

Simultaneous Antiandrogen Withdrawal and Treatment with Ketoconazole and Hydrocortisone in Patients with Advanced Prostate Carcinoma

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BACKGROUND. Although antiandrogen withdrawal has moderate efficacy in patients with hormone refractory prostate carcinoma (HRPC), the effect of the simultaneous suppression of adrenal androgens with ketoconazole at the time of antiandrogen withdrawal is not known.

METHODS. Twenty consecutive patients with HRPC who had developed progressive disease despite combined androgen blockade were treated with antiandrogen withdrawal and simultaneous ketoconazole as a means of inhibiting adrenal steroid production. Prostate specific antigen (PSA) response was defined as a > 50% fall in PSA from baseline that was maintained for at least 8 weeks.

RESULTS. Ten patients had established metastatic disease, 2 had high PSAs and no imaging studies (PSA of 70 and 160 ng/mL, respectively), 3 had microscopically positive lymph nodes and serologic progression, and 5 had serologic progression alone. Overall, of 20 evaluable patients, 11 (55%) had a > 50% fall in PSA (95% confidence interval [CI], 31.5–76.9%). The median PSA response duration was 8.5 months (95% CI, 7–17 months). The median survival was 19 months. Toxicity was mild, with Grade 1 and 2 nausea and emesis in 15% of patients, Grade 1 fatigue in 10% of patients, and reversible Grade 1 or 2 hepatotoxicity in 10% of patients. Mild skin toxicity was observed in 20% of patients.

CONCLUSIONS. The addition of ketoconazole and hydrocortisone to antiandrogen withdrawal appears to increase the PSA response proportion observed with antiandrogen withdrawal alone. Toxicity is mild. *Cancer* 1997;80:1755–9.

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The benefits of the discontinuation of flutamide in patients with metastatic hormone refractory prostate carcinoma (HRPC) have been well described and have been termed the antiandrogen withdrawal syndrome. Approximately 20% of patients with progressive HRPC treated with combined androgen blockade will have a significant decline in serum prostate specific androgen (PSA) when flutamide is discontinued, and some of the patients will experience symptomatic and/or objective improvement.^{1,2} Benefits of the discontinuation of antiandrogens also have been observed with other agents, including bicalutamide³ and megestrol acetate.⁴ Recent evidence suggests that the steroid-binding domain of the androgen receptor is mutated in some patients with HRPC.⁵ When functional studies of some mutant androgen receptors are undertaken, it is apparent that they can be stimulated by agents such as progesterone and estradiol, which normally are nonstimulating to wild type receptors. The exact

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relationship between androgen receptor mutations and the antiandrogen withdrawal syndrome currently is under study. The unexpected antitumor activity manifested by a subsequent hormonal maneuver comprised of antiandrogen withdrawal has led to a number of trials of second-line hormonal maneuvers. Quite clearly, there exists heterogeneity in the HRPC patient population, such that some patients previously labeled as hormone resistant in fact retain some degree of hormonal sensitivity.⁶

These observations have mandated that from a practical standpoint, at a minimum, all patients with progression of their prostate carcinoma while receiving combined androgen blockade should undergo antiandrogen withdrawal before being entered in subsequent trials. It is assumed that those patients who respond to antiandrogen withdrawal are likely to contain a certain proportion of mutant androgen receptors. (In addition to responding to antiandrogen withdrawal, some mutant receptors appear to retain sensitivity to androgens as well.) However, it is reasonable to assume that there remains a population of wild type receptors that retain sensitivity to androgenic stimulation or, alternatively, that not all receptors within a given cell in fact are mutants. For this reason, the authors postulated that the suppression of adrenal androgens with ketoconazole in these patients might result in a clinical benefit. Indeed, the authors have shown a surprisingly high PSA response proportion in patients who have developed progressive disease after antiandrogen withdrawal and who were treated subsequently with ketoconazole and hydrocortisone.⁷ Alternative explanations for the observed activity of ketoconazole include a direct cytotoxic effect, or interaction at a site other than the androgen receptor.

Although we have previously evaluated the utility of ketoconazole in patients who had already progressed after flutamide withdrawal, it is unknown whether simultaneous flutamide withdrawal and suppression of adrenal androgen levels with ketoconazole is a preferable approach. Sartor et al. first reported the utility of adrenal androgen suppression at the time of flutamide withdrawal, utilizing aminoglutethimide. A 48% PSA response proportion was reported, which was considerably higher than that expected with flutamide withdrawal alone.⁸

In anticipation of a multicenter randomized trial comparing simultaneous antiandrogen withdrawal plus adrenal androgen suppression with ketoconazole versus antiandrogen withdrawal alone, we believed it was important to corroborate the data reported by Sartor et al.⁸ regarding the efficacy of simultaneous aminoglutethimide administration and flutamide withdrawal.

Therefore we prospectively studied a cohort of 20 consecutive patients with progressive prostate carcinoma despite combined androgen blockade who were treated with antiandrogen withdrawal and simultaneous ketoconazole as a means of inhibiting adrenal steroidogenesis.

PATIENTS AND METHODS

We reviewed the records of 20 consecutive patients with histologically confirmed prostate carcinoma who had progressed despite combined androgen blockade and who were treated with ketoconazole and replacement doses of hydrocortisone at the time of discontinuation of flutamide. All patients were treated in a prospective fashion in a manner consistent with our standard practice; eligibility criteria, disease assessment, treatment regimen, response assessment and dose modifications, and/or termination of therapy were undertaken in accordance with a standardized procedure. Institutional review board approval was obtained for this retrospective review. To be considered for treatment, patients had to have developed progressive disease while receiving combined androgen blockade. Progressive disease was defined as objective progression on any imaging study, or at least 2 consecutive PSA levels, at least 2 weeks apart, each of which demonstrated a > 50% rise above their nadir level while receiving combined hormone blockade. Metastatic disease was not required. Prior therapy with aminoglutethimide, ketoconazole, or any investigational agent, chemotherapy, or immunotherapy was not permitted. Concurrent or subsequent therapy with systemic steroids was prohibited.

On the first day of therapy, a baseline serum PSA (Hybritech Tandem R assay; Hybritech, Inc., San Diego, CA) and baseline liver function tests (LFTs) (total bilirubin, aspartate aminotransferase, and alkaline phosphatase) were obtained. Because the primary objective of this study was to evaluate the impact of ketoconazole and hydrocortisone along with simultaneous flutamide withdrawal on PSA levels, imaging studies were not routinely obtained prior to therapy. Treatment was comprised of discontinuation of flutamide and administration of ketoconazole, 400 mg orally every 8 hours, and "replacement" hydrocortisone, 20 mg orally in the morning and 10 mg orally at night. If primary gonadal androgen deprivation was undertaken with an luteinizing hormone-releasing hormone agonist, this medication was not discontinued. Patients were encouraged to take their medications on an empty stomach to maximize ketoconazole absorption. However, if this resulted in intolerable gastrointestinal upset, they were allowed to take their medications at meal time. Antacids and H₂ blockers were discour-

TABLE 1
Patient Characteristics

Median age (yrs) (range)	73 (61–83)
Median pretreatment PSA (ng/mL) (range)	13 (1.9–1000)
Bone scan alone (+) at time of Rx	8
Bone scan (+) and CT (+) at time of Rx	1 (liver metastases)
CT scan alone (+) at time of Rx	1 (paraaortic lymph nodes)
Elevated PSA at time of Rx (no imaging undertaken)	2 (PSA 70 and 160 ng/mL)
Serologic progression alone in patients with prior biopsy (+) lymph nodes	3
Serologic progression alone	5

PSA: prostate specific antigen; Rx: treatment; CT: computed tomography; (+): positive.

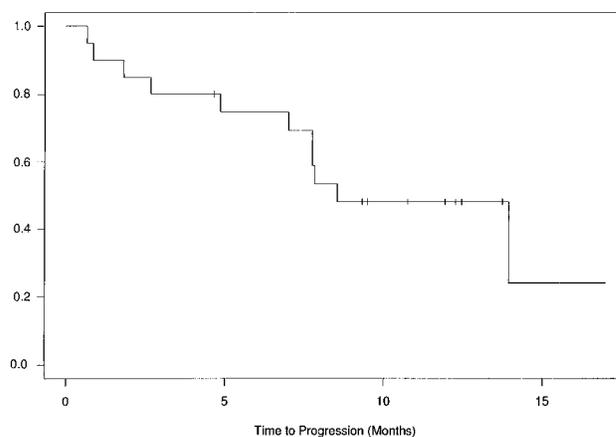
aged, but if necessary were to be taken several hours prior to the ketoconazole dose. Because of potential adverse drug interactions with ketoconazole, concurrent treatment with astemizole, terfenadine, or cispripide was prohibited. Monthly PSA and LFTs were obtained. Patients remained on study until there was evidence of progressive disease or toxicity precluded further therapy. The expanded Cancer and Leukemia Group B toxicity criteria were utilized to grade all toxicity. Progressive disease was defined as objective progression on any imaging study, or at least 2 consecutive PSA levels, at least 2 weeks apart, each of which demonstrated a $> 50\%$ rise above the nadir level achieved while receiving treatment. An arbitrary minimum PSA change of 2 ng/mL was required to declare progressive disease. The primary endpoint was PSA response.

Because the majority of patients were asymptomatic, the definition of progression was PSA-driven, and in an effort to contain costs, routine follow-up imaging studies were not obtained unless warranted clinically. Objective responses required complete resolution of all imaged lesions with no appearance of new lesions (complete response) or a $\geq 50\%$ reduction in the sum of the areas of all bidimensionally measurable lesions (partial response). Prostate lesions were not considered to be evaluable.

A PSA response was defined as a $> 50\%$ fall in PSA from baseline that lasted at least 8 weeks (a minimum of 2 consecutive levels, at least 4 weeks apart).

RESULTS

Twenty patients were enrolled; all were fully evaluable for efficacy and toxicity. Patient characteristics are summarized in Table 1. The median age was 73 years (range, 61–83 years), and the median serum PSA prior to initiating therapy was 13 ng/mL (range, 1.9–1000 ng/mL). Although there was no minimum PSA level required, 15 of 20 patients had a pretreatment PSA

**FIGURE 1.** Probability of progression free survival (Kaplan–Meier plot).

level > 5 ng/mL. Ten patients had metastatic disease: eight had bone-only disease, one had bone disease with soft tissue disease (biopsy proven liver metastases), and one had soft tissue disease only (paraaortic lymph nodes). Two other patients who were not imaged prior to the initiation of ketoconazole were presumed to have systemic disease, with PSA levels of 70 and 160.5 ng/mL, respectively. Eight patients had only serologic evidence of progression after treatment with combined androgen blockade; of these, three patients had previous biopsy proven lymph node involvement.

Nine patients were being treated with a gonadotropin-releasing hormone analog and 11 patients had undergone prior orchiectomy. All patients were receiving flutamide.

There were two patients who came off therapy early (before receiving 8 weeks of therapy) due to Grade 2 nausea and emesis and, in one of the cases, transient LFT elevations. These patients were not censored and were included as evaluable patients. Overall, 11 of 20 patients (55%; 95% confidence interval [CI], 31.5–76.9%) obtained a PSA response ($> 50\%$ decline in PSA for at least 8 weeks, measured at least twice on 2 separate occasions, at least 4 weeks apart). For all patients, the median change in PSA was -73.5% . The median PSA response duration was 8.5 months (95% CI, 7–17 months) (Fig. 1). The median survival for the group was 19 months. Overall, at last follow-up ten patients had come off treatment: six because of PSA progression, one because of objective disease progression, and three because of toxicity.

Known measurable disease was present in two patients, although routine pretreatment scanning was not undertaken. One patient with hepatic metastases achieved an objective partial response.

Toxicity

Toxicity overall was mild. At last follow-up, ketoconazole was discontinued because of toxicity in three patients. Two patients had early toxicity with Grade 2 nausea and emesis. One of these patients also had mild (Grade 1), reversible LFT abnormalities. A third patient discontinued treatment because of nonspecific abdominal pain. There were no Grade 3 and 4 toxicities. Overall, 3 patients (15%) had Grade 1 and 2 nausea and emesis, 2 patients (10%) had fatigue, and 2 patients (10%) had reversible Grade 1 or 2 LFT abnormalities. Grade 1 skin toxicity, including dryness, easy bruising, and "stickiness," was observed in 20% of patients.

DISCUSSION

The results of the current study demonstrated a 55% PSA response proportion in patients with progressive prostate carcinoma treated simultaneously with flutamide withdrawal and ketoconazole with hydrocortisone. No consensus exists regarding the definition of a PSA response. We acknowledge that the response criteria used in this report (> 50% decline on at least 2 occasions at least 1 month apart) is considerably more conservative than their previous definition¹ (> 50% decline on at least 2 occasions at least 2 weeks apart). Direct comparison with other data such as those of Sartor et al.⁸ (which required a > 80% decline maintained for at least 4 weeks) is difficult. In part, our decision to obtain PSA levels every 4 weeks rather than every 2 weeks was based on the desire to reflect both current clinical practice as well as clinical fiscal constraints. Furthermore, it is not clear that these various studies can be directly compared in any event, given the not insignificant differences in the patient populations treated. The median PSA at study entry was considerably lower (13 ng/mL) and 8 of 20 patients had serologic progression alone. We believe that this relatively "early" group of patients reflects the dramatic prostate carcinoma stage migration observed clinically and the trend toward the earlier identification of progressive disease on the basis of PSA.

A median response duration of 8.5 months (95% CI, 7–17 months) was observed. In addition to PSA responses, we also have observed cases of significant objective responses, although for cost containment reasons, abdominal and pelvic computed tomography scans or magnetic resonance imaging scans were not obtained routinely. Nevertheless, a near-complete objective response was observed in one patient with extensive hepatic metastases. The PSA response proportion observed appears to be higher than that previously noted with flutamide withdrawal alone (which has yielded a response proportion of 15%).^{1,2} We be-

lieve these data suggest that simultaneous suppression of adrenal androgens appears to enhance the efficacy of antiandrogen withdrawal and supports the observation first made by Sartor et al., who noted a PSA response proportion of 48% when aminoglutethimide and hydrocortisone were utilized at the time of flutamide withdrawal.⁸

It is not clear whether the simultaneous use of adrenal androgen deprivation with ketoconazole plus antiandrogen withdrawal is superior to the sequential use of antiandrogen withdrawal followed by adrenal androgen ablation at the time of PSA progression. The authors previously reported that in advanced prostate carcinoma patients whose disease progressed after flutamide withdrawal, the subsequent addition of ketoconazole plus hydrocortisone resulted in a > 50% decline in PSA in 60% of patients.⁷ This response proportion is not likely to be significantly different from the 55% response proportion observed in the current trial. However, it is not known whether the duration of responses is superior with either concurrent or sequential therapy. This question currently is being addressed by an ongoing randomized trial.

The relative contribution of hydrocortisone to the efficacy of either ketoconazole or aminoglutethimide is not known, although the use of corticosteroids alone after antiandrogen withdrawal has been reported to have a response proportion of approximately 20%.⁹ Although this issue cannot be adequately addressed in the absence of a randomized trial, the response proportion observed appears to be considerably higher than that expected with hydrocortisone alone, and supports prior experience that suggested that ketoconazole is an active agent in this group of patients. Some studies with ketoconazole at these doses suggest that adrenal insufficiency does not occur, and that replacement doses of hydrocortisone are not required.^{10–12} (In these studies, all of which were undertaken prior to the advent of antiandrogen therapy and prior to the routine use of PSA as a surrogate endpoint, approximately 20–30% of patients obtained objective responses.) Nevertheless, because the addition of hydrocortisone offers minimal added toxicity, it appeared reasonable to include replacement doses of hydrocortisone in the regimen to avoid any potential adrenal insufficiency.

Finally, it should be noted that the clinical and biologic significance of a decline in PSA after antiandrogen withdrawal or additional hormonal maneuvers such as the addition of ketoconazole and hydrocortisone is not fully understood. However, in this study, as in other studies of either antiandrogen withdrawal

or adrenal androgen ablation, instances of significant tumor bulk reduction and symptomatic improvement have been observed, suggesting that this is more than just a biochemical phenomenon. However, the primary endpoint in this trial was PSA response. In this largely asymptomatic, relatively "early" group of prostate carcinoma patients, formal pain and quality of life assessments were not undertaken, and very few patients underwent sequential imaging. Because patients go on to receive such a wide diversity of subsequent treatments, it is not known whether a PSA response in this setting is associated in any significant fashion with improved survival.

We have shown that the addition of ketoconazole and hydrocortisone to antiandrogen withdrawal appears to increase the PSA response proportion observed with antiandrogen withdrawal alone. Although it is not known whether the PSA responses observed translate into clinical benefit, the use of ketoconazole has a favorable toxicity profile. It is not clear whether this approach is superior to the addition of ketoconazole once there is progression after antiandrogen withdrawal, and is the subject of an ongoing randomized trial.

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