original article

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Clinical benefit of fulvestrant in postmenopausal women with advanced breast cancer and primary or acquired resistance to aromatase inhibitors: final results of phase II Swiss Group for Clinical Cancer Research Trial (SAKK 21/00)

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Background: The aim of this study was to evaluate the efficacy and tolerability of fulvestrant, an estrogen receptor antagonist, in postmenopausal women with hormone-responsive tumors progressing after aromatase inhibitor (AI) treatment.

Patients and methods: This is a phase II, open, multicenter, noncomparative study. Two patient groups were prospectively considered: group A (n = 70) with AI-responsive disease and group B (n = 20) with AI-resistant disease. Fulvestrant 250 mg was administered as intramuscular injection every 28 (±3) days.

Results: All patients were pretreated with AI and 84% also with tamoxifen or toremifene; 67% had bone metastases and 45% liver metastases. Fulvestrant administration was well tolerated and yielded a clinical benefit (CB; defined as objective response or stable disease [SD] for ≥24 weeks) in 28% (90% confidence interval [CI] 19% to 39%) of patients in group A and 37% (90% CI 19% to 58%) of patients in group B. Median time to progression (TTP) was 3.6 (95% CI 3.0 to 4.8) months in group A and 3.4 (95% CI 2.5 to 6.7) months in group B.

Conclusions: Overall, 30% of patients who had progressed following prior AI treatment gained CB with fulvestrant, thereby delaying indication to start chemotherapy. Prior response to an AI did not appear to be predictive for benefit with fulvestrant.

Key words: advances breast cancer, aromatase inhibitor, endocrine therapy, fulvestrant, postmenopausal, SAKK Trial 21/00

introduction

Most patients with breast cancer have tumors that express estrogen receptors (ERs) and/or progesterone receptors (PgRs) and therefore can potentially benefit from hormonal therapy. Sequential hormonal treatment represents an established approach for hormone-responsive advanced breast cancer (ABC). In postmenopausal patients, tamoxifen, nonsteroidal (anastrozole or letrozole) and steroidal (exemestane) aromatase inhibitors (AIs), are effective [1]. As it is well tolerated, endocrine therapy is the treatment of choice for patients without extensive visceral metastasis and those who cannot endure chemotherapy. A major concern with endocrine treatments is that some tumors are *de novo* hormone resistant and most acquire resistance eventually [2, 3]. The development of new non-cross-resistant endocrine agents is thus urgently required, especially as tamoxifen, AIs or both are now increasingly used in the adjuvant setting [4, 5].

Fulvestrant (Faslodex®; AstraZeneca Pharmaceuticals, Macclesfield, UK) is a steroidal analogue of 17-beta-estradiol. When fulvestrant binds to the ER, it induces a conformational change preventing receptor dimerization. The receptor is rapidly degraded, resulting in a decrease of cellular ER levels. Fulvestrant disables the function of both transcriptional activating factors, AF1 and AF2, and has no estrogen agonist activity contrary to selective estrogen receptor modulators [6, 7]. A major mechanism of resistance to tamoxifen consists of mitogen-activated protein kinase and PI3K/AKT pathways activation by epidermal growth factor receptor (EGFR) and human EGFR-2 (HER2). *In vitro* models have indicated that fulvestrant may disrupt these resistance pathways [8]. In clinical

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studies, the efficacy of fulvestrant in patients with ER-positive ABC has been shown at first-line [9] and second-line [10–12] therapy with similar efficacy to tamoxifen and AI, respectively. The present study aimed at assessing the efficacy of fulvestrant in postmenopausal patients with ABC progressing after treatment with a steroidal or nonsteroidal AI.

patients and methods

study design

This was a phase II open, multicenter, noncomparative study, conducted at eight centers in three countries. Patients were recruited from March 2000 to June 2004, and data cut-off was June 2005. The trial was designed and monitored in accordance with good clinical practice and the Declaration of Helsinki. It was approved by an Independent Ethics Committee at each center, and written informed consent was obtained from all participants.

patients

The study population included postmenopausal women with metastatic disease who had histological or cytological confirmation of breast cancer. Postmenopause was defined as women older than 55 years or older than 45 years and amenorrhea >12 months or with biochemical evidence of postmenopausal hormonal status or having undergone bilateral oophorectomy. All patients had objective evidence of disease progression after ≥12 weeks of treatment with a steroidal or nonsteroidal AI. Further eligibility criteria included evidence of hormone sensitivity with tumor expression of ER and/or PgR, previous ≥12-months adjuvant hormonal treatment before relapse and tumor regression or stabilization for ≥3 months during endocrine therapy. Adequate liver, renal and bone marrow function were also mandatory for inclusion.

Patients with life-threatening visceral metastases (e.g. extensive hepatic or pulmonary involvement or symptomatic pulmonary lymphangitic spread) or a history of brain or leptomeningeal involvement were not eligible. Previous treatment with fulvestrant, previous endocrine therapy with progestin, estrogens, androgens or treatment of breast cancer with more than two different hormonal agents was not accepted. Patients who had received more than one line of chemotherapy for ABC before AI treatment were excluded. Bone-only disease was accepted in the absence of bisphosphonates.

treatment schedule

Patients received fulvestrant 250 mg as a single 5-ml intramuscular injection every 28 (±3) days until objective evidence of disease progression, withdrawal from the trial due to an unacceptable adverse event (AE) or withdrawal of patient consent.

efficacy and safety evaluations

Patients were evaluated prospectively in two different groups for which the expected response rate was different:

- Group A: AI-responsive patients, defined as patients who had progressed while on an AI (anastrozole, letrozole, exemestane or formestane) treatment of ABC after initially experiencing an objective response (OR) or stable disease (SD) for ≥24 weeks.
- Group B: AI-resistant patients, defined as patients who did not respond to AI treatment of ABC or those who had SD for <24 weeks.

World Health Organisation (WHO) criteria were used for tumor assessment. Initially, the primary end point of the trial was evaluation of the efficacy of fulvestrant in terms of OR rate, duration of response, time to progression (TTP) and time to treatment failure (TTF). After an interim analysis in March 2002, a relatively frequent sustained clinical benefit (CB) was observed despite a low OR rate. The study committee thus judged that CB, defined as OR (complete or partial response [CR or PR]) or SD for ≥24 weeks, was a clinically relevant end point by potentially postponing for >6 months the need for chemotherapy in this patients group, who had already received two lines of hormonotherapy for most of them. Therefore, the primary end point was changed to CB rate. The sample sizes for groups A and B were then recalculated. This amendment was submitted to and approved by the Independent Ethics Committees.

Tolerability (local and systemic) and safety of fulvestrant were also assessed.

Clinic visits took place at screening, on day 1 and then every 28 ± 3 days. Screening assessment included medical history, chest X-ray or thoracic computed tomography (CT) scan, isotopic bone scan or skeletal survey, hematology and biochemistry assessments, tumor assessment and WHO performance status (PS). Patients with elevated liver enzymes at screening were further evaluated with a liver ultrasound or abdominal CT scan. Objective tumor assessments were made at each visit for the first 3 months of treatment in those patients with disease that could be assessed by physical examination. Radiological assessments of the tumor were carried out every third month until disease progression.

Duration of CB was calculated from the date of registration to the date of objective progression or death before objective progression. TTF was measured from registration to treatment withdrawal from any cause. TTP was calculated from registration to progression. Patients were monitored for clinical and laboratory toxic effects at each visit and also for 8 weeks following their final injection of fulvestrant. Drug-related AEs were considered to be any documented change in a patient's condition during the study period that had a reasonable possibility of being caused by the trial treatment. All AEs were graded according to their intensity on the basis of the CTC AE version 2.0 grading and were monitored until the end of the follow-up period.

specific assessments

Tumor samples were analyzed centrally (Institut de Pathologie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, with Maryse Fiche, MD, as the responsible pathologist) for HER2 protein status using immunohistochemistry (HercepTest™; Dako, Glostrup, Denmark). Tumors with a 2+ score were also analyzed using FISH to confirm HER2 status (PathVysion™; Abbott AG, Baar, Switzerland).

statistical plan

The size of the trial population was based on the primary end point (CB rate), and calculated separately for each group. In group A, we expected a CB rate of 35%–45%. For a 90% confidence interval (CI) of ±10%, a sample size of 68 patients was required. Group A was closed on 8 January 2004 due to completed accrual. In group B, we expected a CB rate of 25%–30%. According to an optimal two-stage MinMax design [13], a total of 25 patients were required (amendment 3 of April 2002). Accrual in group B, however, was slower than expected due to the nature of the disease observed in patients not responding to AIs, often requiring chemotherapy rather than third-line hormonal treatment. In light of this difficulty, group B was closed early on 23 June 2005, after the inclusion of 20 patients. CIs for CB rates were calculated using the Clopper–Pearson method [14]. Duration of treatment, CB, TTF and TTP were analyzed using the Kaplan–Meier method. As an exploratory analysis, Fisher's exact test was carried out to investigate the association between CB and selected baseline characteristics (e.g. age, sites of metastases, HER2 status) in group A.

results

patients

A total of 90 patients were included in the study, 70 in group A and 20 in group B. Three patients from group A and one patient from group B did not meet the inclusion criteria; therefore, there were in total 86 eligible patients. Sixty-two patients (72%) had a WHO PS of 0 and 22 patients (26%) a PS of 1. Other patient characteristics are summarized in Table 1.

Fifty-six (84%) patients in group A received tamoxifen ($n = 54$), toremifene ($n = 1$) or goserelin ($n = 1$) as treatments in the adjuvant and/or first-line metastatic settings. In that group, all but one patient received an AI in the metastatic setting before inclusion in the trial. The remaining patient received tamoxifen and letrozole in the adjuvant setting and then relapsed under therapy. The vast majority of patients (82%) received a nonsteroidal AI (anastrozole or letrozole); only 12 patients (18%) received a steroidal AI (exemestane).

In group B, 17 patients (89%) received tamoxifen either in the adjuvant setting or as first-line hormonal treatment of metastatic disease. All patients except one received an AI in the metastatic setting. The remaining patient received letrozole for 13 months as adjuvant therapy before relapse.

Most patients in both groups had bone metastases (70% in group A and 58% in group B). A significant number of patients had visceral disease, with 46% of patients in group A and 42% of patients in group B having liver metastases. Two patients were included in spite of an ER- and PgR-negative tumor because their long clinical history indicated hormonal sensitivity, but no CB was observed. They have been incorporated for results analysis.

efficacy

Sixty-three of the 67 patients in group A and all of the patients in group B were evaluable for the assessment of response (Table 2). In group A, one patient experienced a PR and 18 had SD ≥24 weeks, resulting in a CB rate of 28% (90% CI 19% to 39%). Of note, 11 patients (16%) had a SD for >36 weeks and six patients (9%) for >1 year. In group B, to conclude that the treatment was promising, we needed at least six responders out of 25 patients and this number is reached already in the sample of 19 patients. One patient with bilateral lung metastasis experienced a CR and was still receiving treatment >52 weeks after registration; six other patients had SD ≥24 weeks, resulting in a CB rate of 37% (90% CI 19% to 58%). Interestingly, three patients (16%) had SD for >36 weeks in this group.

The median number of fulvestrant injections per patient was four (range: 1–53 in group A; 2–18 in group B), with 456 injections in total in group A and 118 in group B. Overall, the median duration of treatment was 3.8 (range: 0.9–52) months in group A and also 3.8 months in group B (range: 1.8–17.9+

Table 1. Patient and disease characteristics at baseline

	Group A, *n* (%)	Group B, *n* (%)
Eligible patients	67	19
Median age, years (range)	65 (44–84)	70 (39–86)
Tumor localization[a]		
Breast	14 (21)	8 (42)
Skin	13 (19)	5 (26)
Bone	47 (70)	11 (58)
Liver	31 (46)	8 (42)
Lung	17 (25)	5 (26)
Lymph nodes	31 (46)	8 (42)
Others	18 (37)	5 (26)
Metastatic sites: 1 versus 2–3 versus >3	14 (21) versus 39 (58) versus 14 (21)	4 (21) versus 8 (42) versus 7 (37)
Tumor hormone receptor status		
ER+ and PgR+	45 (67)	14 (74)
ER+ and PgR−	12 (18)	2 (11)
ER− and PgR+	0 (0)	0 (0)
ER− and PgR−[b]	1 (1)	1 (5)
HER2/neu positive	4 (6)	2 (11)
Prior radiotherapy	27 (40)	7 (37)
Prior hormonal therapy		
Adjuvant Ta, To or G	26 (39)	6 (32)
Adjuvant and/or metastatic Ta, To or G	56 (84)	17 (89)
Adjuvant AI	1 (1)	1 (5)
AI for metastatic disease	66 (99)	18 (95)
Nonsteroidal AI (anastrozole or letrozole)	54 (81)	12 (63)
Steroidal AI (exemestane)	12 (18)	6 (32)
Prior chemotherapy for metastatic disease	24 (36)	6 (32)

[a]Multiple sites possible.

[b]Patient's medical history indicated the presence of a potentially hormone-responsive tumor.

ER, estrogen receptor; −, negative; +, positive; PgR, progesterone receptor; Ta, tamoxifen; To, toremifene; G, goserelin; AI, aromatase inhibitor.

months). The median TTP was similar in both groups: 3.6 months (95% CI 3.0–4.8 months) for patients in group A and 3.4 months (95% CI 2.5–6.7 months) for those in group B.

The median TTF was 3.6 (95% CI 3.0–4.6) and 3.4 (95% CI 2.5–6.7) months in groups A and B, respectively. Reasons for discontinuing fulvestrant treatment are presented in Table 3. Altogether, for >90% of patients, the reason for discontinuing fulvestrant was disease progression.

When looking retrospectively for factors potentially predictive of CB to fulvestrant, we found that only 11 of the 53 patients (21%) in group A with multiple sites of metastases experienced a CB versus eight of the 14 patients (57%) with one site of involvement ($P = 0.02$; Fisher's exact test). The presence of liver or lung metastases and type of AI treatment received (steroidal versus nonsteroidal) did not seem to influence treatment efficacy, but age appeared to be a predictive factor for CB. Two of the 23 patients <60 years of age (9%) had CB with fulvestrant versus 17 of the 44 patients ≥60 years of age (39%). This consists of a univariate analysis.

HER2 status

HER2 status was determined in 54 patients in group A and 17 patients in group B. The vast majority of patients (93%) had HER2-negative tumors. None of the six patients with HER2-positive disease (HercepTest 3+) reached CB with fulvestrant. Four cases with a 2+ score did not show amplification by FISH and were considered negative. Among patients with HER2-negative status, 16 of 50 (32%) in group A and six of 15 patients (40%) in group B had CB.

tolerability and safety

All eligible patients who received at least one injection of fulvestrant were included in the safety analysis. Fulvestrant treatment was well tolerated and only two patients discontinued treatment due to AE. Drug-related AEs occurring in patients in both groups are shown in Table 4. All patients experienced grade 1–2 side effects but only three patients (3%) had grade 3 events: injection-site reaction ($n = 1$), hot flashes ($n = 1$) and transient ischemic attack ($n = 1$). The transient ischemic attack was possibly related to fulvestrant, which was then discontinued.

discussion

Three major findings have emerged from this multicenter, phase II study. First, fulvestrant at the registered dose of 250 mg repeated every 28 days is effective in this group of hormonally pretreated patients with 30% of them experiencing CB. Second, previous response to an AI does not appear to be predictive for fulvestrant efficacy since CB rates were similar for patients in group A (those who had previous benefit with an AI) and group B (those who had primary resistance to AIs): 28% (90% CI 19% to 39%) versus 37% (90% CI 19% to 58%), respectively. Third, fulvestrant is well tolerated with only three patients (3%) developing grade 3 toxicity, two of which required therapy to be discontinued. The most frequent side effects with fulvestrant were hot flashes, fatigue, appetite loss and transient discomfort at the injection site, which were mild or moderate in intensity. The most frequent reason for discontinuing treatment was disease progression (92%). This tolerability profile is similar with that previously reported in other trials of fulvestrant [15].

The results of this final analysis are consistent with our preliminary results [16] and those of the North Central Cancer Treatment Group (NCCTG) N0032 study in patients receiving fulvestrant after progression on an AI ± tamoxifen [17]. In that study, 35% of patients receiving fulvestrant experienced CB,

Table 2. Efficacy of fulvestrant

	Group A	Group B
SD ≥24 weeks, *n* (%)	18 (27)	6 (32)
PR, *n* (%)	1 (1)	0 (0)
CR, *n* (%)	0 (0)	1 (5)
Disease progression[a], *n* (%)	44 (66)	12 (63)
Not assessable, *n* (%)	4[b] (6)	0 (0)
CB, *n* [% (90% CI)]	19 [28 (19–39)]	7 [37 (19–58)]
Median duration of CB, months (range)[c]	10.8 (5.6–50.1)	9.0 (5.5–17.0)
Median TTP, months (95% CI)	3.6 (3.0–4.8)	3.4 (2.5–6.7)
Median TTF, months (95% CI)	3.6 (3.0–4.6)	3.4 (2.5–6.7)
Median duration of treatment, months (range)	3.8 (0.9–52)	3.8 (1.8–17.9+)

[a]Disease progression also includes patients with SD for <24 weeks.
[b]One patient withdrew consent and decided to participate in another protocol, two patients were lost to follow-up, one patient discontinued treatment following an adverse event.
[c]Measured from registration to disease progression.
CB, clinical benefit; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; TTP, time to progression; TTF, time to treatment failure.

Table 3. Reasons for discontinuing fulvestrant treatment

	Group A, *n* (%)	Group B[a], *n* (%)
Disease progression	61 (91)	18 (95)
Adverse events	2 (3)	0 (0)
Patient refusal	2 (3)	0 (0)
Lost to follow-up	2 (3)	0 (0)

[a]One patient (5%) is still receiving treatment.

Table 4. Incidence of drug-related adverse events

	All grades, *n* (%)	Grade 3[a], *n* (%)
Hot flashes	14 (16.3)	1 (1.2)
Fatigue	8 (9.3)	–
Injection-site pain	6 (7.0)	–
Loss of appetite	4 (4.7)	–
Nausea	1 (1.2)	–
Injection-site inflammation	1 (1.2)	1 (1.2)
Transient ischemic attack	1 (1.2)	1 (1.2)
Vaginal dryness	1 (1.2)	–

[a]All grade 3 adverse events occurred in group A.

including 14% with an OR. The CB rates in the SAKK and the NCCTG trials fit well, confirming the reproducibility of the results; however, the OR rates were distinct. The difference in terms of OR rate between the two studies is not totally clear but may be related to differences in patient characteristics, e.g. proportion of patients with bone metastases, number and localization of metastases, incidence of HER2-positive disease and previous tamoxifen treatment. The two studies used different criteria for tumor assessment (WHO versus RECIST, respectively). This, however, should not significantly modify the OR rate [18]. Another possible factor of the lower OR rate observed in our study compared with others might be that 58 patients (67%) had bone metastases as part of systemic dissemination of their disease, including eight patients as unique metastatic site. Because of a restriction of technical resources in this multicenter study, we did not use changes in bone scintigraphy or magnetic resonance imaging to precisely assess bone response as reported by others [19]. This may have resulted in a relative underreporting of responses in bone.

Franco et al. [20] described their single-center experience of using fulvestrant in heavily pretreated postmenopausal patients, as part of a compassionate-use program. In line with the hypothesis that the level of pretreatment may affect OR rate, no ORs were reported in this study, although 19% of patients had SD ≥ 24 weeks. A report from a single Austrian center [19], involved in the fulvestrant compassionate-use program, described a CB rate of 43.5% in patients receiving fulvestrant as second-, third- or fourth-line endocrine therapy after prior endocrine therapy, usually including a nonsteroidal AI. The Austrian study also indicated that the CB rate was independent of the number of prior lines of endocrine treatment, but that the OR rate was lower when fulvestrant was given later in the sequence. In our study, previous response to an AI did not appear to be predictive of the effectiveness of fulvestrant. Indeed, with seven patients among 20 presenting a response or a SD of ≥6 months, fulvestrant shows clearly to have an activity against tumors with primary resistance to AIs. The percentage of CB, however, has yet to be interpreted with caution because of the low number of patients in this group and the potential risk of selection bias. One-third of the patients had SD ≥24 weeks and almost 10% of those in group A had CB for >1 year. One responding patient in group B has been receiving treatment for 18 months at the time of data cut-off. This indicates that fulvestrant can overcome initial and acquired resistance to AIs and that both groups of patients may benefit from treatment. Our results are therefore particularly relevant to clinical practice since the third-generation AIs, anastrozole, letrozole and exemestane, are increasingly being used as adjuvant therapy for breast cancer on the basis of recently published randomized trial data [21–26]. Because of this change in clinical practice, new endocrine strategies for relapsing patients with ER-positive tumors are urgently needed.

In our study, as in the NCCTG study, only a small proportion of patients, six out of 71 patients, had HER2-positive tumors. This is expected in a patient population selected according to endocrine responsiveness of the disease. None of them had CB with fulvestrant; however, firm conclusions on the activity of fulvestrant in this setting cannot be drawn based on such small numbers. Indeed other preliminary data have shown that HER2 positivity did not preclude response to fulvestrant [19]. The efficacy of fulvestrant has also been demonstrated in other clinical situations. In the first-line setting, fulvestrant had similar efficacy to tamoxifen in patients with ER-positive ABC [9]. In second line, fulvestrant is the only ER antagonist that has demonstrated efficacy after tamoxifen failure [27]. Furthermore, fulvestrant was as effective and well tolerated as anastrozole after a first-line hormonal therapy (mainly with tamoxifen) [10–12]. As third-line endocrine treatment, in patients progressing after aminoglutetimide [28] or after nonsteroidal AI treatment [29, 30], exemestane has also shown valuable benefit. The ongoing Evaluation of Faslodex and Exemestane Clinical Trial (EFECT) compares fulvestrant and exemestane in patients progressing after nonsteroidal AI treatment.

In conclusion, by inducing a CB in 30% of patients with hormone receptor-positive tumors having received prior steroidal and nonsteroidal AI and most of them having also been exposed to tamoxifen, fulvestrant emerges as an interesting and potentially important player in the sequential endocrine treatment of ABC. In this population of women with lower tumor burden, which does not require immediate use of chemotherapy, delaying >6 months the use of chemotherapy by using monthly injections of fulvestrant is a valuable approach to keep an optimal quality of life.

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