

Postmenopausal women who progress on fulvestrant ('Faslodex') remain ...

Vergote, I.;Robertson, J.F.R.;Kleeberg, U.;Burton, G.;et al
Breast Cancer Research and Treatment; May 2003; 79, 2; ProQuest Central
pg. 207



Breast Cancer Research and Treatment 79: 207–211, 2003.
© 2003 Kluwer Academic Publishers. Printed in the Netherlands.

Report

Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy

I. Vergote¹, J.F.R. Robertson², U. Kleeberg³, G. Burton⁴, C.K. Osborne⁵, and L. Mauriac⁶ (for the Trial 0020 and 0021 Investigators)

¹University Hospitals, Leuven, Belgium; ²Nottingham City Hospital, Nottingham, UK;

³Haematologische/Oncologische Praxis, Hamburg, Germany; ⁴Louisiana State University Health Science Center, Shreveport, LA; ⁵Breast Center at Baylor College of Medicine and Methodist Hospital, Houston, TX, USA;

⁶Bergonie Institute, Bordeaux, France

Key words: advanced breast cancer, estrogen receptor downregulation, fulvestrant, sequential therapy

Summary

Purpose. This retrospective evaluation of data from two randomized, multicenter trials examined whether tumor responses to further endocrine therapy were seen in postmenopausal women with advanced breast cancer who had progressed on both initial endocrine therapy, usually tamoxifen, and on the estrogen receptor (ER) antagonist fulvestrant ('Faslodex').

Patients and methods. A combined total of 423 patients received fulvestrant 250 mg as a monthly intramuscular injection. After progression on fulvestrant, some patients received another endocrine therapy. Responses to subsequent endocrine therapy were assessed using a questionnaire sent to the trial investigators. Best responses were classified as a complete or partial response (CR or PR), stable disease (SD) lasting ≥ 24 weeks, or disease progression.

Results. Follow-up data were available for 54 patients who derived clinical benefit (CB, defined as CR, PR or SD) from fulvestrant and who received subsequent endocrine therapy, resulting in a PR in 4 patients, SD in 21 patients, and disease progression in 29 patients. Data were available for 51 patients who derived no CB from fulvestrant and who received further endocrine therapy, resulting in a PR in 1 patient, SD in 17 patients, and disease progression in 33 patients. Aromatase inhibitors were used as subsequent endocrine therapy in >80% of patients.

Conclusions. After progression on fulvestrant, patients may retain sensitivity to other endocrine agents. Fulvestrant provides an additional option to existing endocrine therapies for the treatment of advanced or metastatic breast cancer in postmenopausal women, and may provide the opportunity to extend the sequence of endocrine regimens before cytotoxic chemotherapy is required.

Introduction

Despite advances in detection and treatment leading to improved survival, breast cancer represents a leading form of cancer-related death in women. In Europe, breast cancer was the major cause of cancer-related death, leading to approximately 17% of all deaths in 1995 [1]. For hormone-sensitive breast cancers, endocrine therapy is established as the treatment of choice. The selective estrogen receptor modulator (SERM)

tamoxifen has for many years been the preferred initial treatment for hormone-sensitive, advanced breast cancer, but aromatase inhibitors (AIs) such as anastrozole and letrozole have been shown recently to be at least as effective [2, 3]. These therapies lead to tumor regression in 40–50% of estrogen receptor (ER)-positive patients [2, 3].

Despite an initial response to tamoxifen, all patients eventually undergo disease progression, necessitating the use of a different therapy. Patients

who respond to initial endocrine therapy may be responsive to subsequent endocrine intervention [4, 5]. This sequential use of endocrine therapies offers significant quality-of-life advantages over cytotoxic chemotherapy [4], particularly in elderly patients or those patients with advanced disease, since they offer disease control without the marked adverse events associated with cytotoxic chemotherapy. This sequential use of endocrine agents relies on them possessing different mechanisms of action to overcome cross-resistance, as seen between different SERMs [6]. As a result, the development of novel agents may extend the period of time during which endocrine therapy can be used, thereby deferring the decision to use chemotherapy.

Fulvestrant ('Faslodex') is a new type of antiestrogen, an ER antagonist that dramatically reduces cellular levels of the ER and, importantly, does not possess the partial agonist activity associated with tamoxifen [7, 8]. In preclinical studies, fulvestrant was effective at inhibiting the growth of breast cancer models, both *in vitro* and *in vivo*, including in models of tamoxifen resistance [9, 10]. Phases I and II clinical studies in postmenopausal women with advanced breast cancer who progressed on tamoxifen have demonstrated the efficacy of fulvestrant, with approximately 13/19 (69%) patients showing clinical benefit (CB), without the adverse events associated with tamoxifen (such as hot flashes and night sweats) [11, 12].

Two multicenter phase III trials, prospectively designed to allow the analysis of combined data, compared fulvestrant with anastrozole in postmenopausal women with advanced breast cancer [13, 14]. Fulvestrant was at least as effective as anastrozole and was well tolerated. The work presented here represents the retrospective analysis of combined data from these trials, to evaluate the effects of further endocrine therapies in patients whose tumors became resistant to fulvestrant.

Patients and methods

Trial 0020 was an open, randomized trial conducted in Europe, Australia and South Africa. Trial 0021 was a double-blind, double-dummy, randomized trial conducted in North America. Detailed methodology and results have been previously reported elsewhere [13, 14]. Both trials were conducted with approval from the relevant ethics committees, and all patients gave written, informed consent.

Patients

Patients recruited to trials 0020 and 0021 were postmenopausal women with locally advanced or metastatic breast cancer not amenable to curative treatment who had progressed following prior endocrine therapy for advanced or early disease. Patients had histologically or cytologically confirmed breast cancer, with objective evidence of disease recurrence or progression, and at least one measurable lesion. In addition, all patients demonstrated evidence of hormone sensitivity (either sensitivity to ≥ 1 prior hormonal treatment or known ER, or progesterone receptor positivity), a life expectancy of ≥ 3 months, and a WHO performance status of ≤ 2 .

Treatment

Patients received fulvestrant 250 mg once monthly and continued treatment until evidence of disease progression or any other significant events warranting withdrawal (e.g., unacceptable adverse events, protocol non-compliance, or withdrawal of patient consent). After this point, treatment ceased and patients undertook standard therapy as determined by their individual clinician. Unless consent was withdrawn, patients were monitored after withdrawal for progression and survival until death.

Data collection

A questionnaire was sent to the trial investigators caring for the fulvestrant-treated patients. Information requested included details of the response to fulvestrant during the trial, details of any subsequent endocrine therapy given after progression, and the best response to this therapy. The efficacy of subsequent endocrine therapy was determined from the investigators responses to the questionnaires. In practice, the treatments used were AIs or megestrol acetate, with some patients receiving medroxyprogesterone acetate.

Results

Of the 423 patients who received fulvestrant in trials 0020 and 0021, 186 derived CB, defined as complete response (CR), partial response (PR), or stable disease (SD) for ≥ 24 weeks, according to UICC criteria. Of these, retrospective follow-up data were available for 66 patients who demonstrated CB on fulvestrant and

Table 1. Age and site of disease at baseline in patients who did and did not derive CB from fulvestrant (combined data from trials 0020 and 0021)

	Number of patients	
	Who derived CB from fulvestrant (n = 54)	Who did not derive CB from fulvestrant (n = 51)
Median age (range), years	61.5 (41–81)	66.0 (42–85)
Site of disease (%) ^a		
Breast	2 (3.7)	6 (11.8)
Skin	8 (14.8)	10 (19.6)
Bone	28 (51.8)	26 (50.9)
Liver	7 (12.9)	15 (29.4)
Lung	19 (35.2)	12 (23.5)
Lymph node	16 (29.6)	17 (33.3)
Other	4 (7.4)	8 (15.7)

^aPatients may be counted in more than one category.

Table 2. Response to subsequent endocrine therapy in patients who derived CB from fulvestrant (combined data from trials 0020 and 0021)

	Number of patients			
	PR	SD ≥24 weeks	Progression	Total
Endocrine therapy total	4	21	29	54
AIs	3	16	27	46
Anastrozole	1	13	23	37
Letrozole	2	3	3	8
Formestane	0	0	1	1
Megestrol acetate	1	5	2	8

for 84 who did not achieve CB. Further endocrine therapy was received by 54 patients who achieved CB on fulvestrant and by 51 patients who did not achieve CB on trial therapy. These patients were generally well matched in terms of age and site of disease at baseline (Table 1).

The majority of the patients who achieved CB on fulvestrant (46/54; 85%) (Table 2) subsequently received an AI, either anastrozole (n = 37), letrozole (n = 8) or formestane (n = 1), with the remaining patients (15%) receiving megestrol acetate (n = 8). Overall, subsequent endocrine therapy in this subset of patients resulted in an objective response (OR) in 4/54 patients and CB in 25/54 patients.

Eighty-two percent (42/51) of the patients who did not derive CB from fulvestrant received an AI as

third-line therapy (Table 3): anastrozole (n = 34) or letrozole (n = 8). The remaining patients (18%) were treated with either megestrol acetate (n = 6) or medroxyprogesterone acetate (n = 3). The proportion of patients gaining an OR or CB in response to endocrine therapy was lower (1/51 and 18/51, respectively), compared with patients who gained an initial CB from fulvestrant.

A preliminary analysis of the duration of response data (defined as being from the start of treatment through to the date of progression; DoR) showed that the median DoR for patients (n = 24) who had CB with fulvestrant was 383 days. For patients (n = 18) who did not derive CB on fulvestrant, the DoR on subsequent endocrine therapy was 318 days. Further assessment of endocrine agents subsequent to fulvestrant

Table 3. Response to subsequent endocrine therapy in patients who did not derive CB from fulvestrant (combined data from trials 0020 and 0021)

	Number of patients			
	PR	SD ≥24 weeks	Progression	Total
Endocrine therapy total	1	17	33	51
AIs	1	15	26	42
Anastrozole	1	11	22	34
Letrozole	0	4	4	8
Megestrol acetate	0	1	5	6
Medroxyprogesterone acetate	0	1	2	3

was not performed, due to an imbalance between the numbers of patients treated with each agent.

Discussion

Extending the period during which endocrine therapy may be used as an effective and viable treatment option for advanced or metastatic breast cancer in postmenopausal women is an important goal. No curative treatment is currently available for many of these patients, and the ability of endocrine therapy to induce responses without producing debilitating toxicities is very valuable. Indeed, many patients are able to derive months, or even years, of high-quality life using sequential endocrine treatment [4]. This sequential use depends on the availability of endocrine agents with differential mechanisms of action, thus avoiding problems of cross-resistance between the various therapies.

This report represents the first examination of sequential endocrine therapy incorporating the ER antagonist fulvestrant before AIs. The results demonstrate that after sequential treatment with tamoxifen and fulvestrant, many patients retain sensitivity to further endocrine therapy with third-generation AIs such as anastrozole and letrozole, or progestins such as megestrol acetate. The rates of CB reported here with endocrine therapy after fulvestrant are similar to those reported for therapy with other endocrine agents (30–50%) [15–17]. Similarly, the CB rates obtained after third-line use of AIs reported here are comparable with previous studies [18]. This indicates that there appears to be incomplete cross-resistance between the different endocrine therapies examined.

The data in this report are limited by the retrospective nature of their collection and the lack of randomization inherent in the use of a questionnaire. Nevertheless, within the limitations imposed by the method used here, responsiveness to fulvestrant appears to be associated with a slightly higher response to subsequent endocrine therapy, compared with those patients who failed to show CB on fulvestrant. Many of these observed responses were SD. The clinical relevance of SD has been demonstrated in a study which showed that patients whose disease stabilized for more than 24 weeks after receiving endocrine therapy, exhibited similar survival to patients who achieved an OR [19]. In addition, patients with an SD response to initial endocrine therapy appear to respond to treatment with subsequent endocrine agents equally as well as patients who derive a CR or PR to initial therapy [20]. Importantly, this suggests that despite the development of resistance, a response to one endocrine agent may predict a response to subsequent agents [20, 21]. Thus, only after failure of multiple prior endocrine therapies would patients be candidates for chemotherapy.

Following progression on tamoxifen, fulvestrant provides an effective treatment option in addition to the currently available endocrine therapies for advanced breast cancer. Progression following treatment with an SERM, and subsequent treatment with an anti-estrogen with pure antagonistic properties, does not appear to lead to complete cross-resistance with AIs. Fulvestrant may therefore extend the opportunity for the use of endocrine therapies before reliance on cytotoxic chemotherapy is necessary. In future studies it will be important to examine the activity of fulvestrant after disease progression on AIs, and initial results

indicate that CB is observed in patients receiving fulvestrant subsequent to progression on prior treatment with AIs [22]. Data from this and similar trials will be important in further establishing the positioning of fulvestrant in the endocrine sequence for the treatment of advanced breast cancer.

References

- Bray F, Sankila R, Ferlay J, Parkin DM: Estimates of cancer incidence and mortality in Europe in 1995. *Eur J Cancer* 38: 99–166, 2002
- Nabholtz JM, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, Steinberg M, Webster A, von Euler M: Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *Arimidex Study Group. J Clin Oncol* 18: 3758–3767, 2000
- Mouridsen H, Gershonovich M, Sun Y, Perez-Carrion R, Boni C, Momnier A, Apffelstaedt J, Smith R, Sleeboom HP, Janicke F, Pluzanska A, Dank M, Becquart D, Bapsy PP, Salminen E, Snyder R, Lassus M, Verbeek JA, Staffler B, Chaudri-Ross HA, Dugan M: Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 19: 2596–2606, 2001
- Buzdar AU, Hortobagyi G: Update on endocrine therapy for breast cancer. *Clin Cancer Res* 4: 527–534, 1998
- Hortobagyi GN: Progress in endocrine therapy for breast carcinoma. *Cancer* 83: 1–6, 1998
- Stenbygaard LE, Herrstedt J, Thomsen JF, Svendsen KR, Engelholm SA, Dombornowsky P: Toremifene and tamoxifen in advanced breast cancer – a double-blind cross-over trial. *Breast Cancer Res Treat* 25: 57–63, 1993
- Wakeling AE, Dukes M, Bowler J: A potent specific pure anti-estrogen with clinical potential. *Cancer Res* 51: 3867–3873, 1991
- Robertson JF, Nicholson RI, Bundred NJ, Anderson E, Rayter Z, Dowsett M, Fox JN, Gee JM, Webster A, Wakeling AE, Morris C, Dixon M: Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentylsulfonyl)-nonyl]estra-1,3,5(10)-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer. *Cancer Res* 61: 6739–6746, 2001
- Osborne CK, Jarman M, McCague R, Coronado EB, Hilsenbeck SG, Wakeling AE: The importance of tamoxifen metabolism in tamoxifen-stimulated breast tumor growth. *Cancer Chemother Pharmacol* 34: 89–95, 1994
- Osborne CK, Coronado-Heinsohn EB, Hilsenbeck SG, McCue BL, Wakeling AE, McClelland RA, Manning DL, Nicholson RI: Comparison of the effects of a pure steroidal antiestrogen with those of tamoxifen in a model of human breast cancer. *J Natl Cancer Inst* 87: 746–750, 1995
- Howell A, DeFriend D, Robertson J, Blamey R, Walton P: Response to a specific antiestrogen (ICI 182780) in tamoxifen-resistant breast cancer. *Lancet* 345: 29–30, 1995
- Howell A, DeFriend DJ, Robertson JF, Blamey RW, Anderson L, Anderson E, Sutcliffe FA, Walton P: Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer. *Br J Cancer* 74: 300–308, 1996
- Howell A, Robertson JFR, Quaresma Albano J, Aschermannova A, Mauriac L, Kleeberg UR, Vergote I, Erikstein B, Webster A, Morris C: 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* 20: 3396–2403, 2002
- Osborne CK, Pippin J, Jones SE, Parker LM, Ellis M, Come S, Gertler SZ, May JT, Burton G, Dimery I, Webster A, Morris C, Elledge R, Buzdar A: A 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* 20: 3386–3395, 2002
- Kaufmann M, Bajetta E, Dirix LY, Fein LE, Jones SE, Cervek J, Fowst C, Polli A, di Salle E, Arkhipov A, Piscitelli G, Massimini G: Survival advantage of exemestane (EXE, Aromasin) over megestrol acetate (MA) in postmenopausal women with advanced breast cancer (ABC) refractory to tamoxifen: results of a phase III randomized double-blind study. *Proc Am Soc Clin Oncol* 18: 108a, 1999 (abstract 412)
- Buzdar A, Jonat W, Howell A, Jones SE, Blomqvist C, Vogel CL, Eiermann W, Wolter JM, Azab M, Webster A, Plourde PV: Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. *Arimidex Study Group. J Clin Oncol* 14: 2000–2011, 1996
- Dombornowsky P, Smith I, Falkson G, Leonard R, Panasci L, Bellmunt J, Bezwoda W, Gardin G, Gudgeon A, Morgan M, Fornasiero A, Hoffmann W, Michel J, Hatschek T, Tjabbes T, Chaudri HA, Hornberger U, Trunet PF: Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 16: 453–461, 1998
- Howell A, Howell SJ, Clarke R, Anderson E: Where do selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) now fit into breast cancer treatment algorithms? *J Steroid Biochem Mol Biol* 79: 227–237, 2001
- Robertson JFR, Howell A, Buzdar A, von Euler M, Lee D: Static disease on anastrozole provides similar benefit as objective response in patients with advanced breast cancer. *Breast Cancer Res Treat* 58: 157–162, 1999
- Cheung KL, Willsher PC, Pinder SE, Ellis IO, Elston CW, Nicholson RI, Blamey RW, Robertson JF: Predictors of response to second-line endocrine therapy for breast cancer. *Breast Cancer Res Treat* 45: 219–224, 1997
- Kurebayashi J, Sonoo H, Inaji H, Nishimura R, Iino Y, Toi M, Kobayashi S, Saeki T: Endocrine therapies for patients with recurrent breast cancer: predictive factors for responses to first- and second-line endocrine therapies. *Oncology* 59: 31–37, 2000
- Perey L, Thürlimann B, Hawle H, Bonnefoi H, Aebi A, Pagani O, Goldhirsch A, Dietrich D: Fulvestrant ('Faslodex') as a hormonal treatment in postmenopausal patients with advanced breast cancer progressing after treatment with tamoxifen and non-steroidal aromatase inhibitors: an ongoing phase II SAKK trial. *Ann Oncol* 13: 172P, 2002

Address for offprints and correspondence: Ignace Vergote, University Hospitals Leuven, Department of Gynecologic Oncology, Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium; *Tel.:* +32-16-34-46-35; *Fax:* +32-16-34-46-29; *E-mail:* Ignace.Vergote@uz.kuleuven.ac.be

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.