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The changing landscape of hormonal therapy in castration-resistant prostate cancer

Androgen deprivation therapy (ADT) is generally the initial treatment for men with advanced prostate cancer. Standard approaches include orchiectomy, a gonadotropin-releasing hormone (GnRH) agonist, or a combination of a GnRH agonist plus an antiandrogen (combined androgen blockade). Despite initial response rates of 80-90%,[1] nearly all men eventually develop castration-resistant prostate cancer (CRPC), which is defined as progressive prostate cancer despite castrate levels of serum testosterone (<50 ng/dl).

Androgenic steroids act as growth factors for prostate cancer. When disease progresses to CRPC, discontinuation of hormonal therapy can result in a rebound increase in serum testosterone and thus contribute to progressive disease. There are no trials that directly address the utility of continued ADT in men with CRPC. However, a multivariate analysis of 341 patients with CRPC who were treated in four clinical trials found observational evidence that continued testicular androgen suppression was associated with a median survival benefit of 2-6 months.[2]

In a patient with CRPC, prior to initiating chemotherapy, several alternative hormonal manipulation strategies exist. These include newer antiandrogens, higher doses of the same antiandrogens, antiandrogen withdrawal, ketoconazole, glucocorticoids, megestrol acetate, and estrogens.[3-5] These have not been demonstrated to improve survival. However, these approaches may induce clinical responses and provide palliation in terms of decrease in pain, improvement of anemia, reduction in prostate specific antigen (PSA), and better quality of life. Secondary endocrine therapies are often used sequentially and may be useful in postponing interventions such as chemotherapy or when no other effective options are available.

The activity of flutamide was illustrated by a series of 209 men treated after failing initial endocrine therapy with orchiectomy, diethylstilbestrol, or a GnRH agonist. The overall response rate was 35%, and the mean duration of response was 24 months.[6] The potential utility of using an alternative nonsteroidal antiandrogen was illustrated by a retrospective series of 232 patients who progressed after initial treatment with combined androgen blockade. There was no significant difference in those who switched from bicalutamide to flutamide compared to those who changed from flutamide to bicalutamide. Multivariate analysis found that any response to second-line antiandrogen therapy was significantly associated with an improved cause-specific survival.[7] The potential role of DES as a second-line agent was evaluated in a trial in which 58 men who had progressed on GnRH agonist therapy were randomly assigned to either DES or bicalutamide. Both the PSA response rate and median response durations were similar in the two groups (23% vs. 31% and 9 vs. 12 months, respectively).[8] The role of antiandrogen withdrawal was studied in men with CRPC in a Phase III trial conducted by the Cancer and Leukemia Group B (CALGB 9583) In this trial, 260 patients who had progressed on ADT were randomly assigned to antiandrogen withdrawal plus simultaneous ketoconazole or antiandrogen withdrawal alone, with ketoconazole reserved for subsequent use upon progression. More patients had a PSA response or an objective tumor response when ketoconazole was initiated immediately rather than waiting to see if an antiandrogen withdrawal response occurred (27% vs. 11% and 20% vs. 2%, respectively). However, there was no statistically significant difference in overall survival with the two treatment strategies (15.3 vs. 16.7 months, $P = 0.94$).[9] Two other observational series that each included over 200 patients observed antiandrogen withdrawal leads to PSA response rates of 15% and 21%, respectively.[7,10] The major drawback of secondary hormonal manipulation is that there is no proven survival benefit. However, until recently, the only other therapeutic option was chemotherapy, which although proven to enhance survival, comes at the cost of significant toxicity.

Contemporary research has demonstrated that even after failure of hormonal therapy, androgen-based pathways continue to play a clinically significant role in the progression of CRPC. In addition to androgen production by the adrenal gland and testis, several of the enzymes involved in the synthesis of testosterone and dihydrotestosterone, including cytochrome P450

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17-alpha-hydroxysteroid dehydrogenase (CYP17), are highly expressed in tumor tissue. This understanding has led to the development of drugs that act by inhibition of the enzymes responsible for androgen production, as well as agents that inhibit the androgen receptor.

Abiraterone, a new androgen synthesis inhibitor was developed through screening chemical derivatives of a parent structure of pregnenolone. The structural changes in abiraterone account for potent and irreversible inhibition of CYP17. In preclinical studies, abiraterone was ten times more potent than ketoconazole as an inhibitor of CYP17 although ketoconazole is a more potent inhibitor of the side chain cleavage enzyme, which plays a critical role in adrenal steroidogenesis; patients treated with either of these agents are at risk for adrenal insufficiency and require steroid replacement therapy. The use of ketoconazole is further limited by the potential for drug-drug interactions, particularly with statins and anti-depressants. Abiraterone is an orally administered small molecule that irreversibly inhibits the products of the CYP17 gene (including both 17,20-lyase and 17-alpha-hydroxylase). In doing so, abiraterone blocks the synthesis of androgens in the tumor as well as in the testes and adrenal glands. The activity of abiraterone was established in two Phase III trials in men with metastatic, castration-resistant prostate cancer, the first in patients who had received prior docetaxel, and the other in patients with chemotherapy-naive disease.

In the first Phase III trial, 1195 men who had previously been treated with a docetaxel-containing chemotherapy regimen were randomly assigned in a 2:1 ratio to abiraterone (1000 mg/day) plus prednisone (5 mg twice a day) or placebo plus prednisone. Treatment was continued until disease progression. Statistically significant improvements were seen in time to PSA progression, progression-free survival, and PSA response rate (10.2 vs. 6.6 months, 5.6 vs. 3.6 months, and 29% vs. 6%, respectively).[11] Abiraterone also delays disease progression and probably prolongs overall survival in men with castrate-resistant prostate cancer who have not received chemotherapy.[12] Side effects that were more common with abiraterone included fluid retention (33%), hypokalemia (18%), non-specific cardiac abnormalities (16%), and transaminase elevation (11%).[11]

Enzalutamide binds to the androgen-binding site in the androgen receptor, thereby leading to inhibition of nuclear translocation of the androgen receptor, and inhibition of the association of the androgen receptor with nuclear DNA. Phase I/II studies showed that enzalutamide had significant activity in men with CRPC.[13] This has led to the assessment of enzalutamide in Phase III trial (AFFIRM trial) which showed an overall survival benefit of 4.8 months. Enzalutamide was also significantly better than placebo in all secondary efficacy endpoints, including PSA response, soft-tissue response, quality-of-life response, time to PSA progression, radiographic progression-free survival, and time to first skeletal-related event. There was a higher incidence of fatigue, diarrhea, hot flashes, musculoskeletal pain, and headache. The concern was the development of seizures, which occurred in seven patients (0.9%) treated with enzalutamide and no patients assigned to placebo.[14]

Thus, after decades, we now have two new medications in the hormonal therapy armamentarium. Abiraterone and enzalutamide will play a significant role in the management of men with advanced prostate cancer. They have proven to be efficacious with a very tolerable toxicity profile. Currently, unanswered questions exist regarding sequencing of these agents with respect to each other and with relation to chemotherapy. With the introduction of a new chemotherapeutic agent, Cabazitaxel, and these two new hormonal therapies, being a medical oncologist taking care of patients with prostate cancer has just become infinitely exciting.

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