Fulvestrant versus Anastrozole for the Treatment of Advanced Breast Carcinoma

A Prospectively Planned Combined Survival Analysis of Two Multicenter Trials

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BACKGROUND. Fulvestrant is an estrogen receptor antagonist with no agonist effects. In the second-line treatment of advanced breast carcinoma, fulvestrant was shown previously to be as effective as the third-generation aromatase inhibitor, anastrozole, in terms of time to disease progression and objective response rates. The authors reported the overall survival results from these studies.

METHODS. A prospectively planned, combined, overall survival analysis was performed, including data from two Phase III trials that compared the efficacy and tolerability of fulvestrant (250 mg monthly; $n = 428$) with anastrozole (1 mg daily; $n = 423$) in the treatment of postmenopausal women with advanced breast carcinoma who had disease progression after receipt of previous endocrine treatment.

RESULTS. At an extended median follow-up of 27.0 months (range, 0–66.9 months), 319 (74.5%) patients in the fulvestrant group and 322 (76.1%) patients in the anastrozole group had died. Prolonged survival was observed with both drugs, with 10–20% of patients still alive > 5 years after randomization. The median overall survival was similar between treatments, being 27.4 months and 27.7 months in fulvestrant and anastrozole-treated patients, respectively (hazards ratio, 0.98; 95% confidence interval, 0.84–1.15; $P = 0.809$). Fulvestrant continued to be well tolerated, and was associated with a significantly lower incidence of joint disorders compared with anastrozole ($P = 0.0234$).

CONCLUSIONS. The current analysis showed that fulvestrant was similar to anastrozole with respect to overall survival in the second-line treatment of postmenopausal women with advanced breast carcinoma. ***Cancer*** **2005;104:236–9.**

KEYWORDS: fulvestrant, anastrozole, advanced breast carcinoma, survival.

Fulvestrant (Faslodex; Astrazeneca, Macclesfield, UK) is a new type of estrogen receptor (ER) antagonist with no agonist effects.[1] Fulvestrant down-regulates cellular levels of the ER and it blocks both AF1 and AF2 transcription-activating functions of ER.[2] It leads to a reduction in cellular levels of the progesterone receptor (PgR)[3] and other estrogen-regulated genes potentially important for tumor growth. Two large Phase III trials (Trials 0020 and 0021) were conducted to investigate the efficacy and tolerability of fulvestrant for the

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treatment of postmenopausalwomen with advanced breast carcinoma who had disease progression after receipt of previous endocrine treatment.[4,5] The comparator in these trials was anastrozole (Arimidex; Astrazeneca, Macclesfield, UK), a highly selective third-generation aromatase inhibitor. Anastrozole has been shown to have a statistically significant survival advantage compared with megestrol acetate as a second-line treatment,[6] and to be modestly superior to tamoxifen in the first-line treatment of advanced breast carcinoma.[7] Use of anastrozole in the adjuvant setting is now also increasing after the initial[8] and updated results of the Arimidex, Tamoxifen, Alone or in Combination trial.[9] Trials 0020 and 0021 were of similar design. Therefore, in addition to the separate analyses for each trial, a combined analysis of the data was planned prospectively.

The initial combined efficacy analysis at a median follow-up of 15.1 months showed that fulvestrant was at least as effective as anastrozole with respect to median time to disease progression (TTP; 5.5 months vs. 4.1 months, respectively; hazard ratio [HR], 0.95; 95.14% confidence intervals [CI], 0.82–1.10; $P = 0.48$), objective response (19.2% vs. 16.5%; treatment difference, 2.75%; 95.14% CI, −2.27 to 9.05; $P = 0.31$) and clinical benefit rates (complete response and partial response and stable disease $\geq$ 24 weeks; 43.5% vs. 40.9%; treatment difference, 2.34%; 95% CI, −4.42 to 9.36; $P = 0.51$).[10]

Both fulvestrant and anastrozole were well tolerated in these studies. In an analysis of predefined adverse events (gastrointestinal disturbances, hot flashes, joint disorders, thromboembolic disease, urinary tract infection, vaginitis, weight gain), the only event found to be significantly different between treatments ($P = 0.0036$) was joint disorders, which occurred more frequently in patients receiving anastrozole compared with patients receiving fulvestrant.[10]

We present a recently conducted combined analysis of overall survival for the patients included in Trials 0020 and 0021. Survival analyses were not conducted for the original reports because the predefined protocol requirements of a $\geq$ 75% mortality rate had not been reached.

MATERIALS AND METHODS

Both Phase III studies were of a multicenter, randomized, parallel-group design. Trial 0020 was an open-label trial conducted in Europe, Australia, and South Africa, and Trial 0021 was a double-blind, double-dummy trial conducted in North America. Written informed consent was obtained from all patients, and approval was obtained from the relevant ethical committees. The full methodology for each trial has been published previously.[4,5]

In brief, patients were randomized to receive either fulvestrant 250 mg (1 × 5 mL or 2 × 2.5 mL monthly intramuscular [i.m.] injections) or oral anastrozole 1 mg (daily) until disease progression or withdrawal, and were followed up until death. Subsequent treatment was given at the investigators' discretion. Eligible patients were postmenopausal women with locally advanced or metastatic breast carcinoma whose disease had progressed after receipt of previous endocrine therapy (primarily with tamoxifen). Patients were also required to have ER-positive or PgR-positive tumors or to have shown previous response to hormonal therapy and to have a life expectancy of > 3 months.

For the survival analysis, treatments were compared using a Cox proportional hazards regression model adjusted for the following baseline covariates: treatment, measurable disease, World Health Organization performance status (included as a stratified variable), age, previous use of cytotoxic chemotherapy, previous response to hormone therapy, receptor status (included as a stratified variable), and use of bisphosphonate therapy for bone disease. In the individual trials, and in the combined analysis, it was proposed that an upper CI limit < 1.25 for HR would be considered indicative of noninferiority for TTP. This approach excludes a potential deficiency of $> 25\%$ for the experimental treatment. By analogy, an upper CI limit for the HR of < 1.25 for overall survival may be considered an indication that fulvestrant is not inferior to anastrozole in terms of survival. An analysis of overall survival was performed after $\geq$ 75% of patients had died. The cutoff dates for the survival analysis were June 30, 2002 for Trial 0020 and January 31, 2003 for Trial 0021. The overall incidence of predefined adverse events was also analyzed using the above cutoff dates. For the tolerability analysis, treatments were compared using logistic regression to calculate an odds ratio, corresponding 95% CI values, and P values.

RESULTS

A total of 851 patients were randomized to receive fulvestrant 250 mg ($n = 428$) or to anastrozole 1 mg ($n = 423$) in the 2 studies. All patients had received previous endocrine treatment (adjuvant or for advanced-stage disease) and the majority of patients in both groups had previously received tamoxifen (96% of the fulvestrant group and 97% of the anastrozole group). Many patients also had received previous chemotherapy (52.1% of the fulvestrant group and 52.0% of the anastrozole group). Treatment groups were well

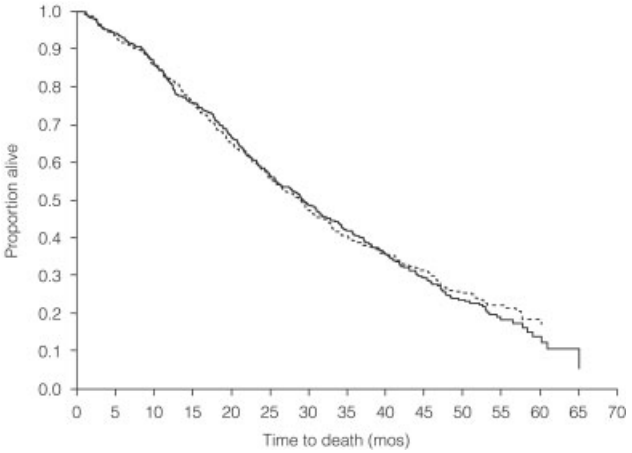

FIGURE 1. Kaplan–Meier curve of time to death: combined analysis of data from Trials 0020 and 0021 including all randomized patients. Dashed line: 250 mg fulvestrant; solid line: 1 mg anastrozole.

TABLE 1
Incidence of Predefined Adverse Events at Data Cut-off for the Survival Analysis: Combined Data from Trials 0020 and 0021

Adverse event	Fulvestrant 250 mg/mo (n = 428) No. (%)	Anastrozole 1 mg/day (n = 423) No. (%)	P value
Gastrointestinal disturbances[a]	206 (48.7)	192 (45.4)	0.4052
Hot flashes	92 (21.7)	94 (22.2)	0.8036
Joint disorders[b]	35 (8.3)	54 (12.8)	0.0234
Thromboembolic disease	15 (3.5)	19 (4.5)	0.4599
Urinary tract infection	37 (8.7)	25 (5.9)	0.1270
Vaginitis	11 (2.6)	8 (1.9)	0.5085
Weight gain	6 (1.4)	9 (2.1)	0.4410

[a] Gastrointestinal disturbances include anorexia, constipation, diarrhea, nausea, and emesis.
[b] Joint disorders include: arthralgia, arthrosis, and arthritis.

matched in terms of age, weight, breast carcinoma history, previous therapy, extent of recurrent disease, and ER/PgR status.[10]

At an extended median follow-up of 27.0 months (range, 0–66.9 months), 319 (74.5%) patients in the fulvestrant group and 322 (76.1%) patients in the anastrozole group had died. The median overall survival was 27.4 months and 27.7 months in the fulvestrant and anastrozole groups, respectively. Figure 1 shows the Kaplan–Meier curve for overall survival for fulvestrant and anastrozole.

Statistical analysis showed that fulvestrant was not significantly different to anastrozole in terms of overall survival (HR, 0.98; 95% CI, 0.84–1.15; $P = 0.809$). Because the upper CI limit was < 1.25, fulvestrant may not be inferior to anastrozole for overall survival. Results from the combined survival analysis were highly consistent with those from the individual trials. The median overall survival periods for fulvestrant and anastrozole, respectively, were 26.4 months and 24.2 months in Trial 0020[11] and 27.7 months and 30.0 months, respectively, in Trial 0021.

Updated safety data indicate that there are no long-term safety concerns with fulvestrant 250 mg treatment. The incidences of predefined adverse events at the time of data cutoff for the survival analysis are shown in Table 1. As previously reported, both treatments were well tolerated, and fulvestrant was associated with a significantly lower incidence of joint disorders.

DISCUSSION

The combined overall survival data from two pivotal Phase III trials suggest that, in the treatment of postmenopausal women with advanced breast carcinoma, fulvestrant is not inferior to anastrozole with respect to overall survival. However, it should be noted that this type of survival analysis is not as robust as the initial TTP and objective response analyses because, after disease progression, patients in each treatment group may receive different subsequent treatments. Nevertheless, prolonged survival was observed with both drugs, with 10–20% patients still alive > 5 years after randomization. Fulvestrant continues to be well tolerated and is associated with a significantly lower incidence of joint disorders compared with anastrozole. The tolerability profiles for the two treatments remain similar to that previously reported.[5,10]

The overall survival data for fulvestrant are similar to values previously observed with third-generation aromatase inhibitors in other second-line treatment studies. For example, at a median follow-up (31 months) in a second-line study comparing anastrozole (1 mg/day) with megestrol acetate (160 mg/day), median overall survival rates of 26.7 months and 22.5 months, respectively, were reported.[6] In addition, at a median follow-up of 45 months, median overall survival values of 25.3 months and 21.5 months were observed in a study comparing letrozole (2.5 mg/day) with megestrol acetate (160 mg/day),[12] and median overall survival values of 29.0 months and 26.0 months were reported in a second study comparing these agents at a median follow-up of 37 months.[13] The median overall survival in a second-line study comparing megestrol acetate with exemestane was 28.4 months for megestrol acetate and has not yet been reached with exemestane.[14] In a further study that compared the efficacy of 2 third-generation aromatase inhibitors, anastrozole and letrozole, median overall survival values were not significantly different for the

2 agents, being 20.3 months and 22.0 months, respectively (HR, 0.95; $P = 0.624$).[15]

In conclusion, fulvestrant is at least as effective as anastrozole with respect to the efficacy end points TTP and objective response, and similar to anastrozole in terms of survival. Fulvestrant treatment is also well tolerated by patients. This, along with its unique mode of action and lack of cross-resistance with tamoxifen, means that fulvestrant is a valuable second-line treatment option for postmenopausal women with hormone-sensitive metastatic breast carcinoma experiencing disease progression or recurrence on tamoxifen.

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