The Case for Secondary Hormonal Therapies in the Chemotherapy Age

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Purpose: Virtually all patients with high risk localized and metastatic prostate cancer who are treated with androgen deprivation therapy eventually have progressive clinical or biochemical disease despite this therapy. Despite this fact numerous therapies are available that target the interaction of androgen and androgen receptor in the castrate testosterone milieu and many clinical investigations are under way in this area.

Materials and Methods: This literature review focuses on the current clinical literature in support of secondary hormonal therapy.

Results: Despite low androgen levels the androgen receptor remains active through the amplification, mutation or alteration of coactivator function. These observations suggest that secondary hormonal therapies remain a reasonable clinical approach. Such approaches can be receptor or ligand directed. Receptor directed approaches to secondary hormonal therapy are antiandrogen withdrawal, sequential use of antiandrogens and estrogenic compounds. Ligand directed therapies are adrenal cortex inhibitors, such as ketoconazole and others in clinical development. Furthermore, in the context of androgen independent tumor growth in patients with metastatic disease clinicians are now faced with the choice of using chemotherapy or secondary hormonal manipulations. Appropriate patient selection is a critical component to the effective use of these agents.

Conclusions: The modest activity of these secondary therapies challenges the notion that advancing prostate cancer uniformly becomes hormone refractory. It offers an alternative to the early use of chemotherapy in patients with androgen independent disease.

Key Words: prostate, prostatic neoplasms, androgen antagonists, ketoconazole, adrenal cortex hormones

The first evidence that an intermediate state exists between what are commonly called hormone sensitive prostate cancer and HRPC developed in 1992 when the antiandrogen withdrawal phenomenon was reported.[1] In these reports it was suggested that flutamide, which was in widespread use as an antiandrogen, had the capability of actually stimulating tumor growth. Thus, simply removing this agent became a therapeutic maneuver and it is now considered mandatory to truly document disease progression while on CAB. More recently a number of secondary hormonal manipulations were described that are now an important part of disease management. Although the use of these approaches is supported by randomized, phase III data, the clinical decision making for when to use them and in whom continues to be defined. In this review we describe the published literature and offer guidelines for the use of secondary hormonal manipulations for AIPC.

THE ANTIANDROGEN WITHDRAWAL PHENOMENON

The description of the flutamide withdrawal syndrome and subsequent characterization of the phenomenon through the 1990s with agents such as bicalutamide and megestrol collectively challenged the definition of HRPC. In 1995 Taplin[2] and Tilley[3] et al reported mutations in the AR ligand binding domain, suggesting that mutations were the underlying mechanism of this syndrome. Subsequent studies performed by CALGB determined that the incidence of AR mutations in AIPC was rare with only 5 of 48 samples (10%) harboring a mutated receptor.[4] Furthermore, no relationship was observed between AR mutations and an AAWD response, defined as a PSA decrease of greater than 50%. Overall an AAWD response is observed in less than 20% of patients. Nevertheless, this observation prompted reexamination of the belief that prostate cancers that progress while on ADT are truly hormone refractory.

TERMINOLOGY RELATIVE TO THE HORMONE SENSITIVITY OF PROSTATE CANCER

There is no current consensus as to the most appropriate nomenclature for advancing prostate cancer. At issue is the difficulty of incorporating terminology that recognizes the importance of tumor growth in the castrate state while acknowledging its sensitivity to secondary hormonal therapies. There is general agreement that patients with testosterone levels greater than 250 ng/ml and tumor that is responsive to castrating therapies may be labeled as "hormone naïve." However, disease progression despite castrate testosterone has been labeled AIPC, defined as resistant to castration but sensitive to secondary hormonal manipulations, or HRPC, defined as resistant to all hormonal manip-

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ulations.[5] The relative inadequacy of this nomenclature is evident when one considers that metastatic disease in the castrate state, which is labeled by many as HRPC, is more sensitive to estramustine containing chemotherapy combinations than to chemotherapy alone.[6] Also, certain patients with rapid progression on initial hormonal therapy may be treated with chemotherapy in lieu of secondary hormonal manipulations, thereby blurring the distinction between AIPC and HRPC. Suffice it to say that not all AIPC is hormone refractory and prostate cancer may, in fact, never become completely hormone "refractory."

MECHANISMS OF ANDROGEN INDEPENDENT TUMOR GROWTH

Numerous mechanisms of androgen independent growth have been proposed, including AR gene amplification, AR gene mutation leading to persistent activation, AR promiscuity for nonandrogen agonists and AR promiscuity leading to activation by pharmacological antagonists such as flutamide and bicalutamide. More recent evidence implicates altered recruitment of coactivators in combination with receptor amplification as a potential underlying mechanism of resistance to antiandrogen therapy.

HOW DO WE ASSESS THE EFFICACY OF SECONDARY HORMONAL MANIPULATION?

The sensitivity of secondary hormonal therapies can be assessed by the PSA response to a drug in an individual. Although it is not widely used as an overall surrogate marker for the response to all therapies, eg chemotherapy and bisphosphonates, PSA responses are more likely a valid intermediate end point when evaluating drugs that affect the AR axis. For example, in the recent CALGB 9583 study of second line hormonal therapy the 4-week landmark analysis showed that patients with a PSA response, defined as a PSA decrease of 50% or greater within 12 weeks of therapy initiation, experienced a median survival of 41 months compared to 13 months in those without a 50% decrease in PSA ($p < 0.001$).[7] These prospective data corroborated a prior retrospective analysis demonstrating that median survival in patients who achieved a 50% or greater decrease in PSA at 12 weeks on various clinical trials (chemotherapy and investigational therapies) at Memorial Sloan-Kettering Cancer Center was 25.3 months compared with 13 months in those who did not (log rank $p = 0.0001$).[8]

WHEN ARE SECONDARY HORMONAL THERAPIES PREFERRED OVER CHEMOTHERAPY?

Chemotherapy is now considered an active therapy for prostate cancer and referral to a medical oncologist is recommended in all patients with disease progression despite initial androgen deprivation therapy. However, AIPC is a diverse clinical entity based on the presence or absence of metastases, the location of metastases (nodal only or bone plus nodal) or symptoms and chemotherapy should not be the automatic choice in all patients. Increasingly patients diagnosed with hormone refractory disease after initiating androgen deprivation have serological-only relapse without metastases. As a result, it is now possible for patients to have nonmetastatic HRPC. The likelihood that such patients will have metastatic disease after androgen independence develops is high but it can be relatively slow to occur. In a recent prospective analysis of such patients median time to bone metastases was 3 years.[9] Therefore, it is reasonable to consider that patients with serological-only relapse are unlikely to become rapidly symptomatic and they also may derive clinical benefit from therapies that decrease the likelihood of PSA progression. It is these patients as well as those who experience disease progression on ADT in the presence of a low volume of metastases who may be the best population for secondary hormonal manipulations.

The Eastern Cooperative Oncology Group 1899 study was designed to test this question. In this study patients with castration resistant nonmetastatic disease were randomized to KC or docetaxel. Unfortunately the question remains unanswered because the study closed due to poor accrual. Early termination of this study is instructive. 1) It tells us that patients with prostate cancer may be unwilling to be randomized to a chemotherapy vs a nonchemotherapy treatment. 2) It suggests that clinicians understand the biological heterogeneity of AIPC and they were already making clinical decisions regarding therapy based on their knowledge of disease biology even in the absence of randomized data. In either case the choice between chemotherapy and secondary hormonal therapy is now relegated to clinical judgment because to our knowledge no prospective trial is under way or planned.

Prognostic models have been developed to assess patients who have progressive castrate metastatic disease despite initial hormonal therapy and they may be useful for making this clinical judgment. In these models the factors with the largest impact on patient survival were those that correlated with the disease burden, including performance status, hemoglobin, lactate dehydrogenase and alkaline phosphatase.[10] Another model validated the importance of these factors but also identified Gleason grade of the primary tumor as prognostic.[11] However, these models were derived from data sets consisting entirely or almost entirely of patients with metastatic disease. These nomograms may be useful for determining whether it is reasonable to consider advancing a patient to chemotherapy in lieu of further hormonal manipulations.

HORMONE THERAPY AFTER AAWD

Broadly characterized, the 3 therapeutic classes of secondary hormonal manipulations are 1) secondary antiandrogen therapy, 2) adrenal androgen targeted therapy and 3) estrogens. Features common to all of them are favorable tolerability, modest response proportions and relatively short response durations. Consequently it is not unusual for patients to receive a series of sequentially administered second line therapies.

While to our knowledge no prospective study has been performed to answer the question, it is generally assumed that maintenance of a castrate testosterone milieu is important even in the face of androgen independent disease. Retrospective data in support of continued androgen suppression come from a retrospective analysis of 341 patients treated in a series of clinical trials performed by the Eastern Cooperative Oncology Group, in which discontinuation of medical castration emerged as an independent predictor of shorter survival. Based on these data and pending further