorticoid production (hypertension, hypokalemia, fluid retention) was corrected by use of eplerenone or low-dose corticosteroids. A dose of 1000 mg was selected for the phase II component. Among 44 men who had not received chemotherapy (70% of whom had bone metastases), more than 60% had PSA reduction of greater than 50%. Among 21 of these patients who had measurable disease, partial response was seen in 12. The median time to PSA progression was 252 days.

Among 28 men who had received docetaxel, 40% had a nadir PSA value less than 50% of baseline. Eighteen had evaluable metastases, and 4 had a partial response. Time to PSA progression was 167 days.

In both groups there was symptomatic improvement, reduction in analgesic requirements, and decrease in circulating tumor cells. This latter finding may offer a unique marker for response in CRPC, as was described by Attard and colleagues.[2]

The fact that ketoconazole targets the same enzyme as abiraterone stimulated an investigation of the efficacy of the latter in patients who had received the antifungal agent. In a phase I trial, Ryan and colleagues[3] compared men with CRPC who did and did not receive ketoconazole with abiraterone at daily doses of 250 to 1000 mg. At the time of the presentation data from 33 men were available; 55% had a more than 50% PSA decrease.

Among the 14 men who had not received ketoconazole, 61% responded, as compared with 53% of those who had been treated with ketoconazole. Importantly, of the 15 men who discontinued ketoconazole owing to progression as opposed to toxicity, 7 had a more than 50% PSA nadir.

The investigators concluded that despite similar targets, a significant number of patients previously treated with ketoconazole will respond to abiraterone.

Medivation (San Francisco, CA) is developing MDV3100. This agent is a novel small molecule that acts as an androgen receptor blocker. It was specifically selected to avoid the resistance seen in conventional antiandrogens (flutamide, bicalutamide). It blocks nuclear translocation.

Scher and colleagues[4] reported the first experience with MDV3100 in men. In this phase I/II dose-escalation study, MDV3100 was administered orally daily beginning with a 30-mg dose in men with progressive CRPC. Scher and colleagues reported on 39 patients treated in this ongoing trial. The agent was well tolerated, with no significant adverse events. In the lowest-dose cohort, 3 of 3 patients had PSA declines between 44% and 87% with follow-up of more than 19 weeks.

In the 60-mg cohort, PSA decreased between 74% and 96% in the 3 men with follow-up of 14 or more weeks. No patents demonstrated progression either clinically or with imaging. Additional patients are receiving 150 mg and 240 mg daily. The investigators conclude that MDV3100 resulted in significant

Main Points

- There is evidence to suggest that although castration removes the gonadal testosterone in prostate cancer, androgens originating from other sources, including the adrenal gland and, intriguingly, the prostate cancer itself, may continue to act as a ligand and result in androgen receptor signaling.
- Two companies are conducting clinical trials of agents that affect the intratumor androgen effect: Cougar Biotechnology is developing abiraterone, and Medivation is developing MDV3100.
- In a phase I/II study of abiraterone, daily oral doses of 250 to 2000 mg were well tolerated; a dose of 1000 mg was selected for the phase II component. Among 44 men who had not received chemotherapy (70% of whom had bone metastases), more than 60% had a reduction in prostate-specific antigen (PSA) of more than 50%. In a phase II study of abiraterone among 28 men who had received docetaxel, 40% had a nadir PSA value less than 50% of baseline.
- In a phase I/II dose-escalation study, MDV3100 was administered orally daily beginning with a 30-mg dose in men with progressive castration-resistant prostate cancer. In 39 patients treated in this ongoing trial, the agent was well tolerated, with no significant adverse events. In the lowest-dose cohort, 3 of 3 patients had PSA declines between 44% and 87% with follow-up of more than 19 weeks. In the 60-mg cohort, PSA decreased between 74% and 96% in the 3 men with follow-up of 14 or more weeks. No patients demonstrated progression either clinically or with imaging.

PSA reduction in a high proportion of patients and was well tolerated.

These two agents are certainly promising. Other molecules are in development to address CRPC, also targeting intratumor androgen activity. Tokai Pharmaceuticals (Cambridge, MA) is developing TOK-001. This molecule, like abiraterone, inhibits the cytochrome P450c17 step in androgen synthesis. Moreover, it is a potent blocker of the androgen receptor and has actually decreased the amount of androgen receptor. Thus, this agent potentially inhibits 3 critical pathways for androgen activity in CRPC. TOK-001 is anticipated to enter clinical trials in 2009.

TOK-001 potentially inhibits 3 critical pathways for androgen activity in castration-resistant prostate cancer.

Despite considerable effort by researchers and the pharmaceutical industry, we have seen little real progress in the management of CRPC. Our reassessment of the ongoing role of androgens after castration has resulted in the development of several intriguing molecules, which we hope will result in new approaches to treating this difficult disease. ■

References

1. De Bono JS, Attard G, Reid AH, et al. Anti-tumor activity of abiraterone acetate (AA), a CYP17 inhibitor of androgen synthesis, in chemotherapy naive and docetaxel pre-treated castration resistant prostate cancer (CRPC) [abstract 5005]. *J Clin Oncol.* 2008;26(suppl):251s.
2. Attard G, Olmos D, Arkenau HT, et al. Pre- and post-treatment circulating tumor cell counts (CTCc) and overall survival (OS) in castration-resistant prostate cancer (CRPC): The Royal Marsden Hospital (RMH) experience [abstract 5072]. *J Clin Oncol.* 2008;26:267s.
3. Ryan C, Smith MR, Rosenberg JE, et al. Impact of prior ketoconazole therapy on response proportion to abiraterone acetate, a 17-alpha hydroxylase C17,20-lyase inhibitor in castration resistant prostate cancer (CRPC) [abstract 5018]. *J Clin Oncol.* 2008;26:254s.
4. Scher HI, Beer TM, Higano CS, et al. Phase I/II study of MDV3100 in patients (pts) with progressive castration-resistant prostate cancer (CRPC) [abstract 5006]. *J Clin Oncol.* 2008;26:251s.