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Article

Life after failure of traditional androgen deprivation therapy

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Abstract

Castrate resistant prostate cancer is a disease state which, counterintuitively, can be successfully treated with additional therapy directed at inhibition of androgen synthesis and/or interfering with the activity of the androgen receptor. Novel androgen biosynthesis inhibitors and antiandrogens are now being tested in large phase 3 clinical trials to clarify their role in the treatment of men who have failed traditional medical castration, with or without currently available nonsteroidal antiandrogens. A renewed interest in studying parenteral delivery of estrogens may provide evidence to revisit the initial medical therapy for advancing prostate cancer.

Keywords: Castrate resistant prostate cancer; Androgen biosynthesis inhibitors; Anti-androgens; Estrogen

Introduction

Against the background of dramatically improving prostate cancer (CaP)-specific survival rates, rising from 67% to 99% between 1974 and 2000, healthcare economists and physicians not familiar with the natural history of CaP might question the urologists' concern about morbidity and mortality because of advancing disease. Early detection and the resultant lead time bias have made CaP 5-year survival statistics relatively meaningless for predicting subsequent outcomes. Follow-up through 10, and even 15 years is necessary to appreciate the lethal phenotype of CaP that will claim the life of approximately 32,000 men in 2011.

Advancing CaP and androgen deprivation

Advancing CaP is a dynamic process. In years past, it was defined by the finding of bulky disease on digital rectal examination, or imaging studies demonstrating adenopathy or bone metastases, but these are now not the usual criteria. "Where have all the signs and symptoms gone?" was the subject of a recent text chapter in Comprehensive Textbook of Genitourinary Oncology, 3rd edition [1]. While there are no absolute criteria to identify this disease state, a combination of risk factors, which include absolute serum prostatic specific antigen (PSA) levels, PSA kinetics (rapid doubling time and velocity), especially if serum testosterone is at castration levels, and/or disease progression by imaging studies (bone scan, CT scan, MRI), are important criteria for identifying advancing disease. Virtually all patients with advancing disease state will receive androgen deprivation, either by luteinizing hormone-releasing hormone (LHRH) agonist monotherapy or an LHRH agonist in combination with a nonsteroidal antiandrogen. Combined androgen blockade was a strategy introduced more than 20 years ago to maximize androgen deprivation by addressing the possibility of adrenal androgen production and the possibility of incomplete gonadal axis suppression, and did indeed demonstrate a 5-year 2.9% survival advantage vs. monotherapy when either nilutamide or flutamide was employed [2]. A retrospective analysis and a prospective combined androgen blockade trial with bicalutamide for patients with T3 or M1 disease have demonstrated an overall survival advantage for the combination compared with LHRH agonist monotherapy [3,4]. An improved understanding of the androgen receptor and its continued activity, even at low levels of androgen, has led to the development of agents to approach more "complete" androgen blockade with more profound and durable response. A critical question to be resolved is the testosterone cutpoint, which defines optimal therapy. Unfortunately, progress towards this end is impeded by nonstandardized methodology and limited sensitivity of testosterone assays [5].

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Parenthetically, as we proceed towards the objective of androgen "annihilation," the resulting adverse consequences will need even greater attention. Bone health has been recognized as a victim of long-term androgen deprivation and, more recently, cardiovascular and metabolic health as well. The American Heart Association, American Urologic Association, and the American Cancer Society have recently issued guidelines with which every physician prescribing androgen deprivation therapy should have familiarity [6]. Estrogen plays a well-defined role in bone health and sexual function, and may play a role in cognitive function and lipid physiology. In the male, estrogen is derived from aromatization of testosterone. It follows that further lowering of the testosterone nadir will be accompanied by increasing estrogen deficiency and, logically, more potential for adverse events. The impact of lower testosterone nadir on quality-of-life when used early in the course of disease, a situation dramatically different from use as currently tested in trials of chemo-naive or post-chemometastatic castrate-resistant CaP, may be found to be problematic or even prohibitive. The role of estrogen supplementation to offset marked estrogen deficiency will become a subject for future consideration.

Definitions of disease state

PSA or imaging progression while the patient is receiving LHRH analogue monotherapy has long been labeled hormone refractory disease. This is obviously inaccurate, since subsequent hormonal interventions are now available to induce disease regression. Another label has been androgen-independent disease, which is also inaccurate as the androgen receptor remains, as discussed above, quite active. The current label for this disease state is castration-resistant. This label depends on the definition of a castrate serum testosterone. Should it be the traditional Food and Drug Administration (FDA) recognized cutpoint of $<$50 ng/dl, or the lower than 20 ng/dl achieved by surgical castration, or should it rely on more sensitive assays that can measure testosterone to $<$1 ng/dl; finally, should the castrate state consider tissue and tumor, as well as serum androgen levels? Androgen levels of CaP tissue had been shown to be comparable to or only slightly less than that of benign prostate tissue, and expression of steroidogenic enzyme transcripts that would facilitate the conversion of cholesterol to androgens are found in higher concentration in metastatic CaP samples vs. tissue from the primary cancer or benign prostate tissue [7,8]. This information clearly defines a paracrine/autocrine phase of CaP that has implications beyond the historical/traditional endocrine phase defined by serum testosterone level.

There is increasing clinical experience that progression of disease to the castration resistant state can be delayed and overall survival prolonged by achieving and maintaining lower testosterone nadirs [9,10]. While it has not been the routine practice of urologists to obtain periodic testosterone monitoring along with PSA determinations after the institution of an LHRH agonist, this will be necessary to clarify/document optimal testosterone nadir levels. Furthermore, testosterone monitoring is recommended in the FDA labeling of the LHRH agonists.

Androgen biosynthesis inhibitor (ABI)

The androgen receptor is active in the "castrate state" based on the number of possible mechanisms, which include amplification, hypersensitivity, mutation, and or ligand-independent activation. There are a number of strategies in development to suppress androgen receptor activation by more effective receptor blockade and/or more effective reduction of the androgen ligand. Ketoconazole is a currently available drug that can accomplish the goal of ligand reduction. Ketoconazole can be considered a forerunner of the androgen biosynthesis inhibitors. It is a general, nonspecific inhibitor of the CYP enzyme family (17α-hydroxylase 0.17,20 lyase) that converts cholesterol to androgens. It carries the disadvantage of interfering with the metabolic degradation of other pharmacologic agents (statins, erythromycin, calcium channel blockers, selective serotonin reuptake inhibitors (SSRIs), and acetaminophen.) Therefore, it is necessary to take a careful medication history and consult with primary care physician for medication changes before prescribing. Abiraterone, orally administered, is a 17α-hydroxylase 17,20 lyase irreversible enzyme inhibitor, which is more specific and more potent than ketoconazole. In addition to its activity in testicular and adrenal tissue, it is also active in blocking androgen production in tumor tissue.

In phase 2 studies, abiraterone demonstrated significant PSA declines ($>$50% in two-thirds of patients and $>$90% in 20% of patients) along with objective responses [11–13]. Patients who had been treated previously with ketoconazole also demonstrated a response. Abiraterone is currently being tested in 2 large randomized controlled trials (RCTs); one enrolling patients with castrate resistant CaP post-docetaxel and the other pre-docetaxel, both trials have met accrual, and one has been published [14]. This large phase 3 trial enrolled men with metastatic castrate resistant CaP who had failed docetaxel chemotherapy, randomizing them to abiraterone 1 g daily plus prednisone 5 mg bid vs. placebo plus prednisone with an endpoint of overall survival. That these men were a cohort with advancing disease who had virtually exhausted all avenues of therapy is illustrated by the fact that 28% had been treated with at least 2 prior chemotherapies and 10%–15% demonstrated liver and lung metastases. The treatment arm demonstrated a 3.9-month survival benefit with a hazard ratio of 0.646 and a P value of $<$0.001. Abiraterone is quite well tolerated. Side effects include hypokalemia, fluid retention, and hypertension, a consequence of downstream excess aldosterone. The administration of prednisone counters the feedback loop that produces excess aldosterone, but periodic blood pres-