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Bicalutamide (Casodex®) in the Treatment of Prostate Cancer: History of Clinical Development

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BACKGROUND. Bicalutamide (Casodex®) is a new nonsteroidal antiandrogen developed for use in patients with prostate cancer. The efficacy and tolerability of bicalutamide as monotherapy and as combination therapy for patients with advanced prostate cancer have been evaluated in randomized clinical trials. Clinical trials are currently in progress to further evaluate bicalutamide as monotherapy in patients with advanced stages of disease and as adjuvant or first-line therapy in patients with early-stage disease.

METHODS. A review of published trials of bicalutamide focusing on dose-ranging investigations, phase II and phase III monotherapy trials, a phase III trial of combined androgen blockade, and a safety overview.

RESULTS. In dose-ranging trials, bicalutamide doses of 10-200 elicited biochemical, objective, and subjective responses; higher bicalutamide doses (up to 600 mg) have also been evaluated. A 50-mg daily dose of bicalutamide was initially evaluated as monotherapy in phase II and phase III trials; in subsequent trials, a 150-mg daily dose was investigated. A 150-mg daily dose is considered to provide equivalent survival outcome compared with castration in patients with locally advanced prostate cancer, whereas the benefits of a better quality of life and better palliation with the 150-mg daily bicalutamide dose relative to castration in patients with metastatic disease needs to be balanced against the small shortfall (median difference, 42 days) in survival. In combination with a luteinizing hormone-releasing hormone agonist analogue (LHRH-A), a 50-mg daily dose of bicalutamide has equivalent efficacy to a corresponding flutamide (250 mg three times daily) combination regimen. Treatment with the bicalutamide combination regimen resulted in a longer median survival than with the flutamide combination regimen. Bicalutamide is well tolerated when used as monotherapy or in combination with a LHRH-A. The benefits of bicalutamide as monotherapy include retention of libido and sexual potency and as combination therapy a lower incidence of diarrhea relative to flutamide.

CONCLUSIONS. A 50-mg daily dose of bicalutamide is sufficient when given in combination with an agent, such as a LHRH-A, that lowers serum testosterone, but higher doses of bicalutamide may be needed when the drug is given as monotherapy. Bicalutamide, 50-mg daily, is a logical first choice for antiandrogen therapy when used in combination with an LHRH-A for the treatment of patients with advanced prostate cancer. Bicalutamide 150-mg daily is considered an effective monotherapy for use in patients with locally advanced disease. Additional clinical trials are currently in progress to further evaluate bicalutamide as a monotherapy for advanced prostate cancer and to assess its value as adjuvant or first-line therapy for early-stage prostate cancer. *Prostate 34:61–72, 1998.* © 1998 Wiley-Liss, Inc.

KEY WORDS: **antiandrogen; combined androgen blockade; bicalutamide; Casodex; prostatic cancer**

INTRODUCTION

Bicalutamide (Casodex®) is a new nonsteroidal antiandrogen, approved in the United States for use in combination therapy, with medical castration, for advanced prostate cancer. The drug is also under inves-

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tigation as primary monotherapy in patients with advanced disease and as adjuvant therapy in patients with early-stage disease.

Bicalutamide, like other nonsteroidal antiandrogens, lacks the progestational activity and side effects associated with steroidal antiandrogens such as cyproterone acetate. Bicalutamide has a unique profile among members of its drug class. Its long plasma-elimination half-life of approximately 1 week is compatible with once-daily dosing [1]. Two other notable advantages for bicalutamide include retention of libido and sexual potency when the drug is administered as a single agent [2,3], and a lower incidence of diarrhea compared with flutamide when either is used in combination with a luteinizing hormone-releasing hormone analogue (LHRH-A) [4].

In early dose-ranging trials in patients with prostate cancer, bicalutamide was assessed using the surrogate disease endpoints of prostatic acid phosphatase (PAP) and later the more sensitive prostate-specific antigen (PSA) [5]. Subsequently, the drug was evaluated in phase II and III trials using subjective and objective measures of disease in patients who had advanced prostate cancer, with castration serving as the control treatment in phase III trials [2,3,6–8]. Doses of 50 mg and, later, 150 mg once daily were administered as monotherapy.

Bicalutamide was also evaluated in conjunction with medical castration (i.e., with an LHRH-A) in the treatment of advanced prostate cancer. This combination of an antiandrogen and castration has been termed "combined androgen blockade" because it suppresses androgen production by the testes and blocks residual adrenal androgens at the receptor level. The combination of the nonsteroidal antiandrogen flutamide and medical castration was shown in some major trials in the 1980s and early 1990s to be more effective than castration alone in the treatment of advanced prostate cancer [9,10]. Thus, bicalutamide (50 mg) combined with an LHRH-A was tested for equivalence to the flutamide (750 mg) plus LHRH-A combination in a phase III study [4,11,12].

This review details key findings regarding the safety and efficacy of bicalutamide at each stage of clinical development, from phase I dose-ranging trials through phase III clinical trials.

CLINICAL EFFICACY AND SAFETY

Dose-Ranging Trials

Doses of 10, 30, and 50 mg were first evaluated in single-dose trials, which demonstrated a linear pharmacokinetic profile and favorable tolerability [1]. These doses were assessed in multiple-dose trials in 116 patients with advanced or metastatic prostate cancer. Initially, the decrease in serum PAP associated with bicalutamide was compared with the decrease commonly observed following castration, i.e., a 50% decrease in the first 8 weeks. The 30- and 50-mg doses were equivalent to castration according to this standard, with 50 mg slightly more effective than 30 mg [13,14]. When the more sensitive PSA marker was assessed in some patients, 50 mg appeared superior to 30 mg and was well-tolerated; thus, 50 mg was selected for evaluation in the initial clinical efficacy trials [15].

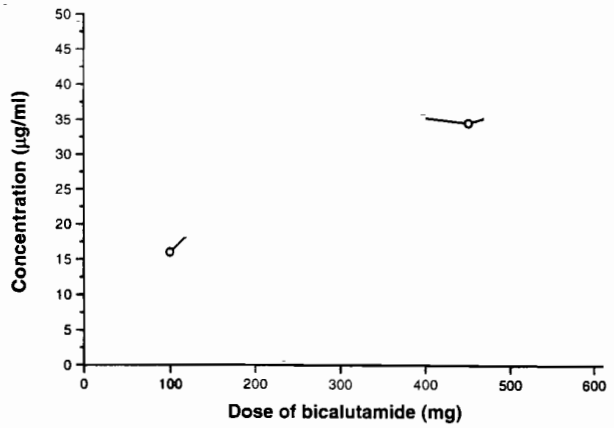

Fig. 1. Steady-state plasma concentrations of bicalutamide as a function of dose.

Although a 50-mg dose was not as effective as castration in clinical trials, evidence of a dose-response curve and the good tolerability profile led to the evaluation of higher doses in an extension of the dose-ranging trial. Doses of 100, 150, and 200 mg were evaluated. At these higher doses, the pharmacokinetic profile continued to be approximately linear, with a small but increasing departure from linearity with doses above 150 mg (Fig. 1). There was an increasing PSA dose-response (Fig. 2), and no dose-related tolerability issues emerged [16,17]. Objective and subjective responses occurred at doses ranging from 10–200 mg (Table I). For these reasons, still higher doses were targeted for evaluation. Notably, at higher doses, bicalutamide was not expected to face increasing competition for receptor sites from testosterone, given that the serum testosterone concentration plateaus during the first month of treatment and remains within the normal range for most patients [18].

A dose of 300 mg once daily was assessed, with higher doses, in increments of 150 mg, to be evaluated against the next lower dose as well as against castration. The 300-mg dose has been administered to 20 patients, the 450-mg dose to 85 patients, and the 600-mg dose to 33 patients. No increase in pharmacological side effects or other adverse events were observed

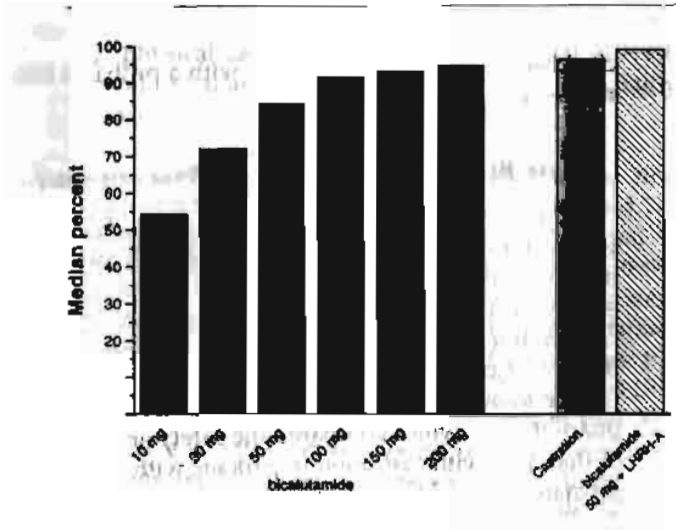

Fig. 2. Prostate-specific antigen response for bicalutamide monotherapy (10–200 mg), castration, and bicalutamide plus a luteinizing hormone-releasing hormone analogue.

TABLE I. Objective and Subjective Response Rates for Bicalutamide as Monotherapy

Dose (mg)	N[a]	Objective response rate (%)	Subjective response rate (%)
10	42 (13)	14	0
30	47 (17)	47	24
50	527 (401)	58	53
100	56 (19)	73	53
150	64 (238)	66	61
200	29 (8)	90	50

[a]N, number of patients assessed for objective response. In parentheses, number of patients assessed for subjective response, i.e., patients with symptoms at entry.

at these doses. The decreases in PSA with these were comparable to that observed with 200 mg and with castration. Furthermore, the plasma steady-state drug concentration curve is less than linear at doses above 200 mg (Fig. 1). Decreases in PSA with the 450-mg and 600-mg doses were comparable with that seen with castration (Fig. 3). A potential for increasing therapeutic benefit at doses higher than 200 mg may exist, although this was not demonstrated by dose-related increases in serum PSA reduction. The tolerability of these high dose levels is well-documented by the lack of a dose-related increase in adverse effects.

Phase II Efficacy Trials Evaluating 50-mg Monotherapy

Based on the theory that adequate blockade of the androgen receptor could result in therapeutic benefits

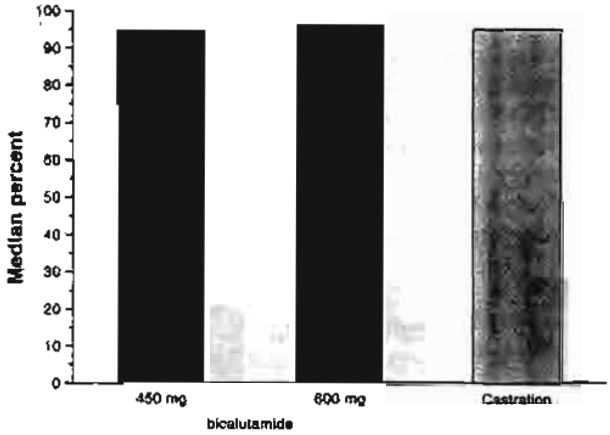

Fig. 3. Prostate-specific antigen response for bicalutamide monotherapy (450 mg and 600 mg) and castration.

for patients with advanced prostate cancer, bicalutamide was evaluated as monotherapy. A 50-mg dose was selected initially because of its effectiveness in reducing serum PAP and PSA, both demonstrated to be surrogate markers of clinical response in earlier castration trials, as well as its excellent tolerability in dose-ranging trials.

Methods. Two multicenter, open-label trials, one in North America [8], and one in Europe and Australia [6,7], assessed the efficacy and tolerability of 50-mg monotherapy. Patients in both trials received daily treatment until their disease progressed, until they died, or until they were withdrawn from the study for any reason, including a serious adverse event. All patients had histologically or cytologically confirmed prostate cancer. North American patients had stage D_2 metastatic disease, and European and Australian patients had either metastatic or locally advanced disease (stage T3 or T4).

The primary indicator of efficacy was objective response relative to the following assessments: prostate size measured (via ultrasound, computerized tomography, or digital rectal exam) at 6-month intervals in North America and 12-week intervals in Europe and Australia; serum PSA concentration measured at 3-month intervals in North America and at 4, 8, and 12 weeks and every 12 weeks thereafter in Europe and Australia; skeletal metastases measured (via bone scan, radiography, or both) at 6-month intervals in North America and at 24-week intervals in Europe and Australia; and extraskeletal metastases measured at 6-month intervals in North America and at 12-week intervals in Europe and Australia. Objective regression or progression were identified by criteria presented in the Appendix.

Subjective response rate was defined as the combined response of changes in bone pain, use of analgesics, and Eastern Cooperative Oncology Group (ECOG) performance status as scored by patients on scales with a range of 0–4 at 1, 2, 3, and 6 months and every 3 months thereafter in North America; and at 4, 8, and 12 weeks and every 12 weeks thereafter in Europe and Australia.

Expected adverse events related to drug class were solicited directly, and other adverse events were solicited indirectly throughout treatment and for 3 months after patients withdrew from treatment.

Results. In the North American trial, 150 patients were treated for a mean of 36 weeks (range, <1–68 weeks). In the European-Australian study, 267 patients were treated for a mean of 49.4 weeks (range, 0.4–113 weeks); overall, 130 patients were treated for more than 1 year.

Among North American patients, the objective response rate was 70%, with 86 (57%) patients exhibiting some degree of regression and 19 (13%) displaying stable disease. Decreases in serum PSA concentration accounted for partial regression in 59 (39%) patients, 32 of whom had a drop of 90% or greater. Of the 60 symptomatic patients, 30 (50%) responded to treatment (95% CI, 36–64%). Among the 88 (59%) patients who reached treatment-failure endpoints, the median time to failure was 34 weeks (95% CI, 26–44 weeks).

Similar to North American results, the objective response rate among European and Australian patients was 71%, with 146 (56%) patients exhibiting some degree of regression and 41 (16%) maintaining stable disease. Of the 66 symptomatic patients, 37 (56%) responded to treatment (95% CI, 44–68%). Among the 174 (65%) patients who reached treatment-failure endpoints, the median time to failure was 35.6 weeks.

Bicalutamide was well-tolerated in both trials, with no significant unexpected adverse events. The most frequently reported events, breast pain and gynecomastia, were attributable to the pharmacological action of the drug. On direct questioning, North American patients reported breast pain and gynecomastia at incidences of 76% and 60%, respectively. The incidence of diarrhea was low (5%). Only 6 patients in the North American trial withdrew because of adverse events; none of these events were considered likely to be related to therapy. Among European and Australian patients, specific querying yielded reports of breast pain and gynecomastia by 63% and 53% of patients, respectively. All other events occurred at an incidence of 5% or lower. A total of 21 patients in this trial withdrew from treatment because of nonfatal adverse events. Of those withdrawals, nine events were deemed probably related to treatment. No patient died because of an adverse event with a probable link to therapy.

Phase III Trials Evaluating 50-mg Monotherapy

In phase II trials, the 50-mg dose of bicalutamide was well-tolerated and was associated with improvement in both objective and subjective measures of disease, with no loss of activity over time, i.e., benefits comparable to those reported for LHRH-A monotherapy. Consequently, evaluation of 50-mg bicalutamide monotherapy was expanded into a controlled phase III trial, which compared the safety and efficacy of that dose with castration in patients with advanced prostate cancer [2]. However, had the current standardized approach to interpreting PSA response been available during analysis of the phase II results, a dose higher than 50 mg might have been chosen for assessment in the first phase III trials; by contemporary standards, the objective response rate in the phase II trials was somewhat low [8].

Methods. Three open-label, randomized trials (designated 301, 302, and 303) compared bicalutamide (50 mg) with castration using a parallel-group design [2]. Patients had histologically or cytologically confirmed prostate cancer with measurable or evaluable metastases (stage D_2) and were physically able to undergo orchiectomy. In two trials (302 and 303), patients chose between surgical and medical castration (3.6 mg goserelin every 28 days); in the other trial (301), patients underwent orchiectomy. Patients underwent treatment until they no longer benefited.

Evaluation of efficacy included: subjective response; time to disease progression as defined by an increase in dimensions of the prostate (on rectal examination), new or worsening bone metastases, new or worsening extraskeletal metastases, or death from any cause; serum PSA concentration (assessed 3 months after patients started treatment); survival; and time to treatment failure, which included death from any cause, objective progression of disease, the addition of a recognized systemic treatment for prostate cancer, any adverse event that led to patient withdrawal from treatment, or patient lost to follow-up. Using an intention-to-treat approach, two overview analyses were performed. The first analysis focused on the endpoints of time to treatment failure and time to objective progression of disease; the second analysis was performed when more mature survival data became available.

Quality of life was assessed by a questionnaire administered at baseline and at 1, 3, and 6 months after patients started treatment, and included queries about the following: pain, limitation of activity, bed disabil-

ity, physical capacity, overall health, sexual interest, sexual functioning, emotional well-being, and vitality scores.

Results. Of the 1,037 patients included in the first combined analysis, 515 received bicalutamide and 522 underwent castration. Treatment failure occurred in 53% of patients on bicalutamide and in 41% of those castrated. Results for time to treatment failure were not consistent across trials. Time to treatment failure was significantly longer for castrated patients vs. patients receiving bicalutamide in trials 301 and 303 ($P < 0.001$ and $P < 0.01$, respectively) but not in trial 302. Objective progression of disease occurred in 46% of patients on bicalutamide and in 35% of those castrated. Here, too, results varied among trials. Subjective response rates attained statistical significance between treatments only in study 301; specifically, symptomatic patients receiving bicalutamide were only 0.43 times as likely to have subjective improvement as were those receiving castration.

Of the 1,196 patients included in the second combined analysis with a longer follow-up time, 595 received bicalutamide and 601 underwent castration. Death occurred in 36% of patients on bicalutamide and in 35% of those castrated. Survival time was not statistically significantly different in two trials (302 and 303). Only in trial 301 was a significant difference ($P < 0.001$) found in favor of castration. In the combined analysis, the difference in median survival time between treatments was only 97 days. After a median follow-up period of 17 months, survival times for patients on bicalutamide vs. those castrated were 25 and 28 months, respectively.

Serum PSA concentration decreased by 85–88% among patients on bicalutamide and by 96–97% for patients castrated. In both groups of patients, the greater the fall in PSA, the smaller the percentage of patients with disease progression (Fig. 4).

Bicalutamide was superior in allowing patients to maintain libido and sexual potency, whereas castration had an advantage at isolated time points in ratings of pain and bed disability. In the first month of treatment, bicalutamide-treated patients were better with regard to overall health, social function, and emotional well-being. At 3–6 months, the castration group had an advantage with respect to these variables. The investigators speculated that this difference might be attributable to the early appearance of hot flashes, which were more prevalent in the castration group, whereas gynecomastia and breast tenderness took several months to develop and were more common in the bicalutamide group.

The most common adverse events were related to pharmacological effects. Gynecomastia occurred in

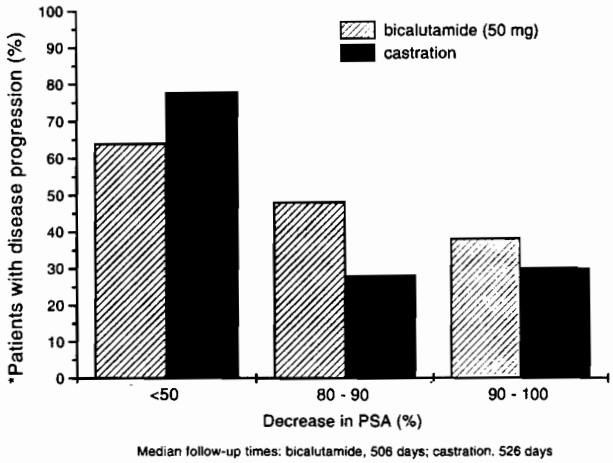

Fig. 4. Percentage of patients with disease progression by percentage decrease in prostate-specific antigen after 3 months. (From Bales and Chodak [2]. Reprinted with permission of Elsevier Science, Inc.).

16–32% of patients on bicalutamide and in fewer than 5% of those castrated; corresponding percentages for breast tenderness were 24–48% for bicalutamide vs. <5% for castration; and respective percentages for hot flashes were 5–10% for bicalutamide compared with 40–45% for castration. Other side effects (such as back pain, bone pain, constipation, infection, and nausea) occurred with comparable frequency in the trials in the bicalutamide and castration groups.

Phase III Trials Evaluating 150-mg Monotherapy

Dose-ranging trials, which had indicated an increasing PSA dose-response from 100–150 mg [16], were expanded into a randomized phase III comparison of the 150-mg dose with castration. The fact that the 50-mg dose had a median survival difference of only 97 days compared with castration suggested that this higher dose might approach equivalence.

Methods. Two multicenter, randomized trials compared bicalutamide (100 and 150 mg) with castration (3.6 mg goserelin/28 days or bilateral orchiectomy) [3]. Initially, patients were randomized to 100 mg/day, 150 mg/day, or castration at a ratio of 2:2:1. However, on the basis of PSA response, the higher dose was chosen for evaluation and patients assigned to the lower dose were excluded from all analyses. All patients had advanced prostate cancer, either stage T3 or T4 nonmetastatic disease with elevated PSA or metastatic disease.

Objective response was rated using the following

assessments: prostate dimensions measured at 12-week intervals; serum PSA concentration measured at baseline and at 4, 8, and 12 weeks and every 12 weeks thereafter; skeletal metastases measured by bone scan and/or X-ray at 24-week intervals; and extraskeletal metastases measured at 12–24-week intervals. Objective regression or progression were identified by criteria presented in the Appendix.

Treatment failure included death from any cause, objective progression of disease, the addition of a recognized systemic treatment for prostate cancer, any adverse event that led to patient withdrawal from treatment, cessation of treatment at the discretion of an investigator or request of patient, or patient lost to follow-up.

Subjective response was determined by changes in bone pain, use of analgesics, and ECOG performance status as scored by patients on scales with a range of 0–4 measured at baseline and at 4, 8, and 12 weeks and every 12 weeks thereafter. A patient's response was considered positive if none of the three components increased in score, if the combined score decreased by three points, or if any of the components decreased in score by two points.

Quality of life was assessed by a questionnaire administered at baseline and at 1, 3, 6, and 12 months after patients started treatment, and included queries about the following: pain, limitation of activity, disability warranting bed rest, physical capacity, overall health, sexual interest, sexual functioning, social functioning, emotional well-being, and vitality scores.

Adverse events were assessed at all visits and for 8 weeks after patients ended treatment.

Results. Patients were randomized in two trials to receive 150 mg of bicalutamide monotherapy (N = 864) or castration (N = 424). They were monitored for a median follow-up time of 200 weeks (data on file, Zeneca Pharmaceuticals). Subjective response ratings were better for metastatic patients with symptoms of disease at entry for those receiving bicalutamide compared with those castrated (odds ratio = 1.68; 95% CI, 1.01–2.79 $P = 0.096$). In patients with metastatic disease (N = 808), castration had a statistically significant advantage compared with bicalutamide in time to treatment failure (hazard ratio = 1.43; 95% CI, 1.20–1.71; $P = 0.0001$), time to disease progression (hazard ratio = 1.44; 95% CI, 1.20–1.73; $P = 0.0001$), and survival time (hazard ratio = 1.30; 95% CI, 1.04–1.64; $P = 0.02$). However, the difference in median survival time between the 150-mg dose of bicalutamide and castration (737 vs. 779 days) was less than the difference between the 50-mg dose of bicalutamide and castration (765 vs. 862 days). In patients with T3 or T4 nonmetastatic disease (N = 480), there appears to be equivalent survival between bicalutamide and castration (hazard ratio = 0.93; 95% CI, 0.66–1.31; $P = 0.67$) with 31% mortality. Because of a qualitative interaction between trials, data for time to treatment failure and survival could not be combined.

Where differences were observed in quality-of-life dimensions, bicalutamide-treated patients showed greater improvement compared with baseline than castrated patients. Both trials indicated that bicalutamide monotherapy had the advantage in allowing patients to maintain libido ($P = 0.029$) and have a better physical capacity ($P = 0.046$).

As expected, the most frequent adverse events (i.e., hot flashes, breast pain, and gynecomastia) were related to pharmacological effects, and relative percentages were consistent with profiles reported in past comparisons of bicalutamide and castration. Generally, other events occurred at similar incidences in both treatment groups. Diarrhea was infrequent in both trials and treatment groups, and was associated with bicalutamide at a rate of 3.9% in one trial and 4.8% in the other. No cardiovascular events occurred at an incidence >5% in either treatment group.

Phase III Trials Evaluating 50 mg of Bicalutamide Combined with LHRH-A

Combined androgen blockade, pairing flutamide with an LHRH-A or nilutamide with orchiectomy, has demonstrated superiority to castration monotherapy in time to disease progression and survival in patients with advanced prostate cancer [9,10,19]. This combination of hormonal manipulations suppresses androgen production by the testes and blocks residual adrenal androgens at the receptor level. Patients with minimal disease appear most responsive [10,20]. However, some trials, including a meta-analysis of 22 trials, have failed to confirm the benefits of combined androgen blockade [21].

The clinical trial program for bicalutamide included a trial to demonstrate the equivalence of bicalutamide combined with LHRH-A to that of flutamide combined with LHRH-A. Equivalence was to be supported by rejecting the null hypothesis that the bicalutamide combination is at least 25% less effective than the flutamide combination, a Food and Drug Administration (FDA) standard of equivalence. A 50-mg dose of bicalutamide was chosen because of its intrinsic activity in patients with advanced prostate cancer; because of animal pharmacokinetic and pharmacodynamic trials, which suggested that this dose is as effective as a 750-mg dose of flutamide when used in combination with an LHRH-A; and because of its tolerability profile in phase II trials. Another factor supporting the selection of the 50-mg dose of bicalu-

tamide was that it has less competition for the androgen receptor when used in conjunction with an LHRH-A, which reduces testosterone concentrations.

Methods. A multicenter, double-blind (for antiandrogen) trial randomized patients in a 2 × 2 factorial design, 1:1 to either bicalutamide (50 mg qd) or flutamide (250 mg tid), and 2:1 to either goserelin acetate (3.6 mg/28 days) or leuprolide acetate (7.5 mg/28 days) [4]. Patients had histologically or cytologically confirmed carcinoma of the prostate, stage D_2 disease, and evaluable bone metastases or at least one measurable nonskeletal lesion.

The primary endpoint was the time to treatment failure, which included: any adverse event that led to withdrawal of the patient from treatment, death, withdrawal of the patient from treatment for any reason, and objective progression of disease as evaluated every 6 months by radionuclide bone scan, serum PSA concentration, and, when indicated, by pelvic or abdominal computed tomography and chest radiograph.

Secondary endpoints were survival, quality of life, and subjective responses. Time to progression was included as an endpoint after the trial commenced. A questionnaire assessing quality of life included 33 multiple-choice questions evaluating pain, limitation of activity, bed disability, social functioning, emotional well-being, vitality, overall health, physical capacity, general symptoms, and treatment-related symptoms. Subjective response rate was defined as the combined response of changes in scored bone pain, use of analgesics, and ECOG performance status.

Adverse events were recorded at every visit until 28 days after the patients completed randomized therapy.

Results. A total of 813 patients participated in the trials; 404 received bicalutamide + LHRH-A and 409 received flutamide + LHRH-A.

At the time of the planned analysis (median follow-up of 49 weeks), 42% of patients receiving bicalutamide + LHRH-A had failed treatment compared with 53% receiving flutamide + LHRH-A (Fig. 5). The time to treatment failure was significantly better for patients on bicalutamide + LHRH-A compared with patients on flutamide + LHRH-A ($P = 0.005$). The hazard ratio for patients on bicalutamide + LHRH-A compared with patients on flutamide + LHRH-A was 0.749, indicative of a 34% greater likelihood of failure in the flutamide combination group (two-sided 95% CI, 0.61–0.92; upper one-sided 95% CI, 0.89). Patients in the flutamide combination group had more withdrawals due to adverse events compared with patients in the bicalutamide combination group (56 vs. 32) and more failures due to progression of disease (98 vs. 73). The advantage of bicalutamide + LHRH-A over flutamide + LHRH-A in the time to treatment failure was largely attributable to a difference in adverse events leading to withdrawal from therapy during the first 200 days, and to a difference in objective progression of disease between 200–500 days.

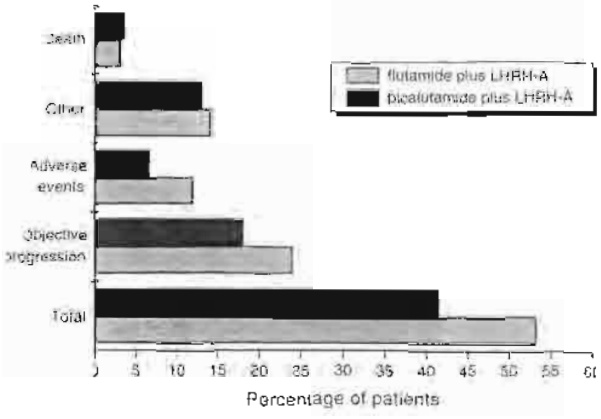

Fig. 5. Reasons for treatment failure, median follow-up of 49 weeks: bicalutamide plus luteinizing hormone-releasing hormone analogue (LHRH-A) vs. flutamide plus LHRH-A (From Kolvenbag and Blackledge [27]. Reprinted with permission of Elsevier Science, Inc.).

After a median of 95 weeks, the improved time to treatment failure for the bicalutamide combination group was upheld, although the difference between treatment groups was no longer statistically significant (Fig. 6) [11]. Treatment failure occurred in 68% of patients in the bicalutamide combination group compared with 72% of patients in the flutamide combination group. The hazard ratio for patients on bicalutamide + LHRH-A compared with patients on flutamide + LHRH-A was 0.87 (two-sided 95% CI, 0.74–1.03, $P = 0.10$). Equivalence between treatments was indicated by the fact that the upper one-sided 95% confidence limit of the hazard ratio was 1.00 (i.e., <1.25). At the time of this analysis, there was a numerical advantage for bicalutamide plus LHRH-A over flutamide plus LHRH-A for time to progression and survival [11].

For the final analysis of the trial, time to progression and survival were reported with a median follow-up time of 160 weeks. Disease progression occurred in 71% of patients on bicalutamide + LHRH-A compared with 72% of patients on flutamide + LHRH-A [12]. The analysis of time to progression included progression data collected prospectively for 561 patients (66%) and retrospectively for 252 patients (34%).

The Kaplan-Meier curve for time to progression is shown in Figure 7. The hazard ratio for patients on bicalutamide + LHRH-A compared with patients on flutamide + LHRH-A was 0.93 (two-sided CI, 0.75–1.10, $P = 0.41$); the two treatments were equivalent, as

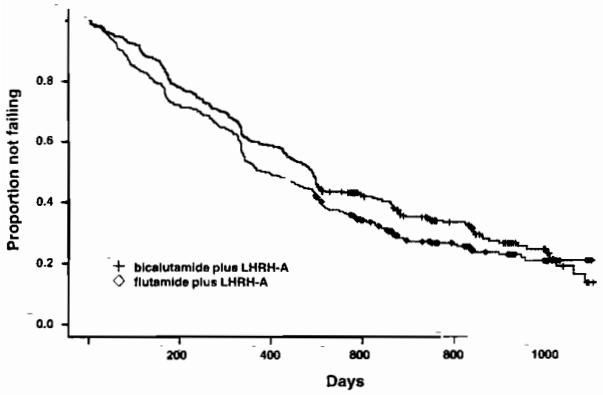

Fig. 6. Time to treatment failure after a median follow-up period of 95 weeks for patients receiving bicalutamide plus luteinizing hormone-releasing hormone analogue (LHRH-A) vs. flutamide plus LHRH-A.

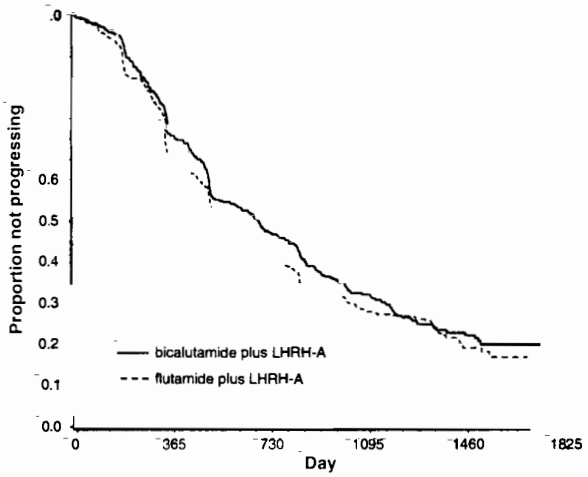

Fig. 7. Kaplan-Meier probability of disease progression (median follow-up time of 160 weeks) for patients receiving bicalutamide plus luteinizing hormone-releasing hormone analogue (LHRH-A) vs. flutamide plus LHRH-A (From Schellhammer et al. [12]. Reprinted with permission of Elsevier Science, Inc.).

indicated by an upper one-sided 95% confidence interval of 1.07 [12].

After a median of 160 weeks, mortality was equivalent between groups (53% bicalutamide + LHRH-A compared with 57% for flutamide + LHRH-A) [12]. The small difference was attributable to differences in disease-specific mortality. The hazard ratio for patients on bicalutamide + LHRH-A compared with patients on flutamide + LHRH-A was 0.87 (two-sided 95% CI, 0.73–1.05, $P = 0.15$). The upper one-sided 95% confidence interval was 1.02, meeting the FDA standard for equivalence. Figure 8 displays the Kaplan-Meier curve for survival. Median survival was 180 weeks for bicalutamide plus LHRH-A and 148 weeks for flutamide plus LHRH-A. Quality of life and subjective responses were also similar between treatment groups [4].

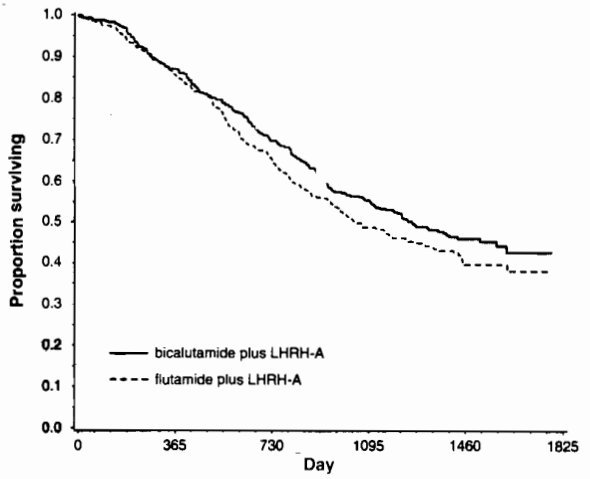

Fig. 8. Survival after a median follow-up period of 160 weeks for patients receiving bicalutamide plus luteinizing hormone-releasing analogue (LHRH-A) vs. flutamide plus LHRH-A (From Schellhammer et al. [12]. Reprinted with permission of Elsevier Science, Inc.).

Except for diarrhea, the overall pattern of withdrawals due to adverse events was similar between treatment groups. Thirty-two patients in the bicalutamide combination group withdrew because of reasons related to safety compared with 56 patients in the flutamide combination group. However, the incidence of diarrhea was more than two times greater in the flutamide combination group compared with the bicalutamide combination group (26% vs. 12%, $P < 0.001$) (Fig. 9). Moreover, 6% of patients withdrew because of diarrhea among patients receiving flutamide + LHRH-A compared with 0.5% of those receiving bicalutamide + LHRH-A. Hematuria was more frequently reported with bicalutamide plus LHRH-A than with flutamide plus LHRH-A (12% vs. 6%, $P = 0.007$). Hematuria did not lead to withdrawal for any patient and was considered unrelated to therapy for 98% of patients in the bicalutamide plus LHRH-A group and 92% in the flutamide plus LHRH-A group (Table II).

As reported in this safety analysis of 808 patients, the incidence of abnormal results of liver function tests was greater in the flutamide combination group (11%) compared with that in the bicalutamide combination group (7%); however, this difference was not significant. Moreover, a higher number of these events were rated as moderate or severe among patients treated with the flutamide combination. Ten patients receiving the flutamide combination were withdrawn from treatment because of abnormalities in liver function, compared with 6 patients receiving the bicalutamide combination.

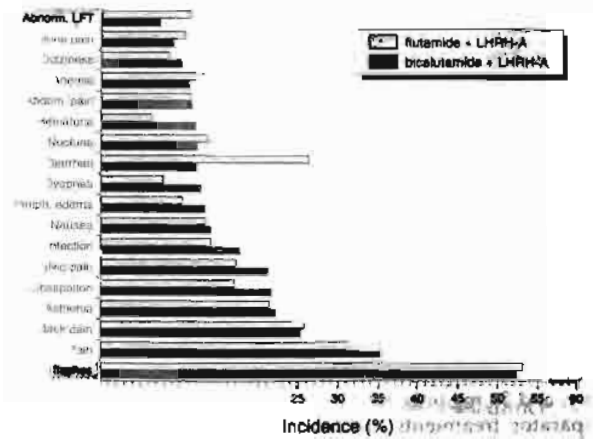

Fig. 9. Adverse events (From Schellhammer et al. [12]. Reprinted with permission of Elsevier Science, Inc.).

TABLE II. Adverse Events Leading to Withdrawal from Therapy in ≥3 Patients in the Bicalutamide plus LHRH-A and Flutamide plus LHRH-A groups*

	Number of patients	
	bicalutamide plus LHRH-A (n = 401)	flutamide plus LHRH-A (n = 407)
Diarrhea	2	25
Liver function abnormalities	6	10
Nausea, vomiting, or both	3	8
Hot flashes	4	2
Kidney failure	1	2
Congestive heart failure		2

*(From Schellhammer et al. [12]. Reprinted with permission of Elsevier Science, Inc.).

Antiandrogen withdrawal syndrome. Reports of withdrawal responses, typically defined as decreases of 50% or greater in serum PSA, after discontinuation of flutamide or bicalutamide therapy underscored the need to determine under double-blind conditions whether the phenomenon is common to both antiandrogens, and to determine to what extent, upon antiandrogen withdrawal, a PSA response is associated with a clinical response.

To achieve these aims, an observational study [22] was initiated as part of a controlled, double-blind (for antiandrogen therapy), multicenter trial [4] comparing the efficacy and tolerability of the antiandrogens bicalutamide and flutamide, each used in combination with LHRH-A therapy, in patients with stage D_2 prostate cancer. The primary study objective was to determine whether reductions of PSA would occur following withdrawal of double-blind antiandrogen therapy (flutamide or bicalutamide) for patients with clinical progression or a rising PSA concentration.

Twenty-two patients, 14 withdrawn from bicalutamide and 8 withdrawn from flutamide, were assessed for serum PSA concentration every week for at least 6 weeks and ever 2 weeks thereafter up to a maximum of 12 weeks.

Four (29%) of the patients withdrawn from bicalutamide and 4 (50%) withdrawn from flutamide displayed decreases of at least 50% in serum PSA concentration, with the greatest drops generally occurring among patients who received bicalutamide. Patients treated with bicalutamide experienced the PSA response over a 4–8-week period, whereas those treated with flutamide responded within the first few days following withdrawal, a pattern probably attributable to the respective 1-week and 5.2-hr half-lives of bicalutamide and hydroxyflutamide (i.e., the active metabolite of flutamide). Although this trial was not designed to make a statistical comparison between the withdrawal responses to flutamide vs. bicalutamide, it is the first to demonstrate the antiandrogen withdrawal syndrome using a double-blind design. Evidence to date suggests that patients who show progression of disease while receiving treatment with an antiandrogen (or any drug having its actions mediated by a steroid receptor) may benefit from a period of withdrawal followed by assessment before receiving additional treatments [23].

Bicalutamide Monotherapy as Secondary Therapy

Fifty-two patients who had failed orchiectomy or therapy with an LHRH-A were treated with bicalutamide (150 mg) [24]. Although there were no objective responses, either partial or complete, 13 (32%) of 41 evaluable patients had stable disease. There was a statistically significant ($P = 0.03$) decrease in pain after 3 months of treatment. The median survival time was 15 months.

Patients with rising serum concentrations of PSA and progressive disease were enrolled in a trial evaluating bicalutamide (150 mg) as treatment for hormone-refractory prostate cancer [25]. All patients received a variety of hormonal therapies and/or chemotherapy prior to treatment with bicalutamide. Six of 30 patients responded to bicalutamide (i.e., >50% decrease in PSA); the patients who responded had failed previous therapy with flutamide and were controlled for the flutamide-withdrawal response, which was observed in only one of these patients.

Scher et al. [26] observed that 10 of 26 patients who previously had shown a response to flutamide withdrawal had greater than a 50% decline in serum PSA

concentration after initiation of bicalutamide (200 mg) as second-line hormonal therapy.

Bicalutamide as Adjuvant Therapy

In 1995, a large trial program was initiated to evaluate bicalutamide (150 mg monotherapy) vs. placebo in patients with early prostate cancer. Patients were randomized to 2 years of treatment after they had received therapy of curative intent (either prostatectomy or radiation); in some trials, patients were randomized after they chose watchful waiting. This trial is pivotal in prostate cancer research in that it will assess not only recurrence-free survival, but also overall survival.

SAFETY OVERVIEW

Bicalutamide has accrued an excellent tolerability profile in more than 3,900 people enrolled in clinical trials who have received doses ranging from 10–600 mg without dose-related increases in adverse events. The most frequent adverse events (breast tenderness, gynecomastia, and hot flashes) are attributable to pharmacological effects of antiandrogen therapy. The incidence of other events associated with withdrawal of androgens, such as changes in the skin (i.e., dryness, pruritis, and rash), is 2% or lower with bicalutamide [27].

It is essential that therapy for a malignant indication does not cause other illness and that it can be well-tolerated. In combination therapy with LHRH-A, flutamide therapy is associated with diarrhea in about 26% of patients compared with about 12% of patients receiving bicalutamide [12]. In the compassionate-use program for bicalutamide, 53 (98%) of 54 patients who had intolerable diarrhea while receiving flutamide therapy were able to continue antiandrogen therapy when switched to therapy with bicalutamide [28]. Moreover, patients receiving monotherapy with bicalutamide report incidences of diarrhea similar to those reported by patients receiving castration or placebo in other trials [29–31].

Other side effects with flutamide have been reported less frequently. Abnormal liver enzyme tests were reported more frequently for patients treated with flutamide plus an LHRH-A (11%) as compared with those treated with bicalutamide plus an LHRH-A (7%); however, this difference was not significant (P = 0.07) [4]. Furthermore, 20 cases of fatal hepatotoxicity have been associated with the use of flutamide [32]; although fewer patients have been exposed to bicalutamide, no cases of fatal hepatotoxicity caused by bicalutamide have been reported to date.

Hypertension, heart failure, angina pectoris, and myocardial infarction were the cardiovascular adverse events reported in >2% of more than 1,500 patients who received bicalutamide, either as monotherapy or combination therapy, during the clinical trial program (Table III). For both the patients who received bicalutamide and those who received a comparator treatment, the incidences of these adverse events are consistent with the disease profile that could be expected in a male population of this age. Preclinical cardiovascular findings in animal experiments, including shortened P-R interval and increased heart rate, were found not to be relevant to human use of bicalutamide.

TABLE III. Most Frequently Reported Cardiovascular Adverse Events, Regardless of Causality, for Patients Who Received Bicalutamide Therapy in Controlled Clinical Trials

Event	Bicalutamide (%)[a]	Comparator treatment (%)[b]
Hypertension	1.4–7.0	1.9–5.2
Heart failure	3.5–3.7	1.9–3.8
Angina pectoris	0.8–3.0	0.8–2.2
Myocardial infarction	0.8–2.1	0.6–2.8

[a]Bicalutamide therapy included: 50 mg and 150 mg as monotherapy, and 50 mg in combination with an LHRH-A.
[b]Comparator treatments included: castration (surgical and medical), and flutamide (750 mg) in combination with an LHRH-A.

Thyroid and adrenal hyperplasia were observed in toxicology studies in rodents, but these findings were considered species-specific. There is no clinical evidence indicating that bicalutamide has an effect on thyroid or adrenal function.

Although hepatocellular tumors were found in studies conducted in mice, further studies showed that this was a nongenotoxic finding similar to that seen with phenobarbitol. There were no primary hepatic, thyroid, or testicular tumors reported in humans, nor was there any evidence that bicalutamide has carcinogenic potential in humans.

CONCLUSIONS

Bicalutamide appears to be a logical first-choice antiandrogen to be used in combination with medical castration for treatment of advanced prostate cancer. Therapy with bicalutamide plus LHRH-A is equivalent to a flutamide plus LHRH-A for time to treatment failure, time to disease progression, and survival. Moreover, bicalutamide has a once-daily dosing regimen, and a lower incidence of diarrhea and withdrawals due to diarrhea than does flutamide when either is used in combination with LHRH-A. Bicalutamide can

also be considered as an effective monotherapy at doses of 150 mg and above in advanced prostate cancer, particularly in patients with nonmetastatic disease. Bicalutamide as monotherapy also has the noteworthy advantage over castration of allowing patients to maintain libido and sexual potency. Clinical trials are in progress to evaluate bicalutamide as monotherapy in advanced disease and as adjuvant therapy or first-line therapy in early stages of prostate cancer are ongoing.

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APPENDIX. Objective Response Criteria*

Classification	Objective response criteria
Partial regression indicated by any criterion	PSA or PAP concentrations decreased by at least 90% or into normal range during treatment if values were at least twice the upper normal limit at entry.
	Prostate dimension (product of the two largest diameters) decreased at least 50%, provided that one measurement was at least 3 cm at entry.
	Skeletal metastases improved or any osteolytic bone metastases showed healing, as indicated by radiological or isotropic evidence.
	Any measureable extraskeletal metastasis decreased by at least 50%.
Progression indicated by any criterion	Prostate dimension increased by at least 50% compared with the minimum dimension recorded during the trial, provided that one measurement was at least 3 cm at entry.
	Skeletal metastases worsened or new ones developed.
	Extraskeletal metastases increased by at least 25% compared with the minimum dimensions recorded during the trial.
Stable disease	No objective progression, and insufficient evidence to classify as partial regression.

*Adapted from Soloway et al. [8].