A Controlled Trial of Bicalutamide versus Flutamide, Each in Combination with Luteinizing Hormone–Releasing Hormone Analogue Therapy, in Patients with Advanced Prostate Carcinoma

Analysis of Time to Progression

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BACKGROUND. A randomized, multicenter trial, double-blind for antiandrogen therapy, compared the antiandrogens bicalutamide and flutamide, each combined with luteinizing hormone–releasing hormone analogue therapy (LHRH-A) in 813 patients with Stage D_2 prostate carcinoma. An analysis of time to progression (median follow-up, 95 weeks) was performed to augment previous analyses of time to treatment failure and time to death.

METHODS. Patients were randomly assigned 1:1 to double-blind antiandrogen therapy, receiving either bicalutamide (50 mg once daily) or flutamide (250 mg three times daily), and were assigned 2:1 to LHRH-A with goserelin acetate (3.6 mg every 28 days) or leuprolide acetate (7.5 mg every 28 days). The primary endpoint of the trial was time to treatment failure, defined as an adverse event leading to withdrawal of randomized therapy, objective progression, death, or withdrawal from study therapy for any reason. Secondary endpoints were time to death, quality of life, and subjective response. The current analysis of time to progression included progression data collected prospectively for 561 patients (69%) and retrospectively for 252 patients (31%).

RESULTS. Disease progression occurred for 223 of 404 patients (55%) in the bicalutamide plus LHRH-A group and for 235 of 409 patients (58%) in the flutamide plus LHRH-A group. The hazard ratio for time to progression of bicalutamide plus LHRH-A to that of flutamide plus LHRH-A was 0.9 (two-sided 95% confidence interval [CI], 0.75 to 1.08; $P = 0.26$). The upper one-sided 95% CI was 1.05, which met the definition of equivalence (<1.25).

CONCLUSIONS. At a median follow-up time of 95 weeks, bicalutamide plus LHRH-A and flutamide plus LHRH-A had equivalent time to progression. ***Cancer* 1996; 78:2164–9.** © *1996 American Cancer Society.*

KEYWORDS: antiandrogen, luteinizing hormone–releasing hormone analogue, combined androgen blockade, bicalutamide, flutamide, time to progression.

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In 1992, a Phase III trial was undertaken to compare the efficacy and tolerability of two antiandrogens, bicalutamide (Casodex, Zeneca Pharmaceuticals, Wilmington, DE) and flutamide (Eulexin, Schering Corp., Kenilworth, NJ), used in combination with luteinizing hormone–releasing hormone analogue therapy (LHRH-A), for patients with advanced prostate carcinoma. The trial was designed to test the hypothesis that combined treatment with bicalutamide plus LHRH-A is equivalent to treatment with flutamide plus LHRH-A in the trial cohort. Time to treatment failure was identified as the primary endpoint; secondary endpoints for the trial were time to death, quality of life, and subjective response.

At the time of the planned analysis[1] (median follow-up, 49 weeks), performed when all patients had a minimum follow-up time of 6 months, bicalutamide plus LHRH-A was associated with a statistically significant ($P = 0.005$) improvement in time to treatment failure as compared with flutamide plus LHRH. The difference between groups was attributed to fewer withdrawals from therapy for adverse events (32 vs. 56) and fewer treatment failures for progression events (73 vs. 98) for the bicalutamide plus LHRH-A group.

Although time to progression was not initially evaluated as a trial endpoint, the revelation in planned analysis of more progression events in the flutamide plus LHRH-A group than in the bicalutamide plus LHRH-A group prompted an analysis of time to progression to determine whether a difference between groups was evident in that regard. The analysis of time to progression was performed when the minimum follow-up time for patients was 18 months, with a median follow-up time of 95 weeks. The analysis included data collected prospectively and retrospectively from patients who were withdrawn from therapy for reasons other than progression.

MATERIALS AND METHODS

A full description of the materials and methods of this trial has previously been published.[1,2]

Patient Population

Patients were age 18 years or older and had histologically or cytologically confirmed adenocarcinoma of the prostate gland, Stage D_2 disease, evaluable bone metastases, or at least one measurable nonskeletal metastatic lesion (irradiated lesions were not considered evaluable). Patients were excluded for any of the following reasons: prior systemic therapy for prostate

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carcinoma, any malignancy (other than cancer of the skin or prostate) within the past 5 years, an Eastern Cooperative Oncology Group (ECOG) performance status score of 3 or 4, a life expectancy of less than 3 months, or any severe concomitant medical condition that either prevented them from participating in the study or would jeopardize compliance with the study protocol. All patients provided written, informed consent, and the study was approved by the appropriate institutional review boards.

Design

Randomization was 1:1 between bicalutamide and flutamide and 2:1 between goserelin acetate and leuprolide acetate. All assessments for patient eligibility were completed in the 30 days before randomization. Study therapy was initiated within 2 weeks of randomization; therapy with antiandrogen and LHRH-A was begun on the same day. Bicalutamide was supplied in green, film-coated tablets; each tablet contained 50 mg of the micronized drug. Flutamide was supplied in ivory-and-brown opaque capsules; each capsule contained 125 mg of the drug. Antiandrogen therapy was double-blind. Bicalutamide and flutamide were supplied in a double-dummy daily pack containing active antiandrogen and placebo that matched the other antiandrogen. Patients randomized to bicalutamide received 6 placebo capsules and a tablet containing the active drug; patients randomized to flutamide received a placebo tablet and 6 capsules containing the active drug. Goserelin acetate (3.6 mg) was supplied as a biodegradable, D,L(dextrorotatory, levorotatory)-lactic and glycolic acids copolymer, contained in a disposable syringe device; it was administered by subcutaneous injection every 28 days. Leuprolide acetate (7.5 mg) was supplied in vials containing lyophilized microspheres for reconstitution with diluent and was administered as an intramuscular injection every 28 days. Patient compliance with antiandrogen therapy was assessed by tablet and capsule counts; for both bicalutamide and flutamide, compliance was 99%.

Concomitant medications, including analgesics for pain, were permitted during the study. Radiation therapy initiated during the first 4 weeks after randomization was permitted as a concomitant therapy; however, the irradiated sites were not included in the assessment of disease status. Transurethral resection of the prostate was also permitted; however, objective tumor assessments were performed before the procedure to assess the extent of disease progression.

A complete general physical examination was performed, and subjective assessments of pain, use of analgesics, and ECOG performance status were made on Day 1 (the date of randomization) and in Month 1, Month 3, and every 3 months thereafter, until documented treatment failure. Objective tumor evaluation, which was performed within 30 days before the start of the randomized therapy and every 6 months thereafter, included a baseline radionuclide bone scan, serum prostate-specific antigen (PSA) concentrations, and, when indicated, pelvic or abdominal computed tomography (CT) and chest radiography. Laboratory tests, which included total white cell count, red cell count, hemoglobin, platelet count, glucose, calcium, blood urea nitrogen, serum creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase, were performed on Day 1 and in Month 1, Month 3, and every 3 months thereafter. SmithKline Beecham Clinical Laboratories (Van Nuys, CA) performed all hematologic and biochemical assays.

Efficacy

Efficacy was assessed on an intent-to-treat basis. For the planned analysis, all patients were included in the analyses of time to treatment failure and time to death. The planned analysis included data from all patient visits completed by the date the last recruited patient completed 6 months of follow-up; the second analysis was performed when all patients had completed at least 18 months of follow-up. The primary end point was time to treatment failure. Secondary end points were time to death, quality of life, and subjective response.

Treatment failure was defined as any of the following: an adverse event leading to withdrawal of randomized therapy, objective progression, death, or withdrawal from study therapy for any reason, such as a patient's unwillingness to continue or an investigator's decision to remove a patient from the study.

Progression was defined as the appearance of one or more new bone metastases or worsening of existing bone metastases on bone scan attributable to metastatic disease, or the appearance of one or more new extraskeletal metastases or an increase by 25% or more (compared to the minimum dimensions recorded during the trial) of any existing measurable extraskeletal metastases. In addition, other assessments, e.g., magnetic resonance imaging or CT scans, could be used as a reference for subsequent assessments. A rising PSA concentration was not considered evidence of progression.

Statistical Analysis

The planned analysis sought to demonstrate the equivalence of bicalutamide plus LHRH-A and flutamide plus LHRH-A therapy by rejecting the null hypothesis that bicalutamide plus LHRH-A is at least 25% worse than flutamide plus LHRH-A. Eight hundred pa-

tients were required to demonstrate equivalence of time to treatment failure between the two therapies with at least 80% power and a one-sided alpha level of 5%, assuming an exponential distribution of treatment failure times (median of 12 months) with uniform accrual over 24 months and 6 additional months of follow-up.

Time to treatment failure and time to death were calculated from the date of randomization to the date of treatment failure or death. The date of the last physical examination was considered the censoring time for patients who had not failed treatment; the date of the last patient contact was considered the censoring time for patients who had not died. Patients who refused the therapy to which they were randomized were classified as failing treatment at Day 0; these patients were monitored to assess survival outcome.

Cox's proportional hazards regression model was used to assess relative effects of the antiandrogens adjusting for relevant covariates (LHRH analogue, baseline extent of disease, and baseline ECOG performance status). The hazard ratios, with 95% confidence intervals (CI), of bicalutamide plus LHRH-A to flutamide plus LHRH-A were calculated, as was the upper one-sided 95% confidence limit of bicalutamide plus LHRH-A to flutamide plus LHRH-A. In addition, Kaplan–Meier plots of estimates of time to treatment failure and survival distributions were generated.

For the analysis of time to progression, data were included from all randomized patients and from all patient visits completed by the date the last recruited patient completed 18 months of follow-up. When patients failed treatment for reasons other than progression or death, assessment of disease status was determined by the investigator. The data for these patients were collected retrospectively, but the criteria for assessment of progression were identical to those stipulated in the protocol.

Time to progression was calculated from the date of randomization to the date of progression. The date of death was considered to be the date of progression for patients who had died without evidence of progression. The date of the last physical examination was considered to be the censoring time for patients who had shown no evidence of disease progression.

Cox's proportional hazards regression model was used to assess relative effects of the antiandrogens, adjusting for relevant covariates such as LHRH-A, baseline extent of disease, and baseline ECOG performance status. The hazard ratios, with 95% CI, of bicalutamide plus LHRH-A to flutamide plus LHRH-A were calculated, as was the upper one-sided 95% confidence limit of bicalutamide plus LHRH-A to flutamide plus LHRH-A. In addition, a Kaplan–Meier plot of time-to-progression distribution was generated.

RESULTS

With the exception of the analysis of time to progression, the results of the trial have previously been reported.[1,2]

Patient Population

Eight hundred thirteen patients participated in the study at 60 investigational sites; 404 patients were assigned to bicalutamide plus LHRH-A and 409 to flutamide plus LHRH-A. The two groups formed by randomization were well balanced with respect to pretreatment and demographic characteristics.[1] All 813 patients were included in the analyses of efficacy in accordance with an intent-to-treat approach. The minimum follow-up time for all patients was 18 months; the median follow-up time was 95 weeks. The trial will remain double-blind for antiandrogen therapy until completion of a final time-to-death analysis.

Time to Treatment Failure and Time to Death

Results of the planned analysis have previously been published.[1] At the time of analysis (median follow-up, 49 weeks), bicalutamide plus LHRH-A was associated

TABLE 1
Progression Status of Patients

Method of data collection	No. of patients						
	Progression		No progression		Not assessed		
	Bicalutamide plus LHRH-A	Flutamide plus LHRH-A	Bicalutamide plus LHRH-A	Flutamide plus LHRH-A	Bicalutamide plus LHRH-A	Flutamide plus LHRH-A	Total
Prospective	160	159	129	113	0	0	561
Retrospective	63	76	39	44	13	17	252
Total	223	235	168	157	13	17	813

LHRH-A: luteinizing hormone-releasing hormone analogue therapy.

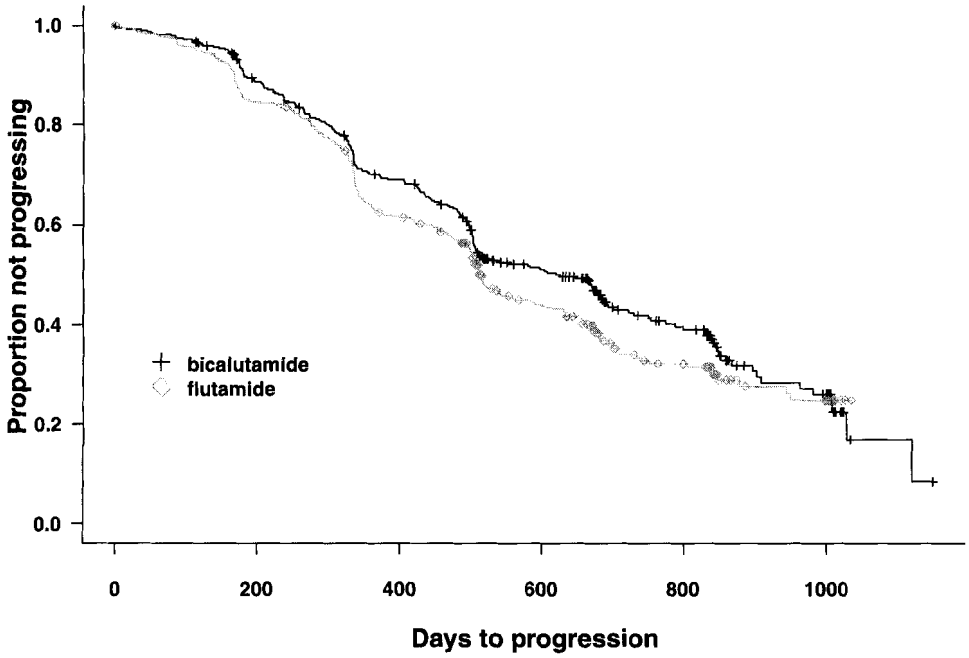

FIGURE 1. Time to progression is represented (median follow-up time, 95 weeks) for patients receiving bicalutamide plus luteinizing hormone–releasing hormone analogue therapy (LHRH-A) and for those receiving flutamide plus LHRH-A. The Kaplan–Meier probability-of-progression model is used.

with a statistically significant ($P = 0.005$) improvement in time to treatment failure as compared with flutamide plus LHRH-A. The results of a subsequent analysis (median follow-up, 95 weeks) supported the previous findings of an improved time-to-treatment failure for the bicalutamide plus LHRH-A group; however, the difference between the groups was not statistically significant.[2]

The hazard ratio of goserelin acetate plus antiandrogen to leuprolide acetate plus antiandrogen was 1.045 for time to treatment failure and 0.84 for time to death; the differences between LHRH-A groups were not statistically significant for either endpoint.

Time to Progression

Table 1 summarizes the progression status of the randomized patients. Of the 813 randomized patients, data were collected prospectively for 561 patients and retrospectively for 252 patients. A total of 458 patients had disease progression (223 bicalutamide plus LHRH-A and 235 flutamide plus LHRH-A), and 325 patients (168 bicalutamide plus LHRH-A and 157 flutamide plus LHRH-A) had no progression. Progression status was not assessed in 30 patients; these patients had only a baseline objective tumor assessment and were censored at Day 0.

TABLE 2
Analysis of Time to Progression, Time to Treatment Failure, and Time to Death (Median Follow-Up, 95 Weeks)

	Hazard ratio[a]	95% CI	*P*-value
Time to progression	0.9	0.75–1.08	0.26
Time to treatment failure	0.87	0.74–1.03	0.1
Time to death	0.88	0.69–1.11	0.29

CI: confidence interval.

[a] Represents hazard ratio for bicalutamide plus luteinizing hormone–releasing hormone analogue therapy (LHRH-A) to flutamide plus LHRH-A.

The Kaplan–Meier probability of progression is displayed in Figure 1. The hazard ratio for time to progression of bicalutamide plus LHRH-A to flutamide plus LHRH-A was 0.9, indicating that patients in the bicalutamide plus LHRH-A group were less likely to have progression of disease over the given period of time than those in the flutamide plus LHRH-A group. This difference between the two groups was not statistically significant (two-sided 95% CI, 0.75–1.08). The upper one-sided 95% confidence limit was 1.05, which meets the definition of equivalence (<1.25).

The hazard ratio of goserelin acetate plus antiandrogen to leuprolide acetate plus antiandrogen for time to progression was 0.981; the difference between LHRH-A groups was not statistically significant.

DISCUSSION

This study was designed to test the hypothesis that bicalutamide plus LHRH-A is equivalent to flutamide plus LHRH-A for the treatment of patients with Stage

D_2 prostate carcinoma. Time to treatment failure was selected as the primary endpoint of the trial because it provided an overall assessment of a therapy's benefit in terms of its efficacy and safety, whereas time to death was considered a secondary endpoint for the trial. Time to progression was not initially evaluated as a trial endpoint; however, an analysis of time to progression was warranted when the planned analysis[1] of the trial disclosed that the number of progression events in the flutamide plus LHRH-A group was higher than in the bicalutamide plus LHRH-A group. This analysis was performed when the minimum follow-up time for patients was 18 months (median follow-up, 95 weeks).

Our results indicate that bicalutamide plus LHRH-A is equivalent to flutamide plus LHRH-A regarding time to progression. As shown in Table 2, the results reported in this article for time to progression are consistent with previously reported results[2] from this trial for the endpoints of time to treatment failure and time to death with an identical median follow-up time of 95 weeks.

There was a limitation to the analysis of time to progression in that data were collected retrospectively from patients who failed therapy for reasons other than progression. As a consequence, outcome with regard to progression was not recorded for all patients at the specified time points. Because assessments obtained retrospectively were likely obtained at longer intervals than assessments obtained prospectively, a potential bias was introduced to favor a longer time to progression for the treatment group with the greater number of withdrawals for adverse events. Conversely, a potential bias to favor a shorter time to progression for the same group of patients was operative for those who were withdrawn from combination therapy and consequently denied the potential therapeutic benefits of antiandrogen therapy.

The results of the current analysis for time to progression, together with previously published analyses[1,2] from this trial for time to treatment failure and time to death, indicate that bicalutamide plus LHRH-A is as effective as flutamide plus LHRH-A when used in the treatment of patients with advanced prostate carcinoma.

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