Use of the Aromatase Inhibitor Anastrozole in the Treatment of Patients with Advanced Prostate Carcinoma

Richard J. Santen, M.D.[1]
Gina R. Petroni, Ph.D.[1]
Michael J. Fisch, M.D.[2]
Charles E. Myers, M.D.[1]
Dan Theodorescu, M.D.[3]
Roger B. Cohen, M.D.[1]

[1] Department of Medicine, University of Virginia Health System, Charlottesville, Virginia.

[2] Symptom Control and Palliative Care, University of Texas M. D. Anderson Cancer Center, Houston, Texas.

[3] Department of Urology, University of Virginia Health System, Charlottesville, Virginia.

Address for reprints: Richard J. Santen, M.D., University of Virginia Health System, P.O. Box 800379, Charlottesville, VA 22908; Fax: (434) 924-9616; E-mail: rjs5y@virginia.edu

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BACKGROUND. Men with prostate carcinoma initially respond to therapies designed to inhibit androgen secretion or block its action. Later, the tumors in these patients become refractory to androgen-related therapies. Therefore, additional hormonal maneuvers that would benefit these men currently are needed. Reports of androgen receptor mutations and historic clinical observations raised the hypothesis that estrogens might be involved in the proliferation of androgen-refractory prostate carcinoma.

METHODS. To explore this hypothesis, 14 men with advanced prostate carcinoma that was refractory to medical or surgical orchiectomy and antiandrogens were entered into a clinical Phase II trial involving suppression of estrogens. After complete evaluation, each patient received 1 mg daily of the third-generation aromatase inhibitor anastrozole until disease progression. Follow-up included serial determinations of prostate specific antigen (PSA), measurements of evaluable lesions, and assessment of intensity of pain.

RESULTS. No patient experienced an objective response or disease stabilization as measured by PSA level or the greatest dimension of the lesion. Minimal improvement of bone pain was reported in two patients receiving intensive analgesic medication.

CONCLUSIONS. It was concluded that the dependence of androgen-insensitive prostate carcinoma on estrogens for proliferation is uncommon and that aromatase inhibitors may not have a place in the treatment of prostate carcinoma at this stage of the disease. ***Cancer* 2001;92:2095–101.**

KEYWORDS: aromatase, prostate carcinoma, androgen receptor, estrogens.

Prostatic carcinoma is androgen-dependent in the majority of men at the time of initial diagnosis.[1] Primary hormonal therapy with medical or surgical orchiectomy results in objective disease regression or stabilization for 12–18 months. Complete androgen blockade with the addition of antiandrogens at the time of initial diagnosis may provide small additional benefit as evidenced by meta-analysis,[2] but to our knowledge the efficacy of this approach remains controversial.[3] Secondary hormonal therapy with antiandrogens at the time of disease recurrence after primary therapy may benefit additional patients but disease progression invariably ensues.[4–7] Chemotherapy, although occasionally providing significant palliation, has limited efficacy in producing durable objective or subjective disease remissions and its appeal is limited due to expense and toxicity.[8–13] Accordingly, additional hormonal strategies would be quite useful for men failing androgen ablative therapy.

Recent studies led us to postulate that prostate carcinoma cells might be estrogen-responsive at the time of regrowth after androgen blockade.[5,14,15] If correct, an additional effective strategy for prostate carcinoma at this stage of the disease would be the inhibition of estrogen synthesis. The "estrogen dependence" hypothesis arose because of structure-function analyses of the androgen receptor.[13–14,16] Certain point mutations of the androgen receptor allow it to respond to estrogen as a ligand-dependent promoter of androgen receptor-induced transcription.[5,14] This concept first was established in the LnCAP (name of the hormone-dependent prostate carcinoma cell line derived from *l*ymph *n*ode metastasis of *ca*rcinoma of the *p*rostate) prostate carcinoma cell line. A point mutation at position 868 of the androgen receptor changed its ligand specificity and allowed both estradiol and flutamide to stimulate transcription.

The seminal observations in LnCAP cells suggested that the development of resistance to androgen deprivation possibly could result from androgen receptor mutations. Putatively, estrogen could take over from androgen in the regulation of cellular proliferation under these circumstances. Support for this hypothesis would require the demonstration of mutations in human prostate tumors that allow estrogen to stimulate androgen receptor-regulated transcription. Taplan et al. addressed this question and sought to detect androgen receptor mutations in men with advanced prostate carcinoma.[16] Knowing that receptor mutations were uncommon in primary prostate tumor tissue,[17–19] they elected to examine mutations in cells that had metastasized to bone marrow. They found that 50% of a small group of men had androgen receptor mutations in prostate carcinoma cells present in the bone marrow. When androgen receptors containing these mutations were transfected into COS cells, estradiol caused an increase in the transcription of reporter constructs.

Historic data also support the hypothesis that estrogens may influence the growth of human prostate carcinoma directly. Glick et al. conducted a trial of the antiestrogen tamoxifen in men with advanced prostate carcinoma[20] and reported a 13% objective response rate and 34% improvement in bone pain (17 of 50 patients). Additional reports describe a strategy analogous to that of tamoxifen, namely the use of agents that block the rate-limiting step in estrogen production, the aromatase enzyme. A summary of several trials using the first-generation aromatase inhibitor aminoglutethimide reported that 13.4% of 231 evaluable men with advanced prostate carcinoma experienced objective tumor regression and 24% experienced stable disease.[5] A more recent study using the second-generation aromatase inhibitor 4-OH androstenedione reported no objective regressions but a 60% improvement in subjective symptoms in men with advanced prostate carcinoma.[21]

The molecular biology and clinical data reviewed earlier make the hypothesis of the estrogen dependence of advanced prostate carcinoma plausible. To test this possibility, we conducted a small Phase II trial with a potent and well tolerated aromatase inhibitor.[22] Subjects included men with advanced prostate carcinoma who had been treated previously with medical or surgical orchiectomy and an antiandrogen. We selected the third-generation aromatase inhibitor anastrozole based on its high potency, selectivity, and demonstrated efficacy in blocking aromatase in women with breast carcinoma.[23] Analysis of data from 14 patients revealed no objective responses and minimal evidence of pain relief. On this basis, we concluded that aromatase inhibitors do not appear to have sufficient therapeutic potential in men with advanced prostate carcinoma to merit further clinical trials.

MATERIALS AND METHODS

For this Phase II study, criteria for study entry included evidence of disease progression after either complete androgen blockade as primary therapy or use of an antiandrogen as a second-line hormonal treatment for progressive disease after initial monotherapy with medical or surgical castration. Progressive disease was defined as either (1) 3 consecutive rising prostate specific antigen (PSA) measurements, each separated from the others by at least 2 weeks with at least 1 level of PSA $>$ 10 ng/mL and 50% above the nadir PSA achieved after previous therapeutic maneuvers or (2) progression of soft tissue metastases (increase of $>$ 25% in the dimension product of any measurable disease) or the appearance of new bone metastases. Patients were observed for withdrawal responses to flutamide, bicalutamide, or nilutamide when applicable. No limitation on the number of prior cytotoxic chemotherapies was imposed. For patients treated with medical orchiectomy, the gonadotropin-releasing hormone (GnRH) analogue was continued during use of anastrozole. Patients were required to have a serum creatinine level $<$ 2.0 mg/dL, a granulocyte count $>$ 1500/mm^3, a platelet count $>$ 100,000/mm^3, hemoglobin $>$ 9.0 g/dL, aspartate aminotransferase/alanine aminotransferase $<$ 3 times higher than normal limits, and bilirubin $<$ 1.5 times higher than normal limits. Additional criteria included an Eastern Cooperative Oncology Group (ECOG) status of 0–3 or its equivalent and a life expectancy $>$ 12 weeks.

Pretreatment evaluation included history and physical examination; complete blood count; multiphasic screening for renal, hepatic, and metabolic assessment; and measurement of testosterone and PSA. Radioisotopic bone scans were obtained in all patients as well as confirmatory skeletal X-rays and computed tomography scans if required. A 10-cm visual analogue scale (0 for no pain, 10 cm for greatest pain intensity) was used for the evaluation of bone pain and either the ECOG, Karnofsky, or FACT-P (Version 3)[24] scales were used to assess performance status and quality of life.

After entry to the study, the patients received 1 mg of anastrozole daily by mouth. They were evaluated every other week, at which time PSA levels were obtained and any palpable lesions measured. The original study planned assessment of pain scores, performance status, and bone scans at 3-month intervals. Because the majority of patients were off study by that time period, chart records were used to assess self-reported pain during therapy.

Standard criteria[25] were planned to define complete and partial responses. Disease progression required the usual anatomic criteria or three consecutive increases in PSA that led to at least a $\geq$ 50% increase over baseline or over the nadir observed during a response.[5] Stabilization of disease required that patients not meet the criteria for complete or partial regression or disease progression for at least 90 days. Subjective responses were based on the visual analogue pain score and required a 50% improvement to qualify as a partial subjective response. Participating physicians were allowed to make the decision that clinical judgment required termination of therapy and change to another modality before predefined criteria for disease progression were reached. For that reason, five patients with a $>$ 50% increase in PSA over baseline were switched to another therapy before three consecutively rising PSA measurements were demonstrated. In four patients, only two consecutively rising PSA values to 50% over the baseline were documented and in one patient only one sample exceeded 50% of baseline.

The initial study design planned the accrual of 45 eligible patients to test the null hypothesis of an objective response rate of 5% against the alternative hypothesis of 15% with approximately 80% power at the 0.73 level of significance. Early stopping rules were not included in the study design. However, the lack of observed objective or subjective responses in the first 14 patients resulted in the decision to terminate the study early. Data from these 14 patients were used post hoc to calculate the upper limit of a one-sided 95% confidence interval.

The protocol was approved by the Institutional Review Board, the General Clinical Research Center Review Committee, and the Cancer Center Protocol Review Committee at the University of Virginia. Signed informed consent was obtained from all patients. MEDLINE was searched from 1980–2000 as the source of the literature.

RESULTS

The study population involved heavily pretreated men with a high proportion of extraskeletal involvement, high PSA levels, low performance status, substantial bone pain, and a low hematocrit level.[26] Key parameters in the study patients (Table 1) included a mean age of 64 years; castrate testosterone levels (range, undetectable to 39 ng/dL); an average of 2 prior hormonal and 0.6 chemotherapeutic modalities; 13 of 14 patients with involvement of the axial skeleton and 6 of 14 patients with appendicular skeletal lesions; 6 patients with soft tissue, lymph node, or visceral metastases; a median PSA of 199 ng/mL (range, 13.5–7776 ng/mL); a mean hematocrit of 36.3; and a median pain score of 2 of 10. Thirteen of the 14 men had received antiandrogen therapy in the form of flutamide, nilutamide, and/or bicalutamide.

No patient experienced complete or partial objective regression nor disease stabilization for $\geq$ 90 days in response to anastrozole. Ten of 14 patients experienced a $\geq$ 50% increase in PSA at an average of 5 weeks from the initiation of therapy (Fig. 1A). Of the remaining 4 patients, (Fig. 1B), 1 died of prostate carcinoma at Week 8, 1 had a $>$ 25% increase in cervical lymph node size at Week 8, and 1 experienced an increase in epidural mass on magnetic resonance imaging at Week 9. The fourth patient had a 39% increase in PSA at Week 6 and clinical deterioration resulting in the discontinuation of therapy. The upper limit of a 1-sided 95% confidence interval for none of 14 responses was 19.3%, which can be interpreted as evidence that anastrozole is unlikely to be effective in $>$ 19.3% of patients.

A subjective benefit from anastrozole was not apparent. In the patients with bone pain, four reported worsening of symptoms and three patients experienced disease stabilization while receiving therapy. Two patients reported minimal improvement in bone pain (5 cm to 3 cm and 6 cm to 4 cm, respectively, on a scale of 10 cm) but the concomitant use of narcotic analgesics made interpretation difficult.

DISCUSSION

Prior studies by Taplan et al. demonstrated androgen receptor mutations in prostate carcinoma cells in the bone marrow of men with advanced disease.[16] These

TABLE 1
Summary of Baseline Characteristics of the Patients Entered on the Study

Patient no.	Age (yrs)	Prior hormone therapies	Prior chemotherapies	Involvement: Axial skeleton	Involvement: Appendicular skeleton	Involvement: Visceral, soft tissue, lymph node	PSA (ng/mL)	BonePain[a]	Testosterone ng/100 mL	Hct
1	74	2	0	0	0	0	13.5	0	< 0.6[b]	37.8
2	56	2	0	+	+	0	15.0	5	22	40.1
3	62	3	1	+	0	+	18.2	Back and hip[c]	4	29.1
4	77	1	0	+	+	0	592	4	13	36
5	56	3	0	+	0	0	16.7	0	19	41
6	58	1	1	+	+	0	199	5	< 0.6[b]	37
7	75	2	1	+	0	0	70.6	0	< 15	35
8	60	2	2	+	+	+	7766	6	26	33
9	80	2	0	+	0	0	86.2	Vague thigh pain[c]	17	42.9
10	45	2	1	+	+	+	686	5	< 15	31.8
11	62	1	0	+	+	+	144	5	18	36.8
12	62	4	0	+	0	+	10.8	0	39	41
13	78	4	0	+	0	0	85	2	< 20	35.6
14	55	1	3	+	0	+	358	1	< 20	31.5
Average	64	2	0.6				719	2.3		36.3
Median							199	2.0		

PSA: prostate specific antigen; Hct: hematocrit.
[a] Analogue scale 0/10 cm.
[b] Free testosterone.
[c] Analogue not recorded.

mutations, similar to those found in the LnCAP prostate carcinoma cell line,[14] allowed estrogen to become an active ligand for the stimulation of androgen receptor-induced transcription of a reporter gene. These observations led to the hypothesis that the use of inhibitors of estrogen biosynthesis might cause tumor regression in men with prostate carcinoma who previously had undergone therapy to block gonadal and adrenal androgens. The current Phase II study was designed to test this hypothesis. Unfortunately, we found no evidence of efficacy of a potent third-generation aromatase inhibitor in prostate carcinoma patients previously treated with medical or surgical castration and antiandrogens. Based on these observations, we concluded that estrogen suppression in this subset of patients with prostate carcinoma is unlikely to cause tumor regression or clinical improvement.

The lack of responses in the current study population could have resulted from a lack of androgen receptor mutations or from mutations that allow estrogen to induce transcription of reporter genes but not to enhance the rate of proliferation. To our knowledge, the frequency of androgen receptor mutations reported in men with prostate carcinoma has been controversial[17–19,27] and most likely depends on the stage of disease, the site of the tumor (primary vs. metastatic), and the method used for analysis of the androgen receptor. The current study did not enable us to provide further insight into this issue.

A potential explanation for the negative results in the current study is that estradiol levels were not suppressed sufficiently by anastrozole. However, this third-generation inhibitor is nearly 1000-fold more potent than the first-generation inhibitor aminoglutethimide and has been found to uniformly inhibit estradiol in women with breast carcinoma.[22] Dose response studies in women indicate no further benefit from 10 mg versus 1 mg of anastrozole daily.[28] Anastrozole has been shown to inhibit estrogen production acutely in healthy men.[29] Escape from suppression could occur in men with intact hypothalamic-pituitary-testicular axes because interruption of the negative feedback effects of estradiol would stimulate levels of the substrate for aromatase. However, this would be precluded in the men in the current study because they had either undergone surgical orchiectomy or were treated continuously with GnRH agonist therapy (medical orchiectomy). Although we did not measure estradiol systematically, these considerations make it unlikely that insufficient estradiol suppression explains the results of the current study.

We cannot conclude from this small Phase II study that aromatase inhibitors are completely inactive in prostate carcinoma. We terminated the study before the originally planned 45 subjects were accrued

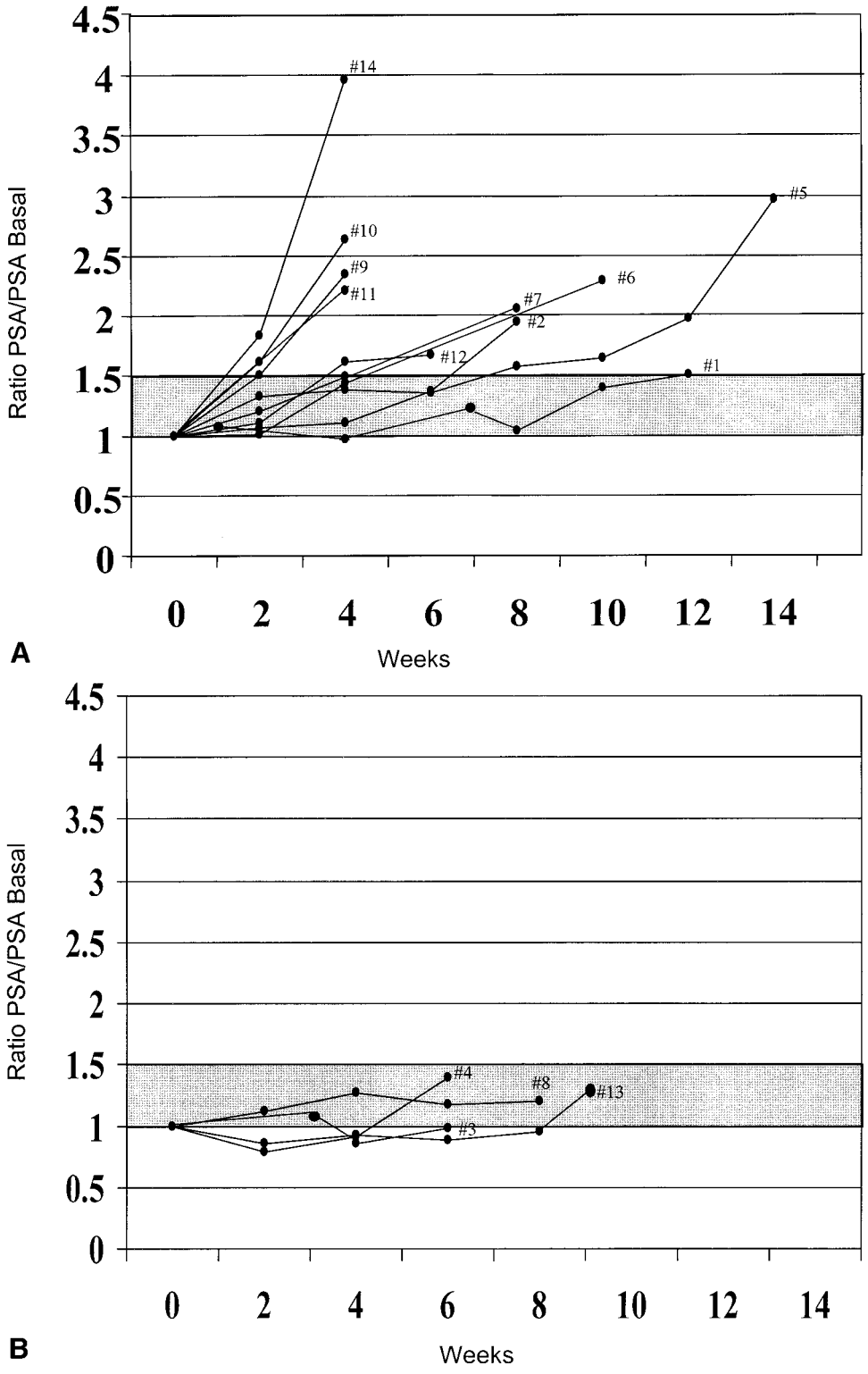

FIGURE 1. (A) Prostate specific antigen (PSA) levels were expressed as the ratio of the basal value to level of treatment for the duration indicated. All data points were rounded off to the nearest week of treatment. Data from individual subjects were numbered to allow correlation with the basal data shown in Table 1. Of the 14 patients, 10 patients were identified as having progressive disease based on an increase in their PSA $>$ 1.5 (i.e., a 50% increase over baseline). (B) The 4 patients whose PSA levels did not exceed 50% of the baseline values while they were receiving treatment. Patient 3 died of prostate carcinoma during Week 8 of therapy. Patient 4 had an only 39% increase in the PSA level but therapy was discontinued based on continued symptoms of disease. Patient 8 had a 25% increase in the size of a cervical lymph node. Patient 13 was found to have an increase in an epidural mass on magnetic resonance imaging.

because of an absence of demonstrable clinical benefit. Originally designed to prove or exclude an objective response rate of 15%, the study now can only exclude a benefit exceeding 19.3% with a 95% confidence interval. With the entry of a larger number of patients, it is possible that objective responses would be observed and that some patients may have estrogen-responsive disease.

The selection of a subgroup of patients who had responded to antiandrogen withdrawal might have

enhanced the response rate to aromatase inhibitor therapy. No patient in the current study was found to exhibit an antiandrogen withdrawal response. The androgen receptor mutations that allow flutamide to stimulate tumor growth most likely explain withdrawal responses. In LnCAP cells and in the tumors studied by Taplin et al., the mutations associated with flutamide stimulation also were associated with estrogen stimulation of an androgen reporter gene.[14,16]

Several pitfalls of the current study must be taken into account when interpreting these data. First, the initial plan was to assess pain score systematically after 3 months of therapy but all patients in the study had developed disease progression by that time period. Consequently, analysis of pain relief at each visit involved use of the investigators' written comments rather than the visual analogue scale. Second, anastrozole was discontinued early in one patient at the discretion of the investigator because of continuing symptoms of disease when PSA levels had increased by only 39%. In four additional patients, only two consecutively PSA values increasing to $>$ 50% above baseline were detected before the termination of therapy and in another patient, only one level was detected. Third, increases in the PSA levels provided the sole means of determining tumor progression in 11 of 14 patients because disease progression occurred prior to the planned reassessment of bone scans and skeletal surveys. Although the majority of investigators agree that this approach is valid,[5] demonstration of anatomic changes in bone lesions would have provided more definitive evidence of disease progression. Fourth, three patients had received prior glucocorticoids either as secondary therapy, in combination with mitoxantrone, or as replacement after suramin therapy. Glucocorticoids can suppress estrogen levels by inhibiting the levels of adrenal androgens, which serve as substrates for aromatase. Pretreatment with these agents possibly could confound interpretation of the later use of aromatase inhibitors. Finally, one patient received pretreatment with the first-generation aromatase inhibitor aminoglutethimide. Hydrocortisone must be given concomitantly with this adrenal inhibitor and, consequently, to our knowledge, the precise mechanism of action of aminoglutethimide in patients with prostate carcinoma is unknown. Initially, stopping rules were not included in the current study because anastrozole has not been reported to be associated with significant toxicity or major side effects and patient accrual was anticipated to be at a higher rate. However, when no objective responses in the first 14 patients were observed, the physicians involved decided to terminate the study early.

Overall, the study objective was to determine whether anastrozole would produce objective responses in at least 15% of prostate carcinoma patients. Analysis of data from 14 patients revealed no objective responses and minimal evidence of pain relief. Although certain pitfalls outlined earlier potentially confounded interpretation of data, the lack of any demonstrable responses provides strong evidence of lack of efficacy. On this basis, we concluded that aromatase inhibitors do not have sufficient therapeutic potential in men with advanced prostate carcinoma to proceed with further clinical trials.

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