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Fulvestrant (Faslodex™) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: combined results from two multicentre trials

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Abstract

The efficacy of fulvestrant (Faslodex™), a novel oestrogen receptor (ER) antagonist that downregulates the ER and has no known agonist effects, was compared with the aromatase inhibitor anastrozole (Arimidex™) for the second-line treatment of advanced breast cancer in postmenopausal women with visceral and non-visceral metastases. Assessment was by means of a retrospective subgroup analysis of combined data from two randomised, phase III trials. Objective response (OR) rates were similar in patients treated with fulvestrant and anastrozole, respectively (21.9% versus 19.3%—patients with no visceral metastases; 15.7% versus 13.2%—all of the patients with visceral metastases; 18.8% versus 14.0%—patients with visceral metastases only). The proportion of patients with clinical benefit (CB) was also similar between treatments and between subgroups with and without visceral disease. Fulvestrant is at least as effective as anastrozole, providing a valuable treatment option for advanced breast cancer in postmenopausal women with visceral metastases who have failed on prior endocrine therapy.

Keywords: Fulvestrant; Oestrogen receptor antagonist; Anastrozole; Advanced breast cancer; Visceral metastases; Objective response; Clinical benefit

1. Introduction

Endocrine therapy is the treatment of choice in hormone-responsive advanced breast cancer, and the selective oestrogen receptor (ER) modulator tamoxifen is well established as a highly effective option [1]. However, at present no alternative anti-oestrogen therapy is available for patients who progress on tamoxifen therapy. Moreover, visceral metastases are often regarded as less likely to respond to hormonal therapy than non-visceral metastases, with the result that patients with visceral metastases are frequently preferentially treated with cytotoxic chemotherapy [2,3].

Fulvestrant (Faslodex™, AstraZeneca Pharmaceuticals, Macclesfield, UK) is a new ER antagonist that downregulates the ER and is devoid of the partial agonist properties associated with tamoxifen [4]. In preclinical studies, using a murine model of human breast cancer, fulvestrant had greater potency than tamoxifen at inhibiting the growth of human breast tumours, and was effective at inhibiting the growth of tamoxifen-resistant tumours [5,6].

Fulvestrant has recently undergone evaluation for the treatment of advanced breast cancer in postmenopausal women progressing on endocrine therapy. The current second-line options used as standard for tamoxifen-resistant disease are the selective non-

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steroidal aromatase inhibitors, anastrozole and letrozole, and the steroidal agent, exemestane. The clinical trial programme for fulvestrant included two randomised, multicentre trials comparing fulvestrant with anastrozole. One trial was conducted in Europe/Australia/South Africa (trial 0020) [7], the other in North America (trial 0021) [8]. Data from each trial, and also combined data from both trials [9], demonstrate that fulvestrant is at least as effective as anastrozole and is well tolerated.

Trials 0020 and 0021 were prospectively designed to allow analysis of combined data. This article describes a retrospective analysis of the combined data comparing the efficacy of fulvestrant and anastrozole in the subgroup of patients from trials 0020 and 0021 with visceral metastases (i.e., metastases to the liver and/or lung) conducted to determine whether visceral metastases are responsive to these agents.

2. Patients and methods

Trials 0020 and 0021 were conducted concurrently, with recruitment between May 1997 and September 1999. Trial 0020 was an open-label, multicentre, randomised, parallel-group study conducted in Europe, Australia and South Africa. Trial 0021 was a double-blind, double-dummy, multicentre, randomised, parallel-group study conducted in North America.

Detailed methodologies for the two trials [7,8] and also a combined analysis of overall trial data [9] have been reported previously. Both trials were conducted in accordance with the Declaration of Helsinki, with the approval of relevant ethical committees, and with the informed, written consent of all patients.

2.1. Patients

Trials 0020 and 0021 recruited postmenopausal women with locally advanced or metastatic breast cancer with objective evidence of disease recurrence or progression on adjuvant endocrine therapy or following first-line endocrine therapy for advanced disease. Further inclusion criteria included histological or cytological proof of breast cancer, the presence of at least one measurable or evaluable lesion, tumours with evidence of hormone sensitivity (i.e., prior sensitivity to hormonal therapy or known ER or progesterone receptor positivity), a life expectancy of >3 months, a World Health Organization (WHO) performance status of $\leqslant 2$, and no prior fulvestrant or aromatase inhibitor therapy.

Patients were excluded if they had life-threatening metastatic visceral disease (defined as extensive hepatic involvement) or symptomatic pulmonary lymphangitic spread. Patients with discrete pulmonary parenchymal metastases were eligible for inclusion, provided their respiratory function was not compromised as a result of the disease.

2.2. Treatment

Patients were randomised to receive either fulvestrant 250 mg as a once-monthly intramuscular (i.m.) injection (1×5 ml (trial 0020) or 2×2.5 ml (trial 0021)) or anastrozole 1 mg as a once-daily oral dose. Treatment continued until there was objective evidence of disease progression, or until early withdrawal from the trial because of an unacceptable adverse event, non-compliance with the protocol, or withdrawal of patient consent. Thereafter, trial treatment was stopped and standard therapy was initiated. All patients were followed up for progression and thereafter until death (unless the patient refused).

2.3. Combined analysis

This combined analysis considered the following subgroups: (a) patients with no visceral metastases; (b) all patients with visceral metastases; and (c) patients with visceral metastases only. Patients with bone metastases only were included in the analysis for comparative purposes. Patients with bone metastases only who were receiving bisphosphonates at entry were only evaluable for progression, and so were excluded from the efficacy evaluations. Efficacy evaluations comprised the rate of objective response (OR), the rate of clinical benefit (CB), and the durations of OR and CB.

OR was defined as a best overall response of complete response (CR) or partial response (PR). Treatment differences in OR were assessed by comparing the proportion of responders (CR and PR) using a logistic regression model (with covariates for trial and treatment). Results have been presented in terms of the estimated difference in response rates (fulvestrant-anastrozole) and the corresponding 95% confidence interval (CI) and P value. Non-inferiority was concluded if the lower limit of this 95% CI was $\geqslant 10\%$, i.e. a deficiency in the difference in response rates of greater than 10% could be ruled out. This is the same criterion as used for assessing non-inferiority of OR in previous US regulatory submissions of hormonal treatments for advanced breast cancer.

The rate of CB was defined as a best overall response of CR, PR or stable disease (SD) for $\geqslant 24$ weeks. Treatment differences for CB were assessed as described above for OR. The duration of OR was defined from randomisation to disease progression or death (patients with OR only) and the duration of CB was defined from randomisation to disease progression or death (patients with CB only).

A CR was defined as no clinical, radiological or biochemical evidence of residual lesions plus no evidence of

disease recurrence or death within the following 4 weeks. A PR was defined as an improvement in disease compared with baseline and no evidence of disease progression plus no evidence of disease recurrence or death within the following 4 weeks. Data were analysed on an intent-to-treat basis.

3. Results

The intent-to-treat population for trials 0020 and 0021 comprised 851 patients: 428 patients were randomised to receive fulvestrant and 423 patients were randomised to anastrozole. Most patients had previously undergone treatment with tamoxifen (96.0% fulvestrant group; 97.4% anastrozole group).

Visceral metastases were present in 381 patients (44.8%). Of those with visceral metastases, 226 patients (59.3%) also had metastases to skin, bone or other non-visceral tissues, and 155 patients (40.7%) had visceral metastases only. Bone metastases only were observed in 104 patients who were not taking bisphosphonates at entry (55 patients treated with fulvestrant and 49 patients treated with anastrozole). Of the patients with visceral metastases only, lung tumours were more frequently observed in both patient groups (fulvestrant 37 (53.6%); anastrozole 42 (48.8%)) compared with liver tumours (fulvestrant 26 (37.7%); anastrozole 26 (30.2%)). More patients with both lung and liver metastases were randomised to anastrozole (18 (20.9%)) than fulvestrant (6 (8.7%)). Patients were followed for a median 15.1 months from randomisation.

3.1. Rates of objective response and clinical benefit

The OR rate was similar between fulvestrant and anastrozole in all three patient subgroups (Table 1). With fulvestrant, the OR rate was 21.9% in patients without visceral metastases, 15.7% in all of the patients with visceral metastases, and 18.8% in patients with visceral metastases only. In patients with bone metastases only, the OR rate was 12.7 and 6.1% for patients treated with fulvestrant or anastrozole, respectively.

The proportion of patients gaining CB was also similar between treatments in each subgroup, and with fulvestrant reached 47.7% in patients without visceral metastases, 38.2% in all of the patients with visceral metastases, and 49.3% in patients with visceral metastases only. In patients with bone metastases, CB was gained by 60.0 and 53.1% of patients treated with fulvestrant or anastrozole, respectively.

The criteria for non-inferiority of fulvestrant relative to anastrozole were fulfilled for OR and CB rates in each of the subgroups (Table 1).

3.2. Duration of objective response and clinical benefit

The duration of OR for the three patient subgroups is presented in Fig. 1. In patients without visceral metastases, the median duration of OR was 14.3 months with fulvestrant and 13.7 months with anastrozole (Figs. 1a and 2a). Among those with visceral metastases, the median duration of OR was 17.5 months with fulvestrant and 11.7 months with anastrozole, both in all patients with visceral metastases and in those with visceral metastases only.

The median duration of CB was 14.3 months with fulvestrant and 13.7 months with anastrozole in patients without visceral metastases, 11.0 and 8.9 months, respectively, in all of the patients with visceral metastases, and 10.8 and 9.1 months, respectively, in patients with visceral metastases only (Fig. 2b). In patients with bone metastases only, who were not treated with bisphosphonates at entry, the median duration of CB was 19.3 and 21.1 months for patients treated with fulvestrant and anastrozole, respectively.

4. Discussion

This retrospective combined analysis of data from trials 0020 and 0021 was conducted to determine whe-

Table 1
Rates of objective response and clinical benefit in patients without or with visceral metastases

	Total population		No visceral metastases		All patients with visceral metastases		Visceral metastases only	
	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole
Patients (*n*)	428	423	237	233	191	190	69	86
Objective response	82 (19.2%)	70 (16.5%)	52 (21.9%)	45 (19.3%)	30 (15.7%)	25 (13.2%)	13 (18.8%)	12 (14.0%)
Difference in OR rates% (95% CI); *P* value	2.63 (−2.24, 8.71); *P* = 0.32		2.62 (−4.08, 11.28); *P* = 0.48		2.51 (−3.68, 11.77); *P* = 0.49		4.73 (−5.12, 21.49); *P* = 0.43	
Complete response	20 (4.7%)	11 (2.6%)	12 (5.1%)	9 (3.9%)	8 (4.2%)	2 (1.1%)	7 (10.1%)	1 (1.2%)
Partial response	62 (14.5%)	59 (13.9%)	40 (16.9%)	36 (15.5%)	22 (11.5%)	23 (12.1%)	6 (8.7%)	11 (12.8%)
Stable disease for ⩾24 weeks	104 (24.3%)	103 (24.3%)	61 (25.7%)	57 (24.5%)	43 (22.5%)	46 (24.2%)	21 (30.4%)	24 (27.9%)
Clinical benefit	186 (43.5%)	173 (40.9%)	113 (47.7%)	102 (43.8%)	73 (38.2%)	71 (37.4%)	34 (49.3%)	36 (41.9%)
Difference in CB rates% (95% CI); *P* value	2.70 (−3.85, 9.49); *P* = 0.43		3.90 (−5.00, 12.97); *P* = 0.40		1.12 (−8.15, 11.31); *P* = 0.82		7.54 (−7.83, 23.11); *P* = 0.35	

95% CI, 95% Confidence Interval; CB, clinical benefit; OR, objective response.

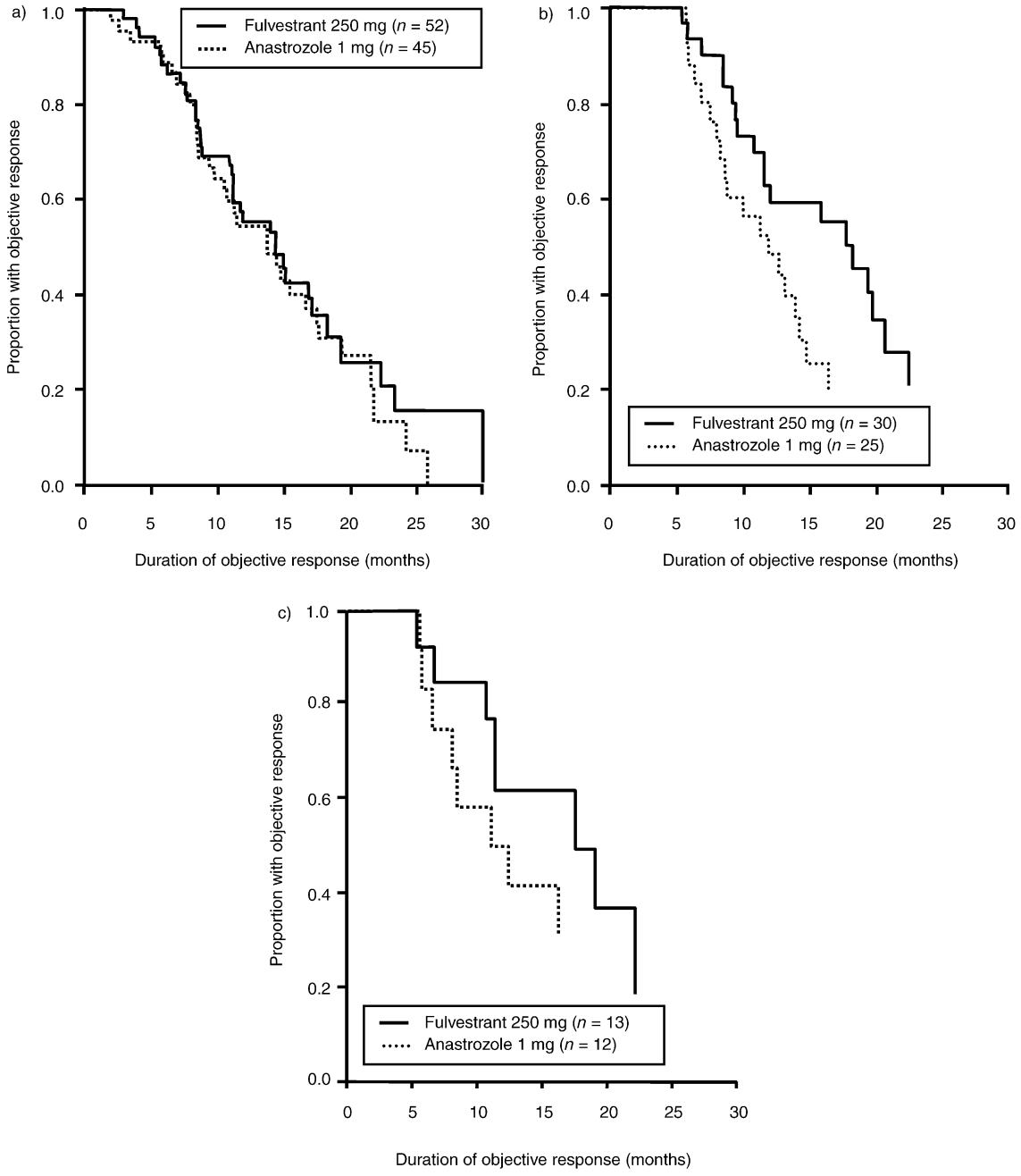

Fig. 1. Duration of objective response in patients (a) without visceral metastases, (b) with visceral metastases and (c) with visceral metastases only.

ther patients with visceral metastases respond similarly to fulvestrant and anastrozole as the overall study population with advanced breast cancer. The two trials had very similar designs and were prospectively designed for combination. Although fulvestrant was administered as a 1 × 5 ml injection in trial 0020 and as 2 × 2.5 ml injections in trial 0021, the pharmacokinetic profiles of fulvestrant given by these two regimens have been shown to be comparable [10] and unlikely to result in different outcomes for fulvestrant treatment.

The results demonstrate that both agents are active in the treatment of visceral metastases and that fulvestrant is at least as effective as anastrozole in patients with or without visceral metastases, as determined by rates of OR and CB. In patients without visceral metastases, the OR rate of 21.9% induced by fulvestrant is comparable to the 19.3% induced by anastrozole.

The activity of fulvestrant and anastrozole in patients with visceral metastases (OR rates: 15.7 and 13.2%, respectively) shows that the presence of visceral metastases is not an indication of non-responsiveness to

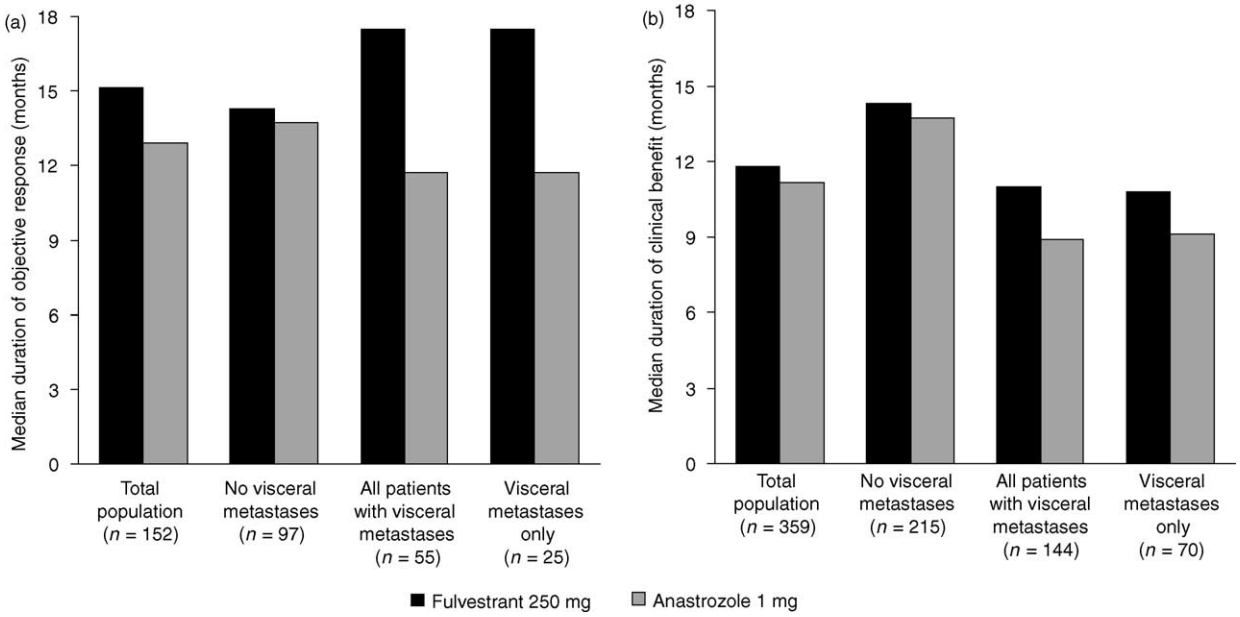

Fig. 2. Median duration of (a) objective response and (b) clinical benefit in patients without or with visceral metastases.

hormonal therapy. In patients with visceral metastases only, the OR rate reached 18.8% with fulvestrant and 14.0% with anastrozole. The median durations of OR of 17.5 months with fulvestrant and 11.7 months with anastrozole (both in all of the patients with visceral metastases and in those with visceral metastases only) suggest that responses to both agents are durable. Notably, in the subgroup of patients with visceral metastases only, seven (10.1%) patients receiving fulvestrant obtained a CR, compared with a single patient (1.2%) in the anastrozole group.

In patients with bone metastases only, 7 (12.7%) patients receiving fulvestrant obtained an OR compared with 3 (6.1%) patients treated with anastrozole. In patients with bone metastases only, both fulvestrant and anastrozole exhibited broadly similar CB rates (60.0 and 53.1%, respectively) and similar median durations of CB (19.3 and 21.1 months, respectively); insufficient patient numbers were available to determine a median duration of response.

Overall, this retrospective analysis demonstrates that the novel oestrogen antagonist fulvestrant, given as a once-monthly 250 mg i.m. injection, is a valuable option for the treatment of advanced breast cancer in postmenopausal women with and without visceral metastases who have failed on prior endocrine therapy. In hormone receptor-positive women and/or those who have shown objective responses to first-line endocrine therapy, the presence of visceral metastases alone should not be a reason for excluding patients from further hormonal treatment, although the clinician should consider additional factors such as the pace of the disease when making a decision regarding further hormonal treatment.

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References

1. Jaiyesimi IA, Buzdar AU, Decker DA, Hortobagyi GN. Use of tamoxifen for breast cancer: twenty-eight years later. *J Clin Oncol* 1995, **13**, 513–529.
2. Ellis MJ, Hayes DF, Lippman ME. Treatment of metastatic breast cancer. In Harris JR, ed. *Diseases of the Breast, 2nd edn*. Philadelphia, Lippincott Williams & Wilkins, 2000, 749–797 [chapter 48].
3. Kuerer HM, Buzdar AU, Singletary SE. Biologic basis and evolving role or aromatase inhibitors in the management of invasive carcinoma of the breast. *J Surg Oncol* 2001, **77**, 139–147.
4. Wakeling AE, Dukes M, Bowler J. A potent specific pure antiestrogen with clinical potential. *Cancer Res* 1991, **51**, 3867–3873.
5. Osborne CK, Jarman M, McCague R, *et al*. The importance of tamoxifen metabolism in tamoxifen-stimulated breast tumor growth. *Cancer Chemother Pharmacol* 1994, **34**, 89–95.
6. Osborne CK, Coronado-Heinsohn EB, Hilsenbeck SG, *et al*. Comparison of the effects of a pure steroidal antiestrogen with those of tamoxifen in a model of human breast cancer. *J Natl Cancer Inst* 1995, **87**, 746–750.
7. Howell A, Robertson JFR, Quaresma Albano J, *et al*. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol* 2002, **20**, 3396–3403.
8. Osborne CK, Pippen J, Jones SE, *et al*. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. *J Clin Oncol* 2002, **20**, 3386–3395.
9. Howell A, Osborne CK, Robertson JFR, *et al*. ICI 182,780 (Faslodex™) versus anastrozole (Arimidex™) for the treatment

of advanced breast cancer in postmenopausal women—prospective combined analysis of two multicenter trials. Abstract presented at ECCO 2001, Lisbon, Portugal.
10. Robertson JFR. A comparison of the single-dose pharmacokinetics of ICI 182,780 ('Faslodex') 250 mg when given as either a one × 5-ml intramuscular injection or two × 2.5-ml injections in postmenopausal women with advanced breast cancer. *Breast Cancer Res Treat* 2000, **64**, 53 (abstr. 172).