Fulvestrant versus Anastrozole for the Treatment of Advanced Breast Carcinoma in Postmenopausal Women

A Prospective Combined Analysis of Two Multicenter Trials

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BACKGROUND. Fulvestrant (ICI 182,780) is a new type of estrogen receptor (ER) antagonist that down-regulates the ER and has no known agonist effects. The authors report the prospectively planned combined analysis of data from 2 Phase III trials comparing fulvestrant 250 mg monthly ($n = 428$) and anastrozole 1 mg daily ($n = 423$) in postmenopausal women with advanced breast carcinoma (ABC) who previously had progressed after receiving endocrine treatment.

METHODS. The primary endpoint was time to progression (TTP). Secondary endpoints included objective response (OR), duration of response (DOR), and tolerability. The trials were designed to demonstrate superiority of fulvestrant over anastrozole. Noninferiority of fulvestrant versus anastrozole was determined using a retrospectively applied statistical test.

RESULTS. At a median follow-up of 15.1 months, ≈ 83% of patients in each treatment arm had progressed. The median TTP was 5.5 months in the fulvestrant group and 4.1 months in the anastrozole group, and the OR rates were 19.2% and 16.5% for fulvestrant and anastrozole, respectively (although the difference between treatments was not statistically significant). In patients who responded, further follow-up (median, 22.1 months) was performed to obtain more complete information on DOR; the median DOR (from randomization to disease progression) in patients who responded to treatment was 16.7 months in the fulvestrant group and 13.7 months in the anastrozole group. In a statistical analysis of DOR (using all randomized patients; from the start of response to disease progression), DOR was significantly longer for patients in the fulvestrant group compared with patients in the anastrozole group. Both drugs were tolerated well; withdrawals due to drug-related adverse events were 0.9% and 1.2% in the fulvestrant group and the

Supported by a grant from AstraZeneca Pharmaceuticals.

Dr. Robertson has received research grants and speaker's honoraria from AstraZeneca and Novartis, and he has served on the advisory board of AstraZeneca. Dr. Howell has received speaker's honoraria from and served on the advisory board of AstraZeneca. Dr. Ellis has received research grants from Genentech and Novartis and speaker's honoraria from AstraZeneca, Genentech, and Novartis; and he has performed consulting work for Johnson & Johnson and Novartis. Dr. Come has performed consulting work for and received speaker's honoraria from AstraZeneca and Novartis. Dr. Buzdar has received research grants from AstraZeneca, Bristol-Myers Squibb, Chugai, Eli Lilly, Genentech, Pharmacia, and Taiho Pharmaceuticals. Dr. Webster and Dr. Morris are employees of AstraZeneca.

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Received January 29, 2003; revision received March 24, 2003; accepted March 24, 2003.

DOI 10.1002/cncr.11468

anastrozole group, respectively. The incidence of joint disorders was significantly lower in the fulvestrant group ($P = 0.0036$).

CONCLUSIONS. Fulvestrant was tolerated well and was at least as effective as anastrozole in the second-line treatment of patients with ABC. This new hormonaltherapy may provide a valuable treatment option for ABC in postmenopausal women. ***Cancer*** **2003;98:229–38.** *© 2003 American Cancer Society.*

KEYWORDS: fulvestrant, estrogen receptor antagonist, duration of response, combined analysis.

The most widely used hormonal treatment for patients with breast carcinoma is the antiestrogen tamoxifen. Most patients with hormone-sensitive breast carcinoma currently receive tamoxifen at some stage during their treatment. Many of these patients eventually develop tamoxifen-resistant disease, which leaves clinicians with the problem of how best to manage patients with hormone-sensitive tumors. Other hormonal therapies include the selective aromatase inhibitors (AIs), including anastrozole and letrozole, and the steroidal agent exemestane. Both anastrozole[1,2] and letrozole[3] are effective and well tolerated. Fulvestrant (Faslodex™) is a new estrogen receptor (ER) antagonist that, unlike tamoxifen, is devoid of agonist activity.[4] Binding of fulvestrant to the ER induces a rapid loss of ER protein from breast carcinoma cells.[5] Fulvestrant down-regulates the ER in a dose dependent manner, as indicated by a dose-related reduction in the ER index.[6] Compared with tamoxifen, fulvestrant consistently reduces tumor progesterone receptor (PgR) content.[6] This novel mode of action distinguishes fulvestrant from all other antiestrogens currently in clinical use (e.g., tamoxifen, toremifene, and raloxifene).

In preclinical studies, fulvestrant was markedly more effective than tamoxifen at inhibiting the growth of human breast carcinoma cells in vitro.[7] Furthermore, fulvestrant was effective against tamoxifen-resistant breast carcinoma xenographs in an in vivo mouse model.[8] Phase I clinical trials demonstrated that a short-acting formulation of fulvestrant administered daily for 7 days before primary breast surgery was tolerated well and had antiestrogenic and antiproliferative effects,[9] whereas a Phase II study with the current long-acting formulation, which was administered once monthly, showed that fulvestrant was effective in women who had breast carcinoma that progressed after tamoxifen therapy.[10–12]

The current article reports the combined analysis of 2 Phase III clinical trials (Trial 0020 and Trial 0021), each of which compared a once-monthly intramuscular (i.m.) injection of fulvestrant 250 mg with a once-daily oral dose of the third-generation, nonsteroidal AI, anastrozole 1 mg. Both were multicenter, randomized, controlled, parallel-group trials. Each trial compared the efficacy and tolerability of fulvestrant and anastrozole in postmenopausal women with advanced breast carcinoma (ABC) who previously had disease progression after receiving endocrine treatment. The results for the individual trials have been reported previously.[13,14] Statistical plans included prospectively designed analyses of the combined data that are presented in the current report.

MATERIALS AND METHODS

Data were combined from 2 trials (Trial 0020 and Trial 0021) comparing the efficacy and tolerability of fulvestrant 250 mg given by intramuscular (i.m.) injection once monthly with anastrozole 1 mg given orally once daily. Trial 0020 was an open-label, randomized, multicenter, parallel-group trial conducted in Europe, Australia, and South Africa. Trial 0021 was a double-blind, double-dummy, randomized, multicenter, parallel-group trial conducted in North America. Recruitment for both trials occurred between May 1997 and September 1999. The full methodology for each trial has been reported previously.[13,14]

Patients

All patients were postmenopausal women with locally advanced or metastatic breast carcinoma that progressed after adjuvant endocrine therapy (primarily with tamoxifen) or after first-line endocrine therapy for advanced disease. All women had tumors with evidence of hormone sensitivity (i.e., $\geq$ 12 months of adjuvant hormonal therapy before recurrence or tumor remission or stabilization from hormonal therapy for at least 3 months before progression in patients with advanced disease or known ER or PgR positivity); a life expectancy $>$ 3 months; and, in the opinion of the investigator, were deemed appropriate candidates for subsequent hormonal therapy.

The main inclusion criteria were as follows: a World Health Organization performance status $\leq$ 2, histologic or cytologic confirmation of breast carcinoma with objective evidence of recurrence or progression of disease, and the presence of at least 1 measurable or evaluable (nonmeasurable) lesion. All

patients had to be postmenopausal (i.e., age 60 years or older, or 45 years or older age with amenorrhea for > 12 months or follicle-stimulating hormone levels within postmenopausal range, or previous bilateral oophorectomy). Patients were excluded if they had received prior treatment for breast carcinoma with fulvestrant or an AI or if they had received prior extensive endocrine treatment (more than one prior endocrine treatment) for ABC. Other factors that resulted in exclusion included extensive radiation therapy within the previous 4 weeks (≥ 30% of bone marrow; e.g., the whole pelvis or half of the spine) or cytotoxic treatment within the past 4 weeks, estrogen replacement therapy within 4 weeks of randomization, treatment with luteinizing hormone-releasing hormone analogs within the 3 months before randomization, or any concurrent medical illness or laboratory abnormalities that would compromise safety or prevent interpretation of results.

Bisphosphonate treatment was permitted and, although initiation of treatment during the trial was discouraged, was allowed in the absence of disease progression. Bone lesions in patients who received bisphosphonates that were initiated before or after trial entry were evaluable for progression only.

Patients in both trials were withdrawn from trial treatment at the discretion of the investigator if they had an unacceptable adverse event (AE); if noncompliance with the protocol was demonstrated; or if the patient was unwilling or unable to continue in the trial or had clinical findings (including disease progression) that conflicted with the trial protocol. All patients were monitored for progression and survival after they withdrew (unless consent was withdrawn). All patients gave written informed consent, and the relevant ethics committees approved the studies.

Trial Design

Patients were randomized to receive either fulvestrant 250 mg (1 × 5 mL on Trial 0020 or 2 × 2.5 mL on Trial 0021; $n = 428$) i.m. once monthly or anastrozole 1 mg ($n = 423$) orally once daily. Patients received the treatment to which they were randomized until there was objective evidence of disease progression or until withdrawal from the trial. The trial treatment was then stopped, standard therapy was initiated, and the patients were monitored until death.

The primary endpoint was time to progression (TTP). Secondary endpoints included the objective response (OR) rate (defined as complete response [CR] + partial response [PR] using the Union Internationale Contre le Cancer criteria),[15] duration of response (DOR), time to treatment failure (TTF), time to death (TTD), and tolerability. Clinical benefit (CB: CR + PR + stable disease [SD] ≥ 24 weeks) and duration of CB also were determined.

Trial Treatments

Fulvestrant was supplied as a single-dose, oily, 5% solution; and anastrozole was supplied as round, white, film-coated tablets. In Trial 0020, treatment was open label, and fulvestrant 250 mg was administered as a single, 5-mL injection into the buttocks. Because Trial 0021 was double blind, patients who received fulvestrant also received daily oral placebo tablets, and patients who received anastrozole also received monthly placebo i.m. injections. In Trial 0021, the fulvestrant dose or placebo was given as 2 2.5 mL injections, with 1 injection into each buttock.

Statistical Methods

The trials were designed to detect the superiority of fulvestrant 250 mg in terms of efficacy and tolerability compared with anastrozole 1 mg in postmenopausal women with ABC. For each trial, the final analysis was scheduled to occur when 340 events (i.e., objective disease progression or death) had occurred across the 2 groups. This would provide 90% power to detect a hazard ratio (HR) ≥ 1.43 or ≤ 0.70 for fulvestrant treatment compared with anastrozole treatment, at a significance level of 5%. To achieve the required number of events, the plan was to recruit 392 patients (196 patients in each treatment group) into each of the 2 trials. In addition to the separate analysis of each trial,[13,14] a prospective plan to undertake a combined analysis to provide more precise estimates of the treatment effects was made.

Data on the efficacy parameters were analyzed and summarized on an *intention-to-treat* basis. The protocols for these trials originally contained a fulvestrant 125 mg treatment arm. Because this dose had not been tested clinically, a preliminary summary was performed when 30 patients (across both trials) had been treated for 3 months with fulvestrant 125 mg. At that time, the lack of an OR in any patient resulted in dropping the treatment arm from the study. In addition, an interim analysis of TTP and OR was performed when 170 events had occurred in each trial. Because of this interim analysis, statistical significance levels for TTP and OR were adjusted from 5.0% to 4.86% (and confidence limits were adjusted from 95% to 95.14%). All significance levels are two-sided.

Time to progression

TTP was defined as the number of days from the date of randomization until the date of objective disease progression or until death from any cause, which ever occurred first. Death was regarded as a progression

event in patients who died prior to disease progression. For patients did not have disease progression at the time of data cut-off, data were right censored to the date of the last assessment to allow analysis.

Treatments were compared using a Cox proportional hazards regression model and included the following covariates: trial, age, performance status, measurable disease compared with nonmeasurable disease, receptor status, previous response to hormone therapy, previous use of cytotoxic chemotherapy, and use of bisphosphonate therapy for bone disease. A global test using a 1% significance level was performed to determine whether there were significant treatment-by-baseline covariate interactions by considering a model that contained all treatment-by-baseline covariate interactions apart from trial. In addition, a separate test for the presence of an interaction between trial and treatment also was undertaken using a 5% significance level. Both tests were nonsignificant. A nonsignificant treatment-by-trial interaction test indicated that it was appropriate to combine the trials. Estimates of the treatment effects are expressed as HRs together with the corresponding confidence intervals (CIs) and *P* values. TTP also was summarized using Kaplan–Meier curves for each treatment group, and the median TTP was calculated.

Best objective response

Each patient was assessed for their OR at each visit to the clinic. A best OR of CR was assigned if a patient had no clinical, radiologic, or biochemical evidence of residual lesions on 1 visit with no evidence of disease recurrence or death within the subsequent 4 weeks. A best OR of PR was assigned when disease progression was not evident and disease was improved compared with the baseline assessment, with no evidence of disease recurrence or death within the subsequent 4 weeks.

The proportions of patients who had an OR were compared across the two treatments using a logistic regression model (with the same covariates that were used for TTP). A global test using a 1% significance level was performed to determine whether there were significant treatment-by-baseline covariate interactions by considering a model that contained all of the treatment-by-baseline covariate interactions apart from trial. In addition, a separate test for the presence of an interaction between trial and treatment also was undertaken using a 5% significance level. Both tests were nonsignificant, and the nonsignificant treatment-by-trial interaction test indicated that it was appropriate to combine the trials.

Fulvestrant was compared retrospectively with anastrozole for noninferiority with respect to OR and TTP using a one-sided CI of 95.57%. These limits were identical to using the upper limit of the 95.14%, two-sided CI for the analysis of TTP and the lower limit of the 95.14%, two-sided CI for the difference in response rates of OR. Based on the historic performance of anastrozole (compared with megestrol acetate) of a median TTP of approximately 5 months, the criterion for noninferiority was established by an independent group of experts who agreed that the two-sided 95% CI for the TTP HR should allow a median TTP of < 4 months for inferiority of fulvestrant to anastrozole. The requirement for showing noninferiority for TTP, therefore, was based on an upper one-sided confidence limit for the TTP HR not greater than 1.25, thus ruling out a deficiency of 25% for the experimental treatment. This criterion was used previously for United States regulatory submissions of hormonal treatments for patients with ABC. In the same submissions, the requirement for demonstrating noninferiority in terms of response rate was based on ruling out a deficiency in the difference in response rates of $> 10\%$ (upper one-sided CI not greater than 1.10). Consequently, these criteria were used to assess the noninferiority of fulvestrant relative to anastrozole in the current trial.

Time to treatment failure

TTF was defined as the number of days from randomization until the earliest occurrence of disease progression, death from any cause, or withdrawal from treatment. For assessment purposes, data from patients who did not have treatment failure at the time of data cut-off were right censored to the last assessment date. Any patient who did not receive any trial therapy was assigned an uncensored TTF of 0 days. Statistically, TTF was analyzed using a method similar to that used to analyze TTP. The tests for treatment-by-covariate interactions were not significant, and the nonsignificant treatment-by-trial interaction test indicated that it was appropriate to combine the trials.

Duration of response

The median DOR at 22.1 months of follow-up was calculated only for patients who had an OR. DOR was defined as the number of days from randomization until the first day on which disease progression was observed. Patients who died before they reached progression were classed as completing their response at time of death. The DOR was summarized using Kaplan–Meier curves for each treatment group, and the median DOR also was calculated for each group. In addition, a statistical analysis of DOR was per-

formed using all randomized patients (defined for responders as the time from onset of response to disease progression and, for nonresponders, as zero).

Duration of clinical benefit

CB was defined as the achievement of an OR or of SD > 24 weeks. For patients who achieved CB, the duration of that benefit was calculated as the time between the date of randomization and the first date when disease progression was observed or when death occurred. Data for CB were summarized in the same manner as data for DOR.

Time to death

The protocol called for analyzing the TTD when > 50% of patients had died. At the time of data analysis, only 35.6% of patients had died: Therefore, no formal statistical analyses were conducted for TTD.

Tolerability

All safety data were listed and summarized according to the treatment received. AEs were presented using the *Coding Symbols for Thesaurus of Adverse Reaction Terms* terminology. At the outset of the trial, seven AEs that were considered relevant to endocrine therapy were predefined for statistical analysis. These were gastrointestinal disturbances, hot flashes, vaginitis, weight gain, thromboembolic disease, urinary tract infection, and joint disorders (including arthralgia, arthrosis, and arthritis). The analysis of the predefined AEs was performed using a logistic regression analysis. Results are presented as an ORs, 95% confidence limits, and *P* values.

RESULTS

Patient Characteristics

The intention-to-treat population for the current combined analysis was 851 patients, including 428 patients in the fulvestrant 250 mg group and 423 patients in the anastrozole 1 mg group. The majority of patients (96% in the fulvestrant group and 97% in the anastrozole group) had been treated previously with tamoxifen, and a few had received megestrol acetate (0.70% in the fulvestrant group and 0.71% in the anastrozole group) and droloxifene (0.93% in the fulvestrant group only).

Characteristics of the patients in the two treatment groups are shown in Table 1. The fulvestrant-treated and anastrozole-treated groups were matched well in terms of age, weight, breast carcinoma history, prior therapy, extent of recurrent disease, and ER/PgR status. Patients in Trial 0021 were slightly heavier (fulvestrant group: mean weight, 71.2 kg; anastrozole group: mean weight, 72.7 kg) compared with patients in Trial 0020 (fulvestrant group: mean weight, 68.9 kg; anastrozole group: mean weight, 67.8 kg). Prior use of cytotoxic chemotherapy was more common among patients in Trial 0021 than among patients in Trial 0020 (63% vs. ≈ 43%, respectively), and more patients in Trial 0020 had unknown ER and PgR status (Table 2).

TABLE 1
Demographic Characteristics of Patients[a]

	Combined studies (Trials 0020 and 0021)	
	Fulvestrant 250 mg/month (*n* = 428)	Anastrozole 1 mg/day (*n* = 423)
Characteristic	No. (%)	No. (%)
Age (yrs)		
Mean	63 (—)	63 (—)
Range	33–89 (—)	33–94 (—)
Weight (kg)		
Mean	70 (—)	70 (—)
Range	37–127 (—)	40–134 (—)
Prior treatment		
Cytotoxic chemotherapy	223 (52.1)	220 (52.0)
Endocrine therapy for advanced disease	236 (55.1)	226 (53.4)
Adjuvant endocrine therapy	243 (56.8)	235 (55.6)
Hormone receptor status		
ER and/or PgR positive	342 (79.9)	352 (83.2)
ER/PgR status unknown	64 (15.0)	52 (12.3)
ER/PgR negative	22 (5.1)	19 (4.5)
Metastatic or recurrent disease at baseline		
Breast	29 (6.8)	38 (9.0)
Skin	83 (19.4)	76 (18.0)
Bone	205 (47.9)	202 (47.8)
Liver	95 (22.2)	101 (23.9)
Lung	119 (27.8)	120 (28.4)
Lymph nodes	136 (31.8)	139 (32.9)
Other	49 (11.4)	26 (6.1)
Extent of metastatic or recurrent disease at baseline		
Soft tissue only	23 (5.4)	21 (5.0)
Bone only	85 (19.9)	83 (19.6)
Visceral only	69 (16.1)	86 (20.3)
Lymph node only	37 (8.6)	38 (9.0)
Not recorded	1 (0.2)	3 (0.7)
Mixed[b]	213 (49.8)	192 (45.4)
Measurable lesions[c]	245 (57.2)	249 (58.9)
Nonmeasurable lesions	183 (42.8)	174 (41.1)

ER: estrogen receptor; PgR: progesterone receptor.

[a] Patients may have been in more than one category.

[b] Mixed was defined as breast and /or a combination of skin, bone, liver, lung, or lymph nodes.

[c] Measurable lesions were lesions that were measurable clinically in 2 perpendicular axes with at least 1 dimension that measured ≥2.5 cm or measurable using imaging in 2 perpendicular axes with at least 1 dimension that measured ≥1.0 cm.

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