Selective Aromatase Inhibition for Patients with Androgen-Independent Prostate Carcinoma

A Phase II Study of Letrozole

Matthew R. Smith, M.D., Ph.D.[1]
Donald Kaufman, M.D.[1]
Daniel George, M.D.[2]
William K. Oh, M.D.[2]
Maryanne Kazanis,
Judith Manola, M.S.[2]
Philip W. Kantoff, M.D.[2]

[1] Department of Hematology Oncology, Massachusetts General Hospital, Boston, Massachusetts.

[2] Department of Medical Oncology, Dana Farber Cancer Institute, Boston, Massachusetts.

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Address for reprints: Matthew R. Smith, M.D., Ph.D., Massachusetts General Hospital, Cox 640, 100 Blossom Street, Boston, MA 02114; Fax: (617) 726-4899; E-mail: smith.matthew@mgh.harvard.edu

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BACKGROUND. First and second-generation aromatase inhibitors have shown activity in patients with androgen-independent prostate carcinoma. These early-generation aromatase inhibitors are nonselective, however, and inhibition of other steroidogenic enzymes may contribute to their reported clinical activity. The authors conducted a Phase II clinical study of letrozole to determine the safety and efficacy of a potent and selective third-generation aromatase inhibitor in men with androgen-independent prostate carcinoma.

METHODS. Forty-three men with androgen-independent prostate carcinoma were treated with oral letrozole (2.5 mg daily). Treatment was continued until progressive disease or Grade 3 toxicity developed. Response and progressive disease were defined according to recommendations of the Prostate Specific Antigen Working Group.

RESULTS. In total, 380 weeks of treatment were administered to the 43 study patients. The median duration of treatment was 8 weeks. Forty men discontinued treatment due to progressive disease. Only one patient responded to treatment with a sustained decrease $>$ 50% in serum prostate specific antigen (PSA) levels. Three other patients experienced transient minor decreases ($<$ 50%) in serum PSA levels. There were no serious treatment-related adverse events.

CONCLUSIONS. Selective aromatase inhibition with letrozole is not active in men with androgen-independent prostate carcinoma. ***Cancer* 2002;95:1864–8.**

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Androgen deprivation therapy by either orchiectomy or chronic administration of a gonadotropin-releasing hormone agonist is the mainstay of treatment for patients with advanced prostate carcinoma. Androgen deprivation therapy results in objective responses in most men with advanced prostate carcinoma, although the median duration of response is less than 2 years.

Estrogens and estrogen receptor signaling have been implicated in prostate carcinoma progression after androgen deprivation therapy. Estrogen receptors are expressed in normal prostate epithelium and in most primary prostate carcinomas.[1] Androgen deprivation therapy appears to increase prostate estrogen receptor density.[2] In addition, specific missense mutations in the androgen receptor allow it to bind estrogens and activate transcription in a ligand-dependent manner.[3–5]

Estrogens and selective estrogen receptor modulators have some activity in men who have disease progression after androgen depri-

vation therapy. Phase II clinical trials of diethystilbesterol and stilbestrol disphosphate reported responses in 43–79% men with progressive disease after androgen deprivation therapy.[6,7] A prospective Phase II clinical trial of PC-SPES, a combination of herbs with estrogenic activity, reported prostate specific antigen (PSA) responses in 54% of men with androgen-independent prostate carcinoma.[8] Several Phase II clinical trials of the selective estrogen receptor modulators tamoxifen and toremifene reported more modest activity with objective responses in 0–24% men.[9–15]

First and second-generation aromatase inhibitors also appear to have some activity in men with androgen-independent prostate carcinoma. Clinical studies of the first-generation aromatase inhibitor aminoglutethimide reported objective responses in 13% of men and stable disease in 24% of men with advanced prostate carcinoma.[16] A Phase II study evaluating the second-generation aromatase inhibitor 4-hydroxyandrostenedione in 25 men with androgen-independent prostate carcinoma[16,17] found no objective responses, although subjective improvements in pain or performance status were observed in 75% of the patients. A Phase I–II study evaluated the second-generation aromatase inhibitor rogletimide in 23 men with androgen-independent prostate carcinoma.[18] In that study, among 13 men who were treated at the highest dose level, there were two subjective responses and two PSA responses. Because the first and second-generation aromatase inhibitors are nonselective, however, inhibition of other steroidogenic enzymes may contribute to their reported clinical activity. For example, aminoglutethimide inhibits aromatase and several enzymes involved in adrenal steroid synthesis.

Letrozole is a third-generation aromatase inhibitor that is indicated for the treatment of postmenopausal women with advanced breast carcinoma.[19] Letrozole is approximately 10,000 times more potent than aminoglutethimide and has no clinically relevant effects on serum concentrations of androgens or adrenal steroids.[20] We conducted a prospective Phase II study of letrozole to evaluate the safety and efficacy of selective aromatase inhibition in men with androgen-independent prostate carcinoma.

MATERIALS AND METHODS

Patients

Patients were recruited from medical oncology, radiation oncology, and urology clinics at the participating institutions. Patients had histologically confirmed adenocarcinoma of the prostate, a serum PSA level $\geq$ 5 ng/mL, and biochemical disease progression (defined as two rises in serum PSA level with each determination at least 1 week apart) after androgen deprivation therapy (by either bilateral orchiectomies or treatment with a gonadotropin-releasing hormone agonist) and antiandrogen withdrawal. Men with symptomatic metastatic disease or prior treatment with chemotherapy for prostate carcinoma were excluded. Men were excluded if they had received chemotherapy for prostate carcinoma or ketoconozole, aminoglutethimide (an antiestrogen), a selective estrogen receptor modulator, or an aromatase inhibitor. Men also were excluded if they had received radiation therapy, antiandrogens, secondary hormonal therapy, or investigational agents within 4 weeks.

Study Design

Pretreatment evaluation included physical examination, determination of Cancer and Leukemia Group B performance status, and measurement of serum PSA, alanine aminotransferase, and aspartate aminotransferase levels. All patients were treated with oral letrozole at a dose of 2.5 mg daily (Femara®; Novartis Oncology; East Hanover, NJ). Letrozole was continued until progressive disease occurred or until any Grade $\geq$ 3 toxicity developed. Men who were not castrated surgically continued treatment with a gonadotropin-releasing hormone agonist throughout the study.

Adverse event assessments and laboratory testing were repeated at 4-week intervals. Serum PSA, alanine aminotransferase, and aspartate aminotransferase levels were measured at each visit. Radiographic studies were obtained at the discretion of the treating physician. A serum sample was obtained at each visit and stored at -80 °C. The study was reviewed and approved by the Institutional Review Board of Dana Farber Partners Cancer Care, and all patients provided written informed consent.

Response Evaluation

All patients were evaluated for response and toxicity. Response and progressive disease were defined according to the recommendations of the PSA Working Group.[21] Response was defined as a decrease $>$ 50% in the PSA level from baseline on two determinations at least 4 week apart and no new sites of metastatic disease. Progressive disease was defined as an increase $>$ 25% in the PSA level from the nadir PSA level on two determinations and an absolute increase in the PSA level by at least 5 ng/mL or new metastatic disease. Adverse events were reported using the National Cancer Institute Common Toxicity Criteria. Serum concentrations of estradiol were measured at the end of the study from stored samples using a radioimmunoassay with a sensitivity of 3 pg/mL and intra-assay and interassay coefficients of variation of 10% and

TABLE 1
Baseline Characteristics

Characteristic	Value
Age (yrs)	
Median	71
Range	55–84
Performance status	
Median	0
Range	0–1
Gleason score (%)	
2–4	23
5–7	44
8–10	23
Unknown	9
Metastases (%)	
Bone	30
Visceral	12
PSA only	58
Serum PSA (ng/mL)	
Median	19.9
Range	5.4–984

PSA: prostate specific antigen.

14%, respectively (Nichols Institute, San Juan Capistrano, CA).

Statistical Analyses

The primary objective of the study was to determine whether letrozole would produce responses in at least 20% of men with androgen-independent prostate carcinoma. The study met the planned accrual goal of 43 patients. The overall probability of rejecting the study drug as inactive was 91% if the true response rate was $< 5\%$. The overall probability of rejecting the study drug as inactive was $< 10\%$ if the true response rate was $> 20\%$. Changes in serum concentrations of estradiol, testosterone, and sex hormone-binding globulin between baseline and 8 weeks were expressed as mean percent changes $\pm$ standard error. The magnitude of these changes was assessed using the Wilcoxon matched-pairs, signed-rank test. Serum concentrations of gonadal steroids at baseline and at 8 weeks were compared using paired *t* tests. All *P* values are two sided, and values < 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Table 1 summarizes the clinical characteristics of the 43 men who entered the study. Their median age was 71 years. All patients had a performance status of 0 or 1. Thirteen men (30%) had bone metastases, five men (12%) had visceral metastases, and 25 men (58%) had PSA-only disease. Their median baseline serum PSA concentration was 19.9 ng/mL (range, 5.4–984 ng/mL).

TABLE 2
Median Serum Concentrations of Gonadal Steroids

Steroid	No.	Week 0	Week 4	Change	*P* value
Estradiol (pg/mL)	31	<5	<5	—	—
Testosterone (ng/mL)	31	11.5	11	− 1	0.84
SHBG (nmol/dL)	35	36	39	0	0.73

SHBG: sex hormone-binding globulin.

Response and Toxicity

In total, 380 weeks of treatment were administered to the 43 patients. The median treatment duration was 8 weeks (range, 4–56 weeks). Forty men (93%) discontinued treatment due to progressive disease, and, of these patients, 2 men had new metastases, and the remaining 38 men had progressive disease based on rising serum PSA concentrations. Three men (7%) discontinued treatment due to adverse events.

The overall response rate was 2.3% (95% confidence interval [95%CI], 0.6–15.8%). Only one man experienced a response, and he remained on therapy until he developed progressive disease at 28 weeks. Three other men experienced transient minor decreases ($< 50\%$) in serum PSA concentrations.

Seven men (16.3%; 95%CI, 6.8–30.7%) had a Grade ≥ 3 adverse event, including urinary tract infection (three men), hematuria (two men), lumbar disc herniation (one man), and atrial fibrillation (one man). None of these serious adverse events were considered related to study treatment. The most common adverse events were fatigue and gastrointestinal toxicity. Four men experienced Grade 1 or 2 fatigue, and two men had Grade 1 or 2 diarrhea. Other Grade 1 or 2 adverse events included lower extremity edema (one man) and muscle cramps (one man).

Gonadal Steroid Levels

Table 2 summarizes the changes in serum concentrations of adrenal and gonadal steroids for the men who had baseline and post-treatment measurements. Serum concentrations of testosterone, and sex hormone-binding globulin did not change significantly. Serum estradiol concentrations were below the lower limits of detection in all the patients at baseline and remained undetectable after treatment.

DISCUSSION

This study demonstrated that selective aromatase inhibition with letrozole is not active in men with an-

drogen-independent prostate carcinoma. Post-treatment declines in serum PSA levels were observed in $< 10\%$ of men, and only one man had a decrease $> 50\%$ in his serum PSA level.

The current results are similar to results from a recent study of anastrozole, another third-generation aromatase inhibitor, in men with androgen-independent prostate carcinoma. In a Phase II prospective study, Santen et al. reported no response or disease stabilization among 14 men who were treated with anastrozole.[16] However, patients in that study had higher median PSA levels and more extensive prior treatment compared with the men in our study.

Testosterone is converted to estradiol by the action of the aromatase enzyme system in peripheral tissues. In normal men, mean serum estradiol concentrations are approximately 50% of the levels in premenopausal women, and they are higher than the levels in postmenopausal women.[22] Androgen deprivation therapy decreases serum concentrations of testosterone by $> 95\%$ and decreases serum concentrations of estradiol by $>80\%$.[23] Baseline serum concentrations of estradiol were below the lower limit of detection in all of our study patients. Accordingly, we were unable to document any further decrease in serum estradiol concentrations after letrozole treatment. We did not evaluate the effect of treatment on tissue levels of estrogens. Our study does not exclude the possibility that aromatase inhibitors are active in men with higher baseline serum estradiol concentrations, and additional studies are needed to evaluate the activity of aromatase inhibitors prior to androgen deprivation therapy.

Previous studies of selective first and second-generation aromatase inhibitors reported higher response rates compared with the rates reported in our study or in the study of another third-generation aromatase inhibitor by Santen et al.[16] Because the first and second-generation aromatase inhibitors are nonselective, their clinical activity probably results from inhibition of sterodogenic enzymes other than aromatase. Other factors also may have contributed to the higher response rates with first and second-generation aromatase inhibitors, including differences in the study populations, concurrent use of glucocorticoids in some studies, and different methods of response evaluation. The inactivity of selective third-generation aromatase inhibitors suggests that future research should focus on other pathways in steroid biosynthesis.

REFERENCES

1. Signoretti S, Loda M. Estrogen receptor beta in prostate cancer: brake pedal or accelerator? *Am J Pathol.* 2001;159: 13–16.
2. Kruithof-Dekker IG, Tetu B, Janssen PJ, Van der Kwast TH. Elevated estrogen receptor expression in human prostatic stromal cells by androgen ablation therapy. *J Urol.* 1996;156: 1194–1197.
3. Veldscholte J, Ris-Stalpers C, Kuiper GG, et al. A mutation in the ligand binding domain of the androgen receptor of human LNCaP cells affects steroid binding characteristics and response to anti-androgens. *Biochem Biophys Res Commun.* 1990;173:534–540.
4. Veldscholte J, Berrevoets CA, Ris-Stalpers C, et al. The androgen receptor in LNCaP cells contains a mutation in the ligand binding domain which affects steroid binding characteristics and response to antiandrogens. *J Steroid Biochem Mol Biol.* 1992;41:665–669.
5. Taplin ME, Bubley GJ, Shuster TD, et al. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *N Engl J Med.* 1995;332:1393–1398.
6. Smith DC, Redman BG, Flaherty LE, Li L, Strawderman M, Pienta KJ. A Phase II trial of oral diethylstilbesterol as a second-line hormonal agent in advanced prostate cancer. *Urology.* 1998;52:257–260.
7. Orlando M, Chacon M, Salum G, Chacon DR. Low-dose continuous oral fosfestrol is highly active in "hormone-refractory" prostate cancer. *Ann Oncol.* 2000;11:177–81.
8. Small EJ, Frohlich MW, Bok R, et al. Prospective trial of the herbal supplement PC-SPES in patients with progressive prostate cancer. *J Clin Oncol.* 2000;18:3595–3603.
9. Glick JH, Wein A, Padavic K, Negendank W, Harris D, Brodovsky H. Tamoxifen in refractory metastatic carcinoma of the prostate. *Cancer Treat Rep.* 1980;64:813–818.
10. Glick JH, Wein A, Padavic K, Negendank W, Harris D, Brodovsky H. Phase II trial of tamoxifen in metastatic carcinoma of the prostate. *Cancer.* 1982;49:1367–1372.
11. Spremulli E, DeSimone P, Durant J. A Phase II study Nolvadex: tamoxifen citrate in the treatment of advanced prostatic adenocarcinoma. *Am J Clin Oncol.* 1982;5:149–153.
12. Torti FM, Lum BL, Lo R, Freiha F, Shortliffe L. Tamoxifen in advanced prostatic carcinoma. A dose escalation study. *Cancer.* 1984;54:739–743.
13. Horton J, Rosenbaum C, Cummings FJ. Tamoxifen in advanced prostate cancer: an ECOG pilot study. *Prostate.* 1988; 12:173–177.
14. Smith MR, Kantoff PW, Oh W, et al. Phase II trial of the antiestrogen toremifene for androgen-independent prostate cancer. *Prostate J.* 1999;1:185–189.
15. Stein S, Zoltick B, Peacock T, et al. Phase II trial of toremifene in androgen-independent prostate cancer: a Penn Cancer Clinical Trials Group trial. *Am J Clin Oncol.* 2001;24:283–285.
16. Santen RJ, Petroni GR, Fisch MJ, Myers CE, Theodorescu D, Cohen RB. Use of the aromatase inhibitor anastrozole in the treatment of patients with advanced prostate carcinoma. *Cancer.* 2001;92:2095–2101.
17. Davies JH, Dowsett M, Jacobs S, Coombes RC, Hedley A, Shearer RJ. Aromatase inhibition: 4-hydroxyandrostenedione (4-OHA, CGP 32349) in advanced prostatic cancer. *Br J Cancer.* 1992;66:139–142.
18. Dearnaley DP, Shearer RJ, Gallagher C, et al. A Phase I/II study with rogletimide in patients with hormone resistant prostatic cancer. *Ann Oncol.* 1994;5(Suppl 8):179.

19. Buzdar A, Howell A. Advances in aromatase inhibition: clinical efficacy and tolerability in the treatment of breast cancer. *Clin Cancer Res.* 2001;7:2620–2635.
20. Trunet PF, Bhatnagar AS, Chaudri HA, Hornberger U. Letrozole (CGS 20267), a new oral aromatase inhibitor for the treatment of advanced breast cancer in postmenopausal patients. *Acta Oncol.* 1996;35(Suppl 5):15–18.
21. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for Phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol.* 1999;17:3461–3467.
22. Khosla S, Melton LJ III, Atkinson EJ, O'Fallon WM. Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. *J Clin Endocrinol Metab.* 2001;86:3555–3561.
23. Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med.* 2001;345:948–955.