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Original article

First-line fadrozole HCl (CGS 16949A) *versus* tamoxifen in postmenopausal women with advanced breast cancer

Prospective randomised trial of the Swiss Group for Clinical Cancer Research SAKK 20/88

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Summary

Background: In a phase III randomized trial, we compared the effectiveness and tolerability of fadrozole (CGS 16949A), a non-steroidal aromatase inhibitor, to tamoxifen as first-line endocrine therapy in postmenopausal women with advanced breast cancer.

Patients and methods: Two hundred twelve eligible patients were randomized to receive tamoxifen 20 mg daily, or fadrozole 1 mg twice daily orally until disease progression or the advent of undue toxicity. The treatments were to be discontinued upon disease progression.

Results: Prognostic factors were well balanced between the treatment groups, except for sites of metastatic disease. Fadrozole-treated patients had significantly more visceral, especially liver, involvement and less bone-dominant disease. Response rates for fadrozole and tamoxifen were similar, 20% and 27% (95% Confidence Limits (CL): 13%–29% and 21%–35%), respectively. Time to treatment failure was longer in patients randomized to tamoxifen (8.5 months for tamoxifen vs. 6.1 months for fadrozole), but did not reach statistical significance after adjustment for prognostic factors ($P = 0.09$). Fadrozole, for which a significantly lower percentage of clinically relevant toxic effects (WHO toxicity grade ≥ 2) was recorded (27% vs. 13%, respectively; $P = 0.009$), was better tolerated than tamoxifen. Severe cardiovascular events including 3 fatalities were seen only in patients treated with tamoxifen. Eighty-two patients crossed over to tamoxifen and 66 patients to fadrozole. Crossover endocrine therapy led to response or stable disease in 64% of the patients. The overall survival times of the two treatment groups were similar.

Conclusions: Fadrozole and tamoxifen showed similar efficacy as first-line treatments in postmenopausal patients with advanced breast cancer. Fadrozole was significantly better tolerated and may therefore be an appropriate alternative to tamoxifen, especially for patients predisposed to thromboembolic events.

Key words: aromatase inhibitor, breast cancer, CGS 16949A, fadrozole, tamoxifen

Introduction

Breast cancer is the principal site of incidence and mortality in females in most developed countries. The incidence in Switzerland ranges from 59.1 in the eastern part of the country to 73.5 per 100,000 in the west, for a total of approximately 3500 new cases per year in the country as a whole. The standardized mortality rate for Switzerland is 7.0 per 100,000, or more than 1600 deaths per year, i.e., over 20% of all cancer deaths in females [1].

Tamoxifen (TAM) is the standard treatment for postmenopausal patients with hormone-dependent breast cancer both in the adjuvant setting [2] and in advanced disease [3]. Although other endocrine therapies such as progestins or aromatase inhibitors displayed similar [4, 5] or even higher response rates [6] and duration of disease control [7], the widespread use of TAM continued because of its low toxicity.

Estrogens play the most important role in maintaining the growth of established hormone-dependent breast cancer. Therefore, suppression of circulating plasma levels of estrogens may induce regression of the tumour. In postmenopausal women estrogens are mainly derived from aromatisation of androgenetic precursors. The most important source is androstenedione of adrenal glands [8].

The role of the aromatase microsomal cytochrome P-450-dependent enzyme system is well established as key in the biosynthesis of estrogens in males and females [9].

Aromatase is found not only in the ovaries of premenopausal patients but also in the adipose tissue and muscle, liver, brain, placenta and breast cancer tissue [10].

Aminoglutethimide (AG) was originally introduced

as an anticonvulsant agent an subsequently found to inhibit steroid genesis. It was first successfully used in a patient with functional disseminated adrenocortical carcinoma in 1966 [11] and introduced in the palliative treatment of advanced breast cancer in 1967 [12].

Fadrozole (CGS 16949A), an imidazol derivate, was the first second-generation non-steroidal aromatase inhibitor to be developed and clinically tested following the introduction of AG. At a standard dose of 1 mg b.i.d., with no inhibitory effect on other cytochrome enzymes of steroid synthesis, the estrogen level was reduced to 30% of baseline values. Phase I studies showed fadrozole to be very well tolerated [13, 14].

The current study was activated in 1988 to assess the role of fadrozole as primary endocrine therapy for metastatic breast cancer as compared to tamoxifen. Patients with either disease progression or unacceptable toxicity were given the opportunity to use the alternative drug, if feasible.

Patients and methods

Eligibility criteria included: histologically and/or cytologically proven breast cancer, objective evidence of progressive disease, measurability/evaluability of the disease, ECOG performance status <2, postmenopausal status (≥ 12 months amenorrhea, >52 years with hysterectomy or biochemical evidence of ovarian function cessation), indication for hormonal treatment according to the attending physician, and informed consent. Exclusion criteria were: previous or concurrent malignant disease, significant renal, cardiac, hepatic or metabolic dysfunction, any concomitant endocrine disorder or treatment, and any prior systemic treatment for breast cancer except adjuvant therapy completed ≥ 12 months before randomization. In November 1992 the exclusion criteria were modified to allow entry of patients with thyroid hormone medication or with diabetes mellitus which was under control.

Treatment assignment followed a telephone call to the Coordinating Center where randomization by strata (according to performance status (0–1 vs. 2), ER status (positive vs. negative vs. unknown) and previous hormonal adjuvant treatment (yes vs. no)) took place. The 'minimization' method was used for treatment assignment in each stratum [15].

The treatment groups were as follows: arm A, TAM 20 mg/day p.o. and arm B, fadrozole 1 mg p.o. twice a day. No dose modifications were prescribed. Concurrent radiation therapy was allowed except on parameter lesions. Patients were expected to continue the first treatment until progression or excessive toxicity and investigators were urged to cross to the other drug rather than withdraw patients from the study. Cross-over dosages for both regimens were identical to dosages used in the first-line treatment in all cases with indication for further hormonal treatment. After the second progression patients were considered to be off study, treated individually and followed until death.

Fadrozole was supplied to the participating institutions through the SAKK Coordinating Center by the Ciba-Geigy Pharma, Switzerland, and was free of charge.

Therapeutic efficacy and toxicity were assessed according to WHO criteria [16]. A minimum of 2 months of treatment was required to consider a case evaluable for response; however, progressive disease could be attributed at any time when clinically suspected. All cases were reviewed for eligibility, treatment response and time to treatment failure by two chairpersons (BT and KB).

Study endpoints were defined as follows: time to treatment failure (TTF), response rate including partial remissions (PR) and complete remissions (CR), toxic events, overall survival (OS) and subjective benefit (the latter not evaluated in the present report). For the TTF, measured from randomization date, the following events were considered as failures: disease progression, excessive toxicity, treatment refusal, addition of other treatments (irradiation, chemotherapy etc.), crossover and death, whichever occurred first. All types of failures were recorded. OS was measured from date of randomization.

Additional end points were: time to progression (TTP), measured from randomization date until progression); duration of response (DR), measured from randomization date for patients in CR or PR; 'early failure' rate defined as any failure occurring within the first 12 weeks of treatment; clinically relevant toxicity (any WHO toxic event classified as grade ≥ 2).

Statistical analysis

The study was planned to detect a response rate increased from 40% to 60% for patients receiving fadrozole compared with tamoxifen. The required sample size was estimated to be 320 patients (alpha error = 0.05, power = 0.80) and a maximal accrual duration of 6 years was planned. The study was closed in December 1994 after 6.5 years with 221 patients, yielding a statistical power (0.80) to detect any 20% difference in response rate. The current analysis on data updated to December 1995 was performed one year after the last accrual, including all randomized patients. The median follow-up time of surviving patients was 3 years. The main analysis focussed upon the main comparison. Since treatment selection after first failure was not based upon randomization, 'crossover treatments' were not statistically compared.

The chi-square or Fisher's exact tests were used for contingency tables [17]. The Wilcoxon rank sum test was used for ordered categorical tables (types of toxicities). Logistic regression was used to verify which variables predicted response to therapy [18]. TTF, TTP, DR and OS were estimated according to the Kaplan–Meier product limit method [19]. The prognostic importance of several variables with respect to TTF and OS was assessed using both univariate (log-rank test) and multivariate methods [20].

Dominant disease site was categorized as follows: soft tissue (breast, primary tumor, lymph nodes and other soft tissues), bone and viscera. When several sites were involved, viscera were considered dominant over bone and bone dominant over soft tissue. All P-values are two sided.

Results

Accrual and patient characteristics

Two hundred twenty-one patients were randomized between June 1988 and December 1994 by 7 centers of the SAKK. Three centers (Tessin, St. Gallen and Bern) contributed 85% of the cases. The remaining 4 centers (Lausanne, Zürich, Basel and Neuchâtel) each contributed $<10\%$ of the cases.

Eligibility and evaluability were reviewed for all cases. Nine patients (4%, 3 in the TAM and 6 in the fadrozole arm) were ineligible. The reasons in the TAM arm were: no metastases and pretreatment with TAM for advanced disease; in the fadrozole arm: no metastases, lung carcinoma (diagnosed bioptically after treatment failure for lung metastasis), premenopausal status and altered hepatic function.

One patient in each arm received the other treatment. The characteristics of the 212 eligible patients are listed in Table 1. Median age at study entry was 65-

years (range: 40–83 years) in the TAM arm and 65 years (range: 39–87 years) in the fadrozole arm. The median disease-free interval (calculated from date of surgery to date of relapse) was 49 months (range: 0–224 months) in the TAM and 43 months (range: 0-230 months) in the fadrozole arm.

Initial sites of disease are listed in Table 2. The distribution of main localization of metastases is significantly different ($P = 0.005$) between the 2 arms. Fadrozole-treated patients had more visceral and less bone dominant disease. Looking at initial disease sites, the fadrozole arm has significantly more pleura ($P = 0.03$) and liver ($P = 0.009$) localizations. There was also a trend for more lung localisations ($P = 0.17$) and a higher overall number of involved metastatic sites ($P = 0.18$).

First treatment: Response and early failure

Three eligible patients (3/212, 1%) were not evaluable for response to first treatment: one patient on TAM received radiotherapy on parameter bone lesions. added after 4 weeks, and no data was available on two patients on fadrozole about follow-up and evaluations. Patients with early treatment stop (with or without crossover) due to side effects or physician decision, were considered as non-responders and included in the calculation of response rates. Response (and early failure) according to first treatment were comparable, 27% and 20% in the TAM and in the fadrozole arms, respectively ($P = 0.26$). The approximate 95% confidence limits for CR/PR rate were: 21%–35% for TAM and 13%–29% for fadrozole. Details can be seen in Table 3.

Overall, response occurrence was associated with previous adjuvant hormone therapy ($P = 0.05$) and limited number (1–2) of localizations ($P = 0.09$). Patients with previous adjuvant hormone therapy experienced more responses (9/21, 43%) than those without (41/188, 22%). Patients with limited number (1–2) of localizations had more responses (42/156, 27%) than those with ⩾3 localizations (8/53, 13%).

Patients with soft tissue as dominant disease site experienced more responses (9/26, 35%) than those with visceral (27/100, 27%) or bone (13/71, 15%). Three of the receptor-negative patients (3/26, 12%) responded to treatment; 41/164 (25%) ER-positive and 6/19 (32%) ER-unknown responded.

Logistic regression was used to assess treatment effect after adjustment for other covariates. After ad-

Table 1. Eligible patients characteristics.

	TAM no. (%)	Fadrozole no. (%)	Total no. (%)
Performance status			
0	55 (51%)	55 (53%)	110 (52%)
1	39 (36%)	36 (34%)	75 (35%)
2	13 (12%)	14 (13%)	27 (13%)
Estrogen receptor status			
Negative			
0–9 fm/mg prot	14 (13%)	13 (12%)	27 (13%)
Positive			
⩾10 fm/mg prot	81 (76%)	85 (81%)	166 (78%)
Unknown	12 (11%)	7 (7%)	19 (9%)
Disease free interval			
0–12 months	20 (19%)	18 (17%)	38 (18%)
13–24 months	9 (8%)	11 (10%)	20 (9%)
25–60 months	30 (28%)	27 (26%)	57 (27%)
>60 months	40 (37%)	33 (31%)	73 (34%)
Unknown	8 (7%)	16 (15%)	24 (11%)
Prior endocrine adjuvant treatment			
No	97 (91%)	93 (89%)	190 (90%)
Yes	10 (9%)	12 (11%)	22 (10%)
Prior adjuvant chemotherapy			
No	72 (67%)	72 (69%)	144 (68%)
Yes	35 (33%)	33 (31%)	68 (32%)
Prior radiation therapy			
No	72 (67%)	77 (73%)	149 (70%)
Yes	35 (33%)	28 (27%)	63 (30%)
Total	107	105	212

Table 2. Initial sites of metastatic disease.

	TAM no. (%)	Fadrozole no. (%)	Total no. (%)
Main localization of metastases			
Visceral	42 (39%)	60 (57%)	102 (48%)
Bone	54 (50%)	30 (29%)	84 (40%)
Soft tissue	11 (10%)	15 (14%)	26 (12%)
Number of involved metastatic sites			
1	50 (47%)	45 (43%)	95 (45%)
2	35 (33%)	27 (26%)	62 (29%)
⩾3	22 (20%)	33 (31%)	55 (26%)
Initial sites[a]			
Local skin	15 (14%)	14 (13%)	29 (14%)
Distant skin	3 (3%)	5 (5%)	8 (4%)
Local lymphnodes	23 (22%)	19 (18%)	42 (20%)
Distant lymphnodes	24 (22%)	22 (21%)	46 (22%)
Lung	26 (24%)	35 (33%)	61 (29%)
Pleura	21 (20%)	35 (34%)	56 (26%)
Bone	72 (67%)	62 (59%)	134 (63%)
Liver	3 (3%)	13 (12%)	16 (8%)
Brain	2 (2%)	–	2 (1%)
Total	107	105	212

[a] More than one site can be present in each patient.

Table 3. Response and early failure according to first treatment.

	TAM no. (%)	Fadrozole no. (%)	*P*-value
CR/PR	29 (27%)	21 (20%)	0.26
CR	7	5	
PR	22	16	
NC	52	56	
PD	18	23	
Early toxic death	3	0	
Early non toxic death	0	1	
Early stop of treatment	4	4	
Total	106	103	
Early failure (occurring in the first 12 weeks)	26 (25%)	34 (33%)	0.22

justment for previous hormonal treatment, number of localizations, receptor status and dominant disease site in bone, treatment regimen was not significantly associated with response ($P = 0.10$). The estimated odds ratio (OR) for CR/PR for fadrozole vs. TAM was 0.56 (95% CL: 0.28–1.11). Previous hormonal treatment (OR: 2.9, $P = 0.03$) and a small number of disease localizations (OR: 2.6, $P = 0.03$) were significantly associated with higher response rate. Dominant disease site in bone (OR: 0.3, $P = 0.04$) was significantly associated with lower response rate.

Patients not pretreated with adjuvant endocrine therapy responded slightly better to TAM ($P = 0.07$) as well as initial sites in lung ($P = 0.15$) and in bone ($P = 0.15$). Patients pretreated with adjuvant endocrine therapy and with main localizations in soft tissue responded better to fadrozole but the number of patients in both groups is small (see Table 4).

Table 4. Response by ER status, pretreatment and metastatic site.

	TAM			Fadrozole		
	N	CR/PR	%	N	CR/PR	%
Estrogen receptor status						
Negative						
0–9 fm/mg prot	14	1	(7%)	12	2	(17%)
Positive						
≥10 fm/mg prot	80	24	(30%)	84	17	(20%)
Unknown	12	4	(33%)	7	2	(29%)
Prior endocrine adjuvant treatment						
No	96	26	(27%)	92	15	(16%)
Yes	10	3	(30%)	11	6	(55%)
Prior adjuvant chemotherapy						
No	71	21	(30%)	70	16	(23%)
Yes	35	8	(23%)	33	5	(15%)
Main localization of metastases						
Visceral	42	15	(36%)	58	12	(21%)
Bone	53	11	(21%)	30	3	(10%)
Soft tissue	11	3	(27%)	15	6	(40%)
Number of involved metastatic sites						
1	49	15	(31%)	45	11	(24%)
2	35	11	(31%)	27	5	(19%)
≥3	22	3	(14%)	31	5	(16%)
Initial sites[a]						
Local skin	15	5	(33%)	14	5	(36%)
Distant skin	3	0	–	5	1	(20%)
Local lymphnodes	23	6	(26%)	18	5	(28%)
Distant lymphnodes	24	7	(29%)	22	5	(23%)
Lung	26	9	(35%)	33	6	(18%)
Pleura	21	6	(29%)	34	8	(24%)
Bone	71	15	(21%)	60	7	(12%)
Liver	3	2	(67%)	13	2	(15%)
Brain	2	0	–	0	0	–
Total	106	29		103	21	

[a] More than one site can be present in each patient.

First treatment: Time to failure, duration of response and survival

The estimated median TTF is longer in the TAM group, 8.5 months *versus* 6.1 months in the fadrozole group (log-rank $P = 0.05$) (Figure 1). The one-year failure- free survival was 36 + 5% and 27 + 4%. The most frequent cause of failure was disease progression. Other causes were: cross-over (7 TAM, 5 fadrozole), addition of other treatments such as irradiation or surgery (4 TAM, 1 fadrozole), early stop (1 fadrozole), refusal (1 TAM) and death (4 TAM, 2 fadrozole).

Cox regression analysis was used to assess the treatment effect on TTF after adjustment for other covariates. TTF was not significantly associated with initial treatment after adjustment for performance status, disease-free interval, number of localizations, receptor

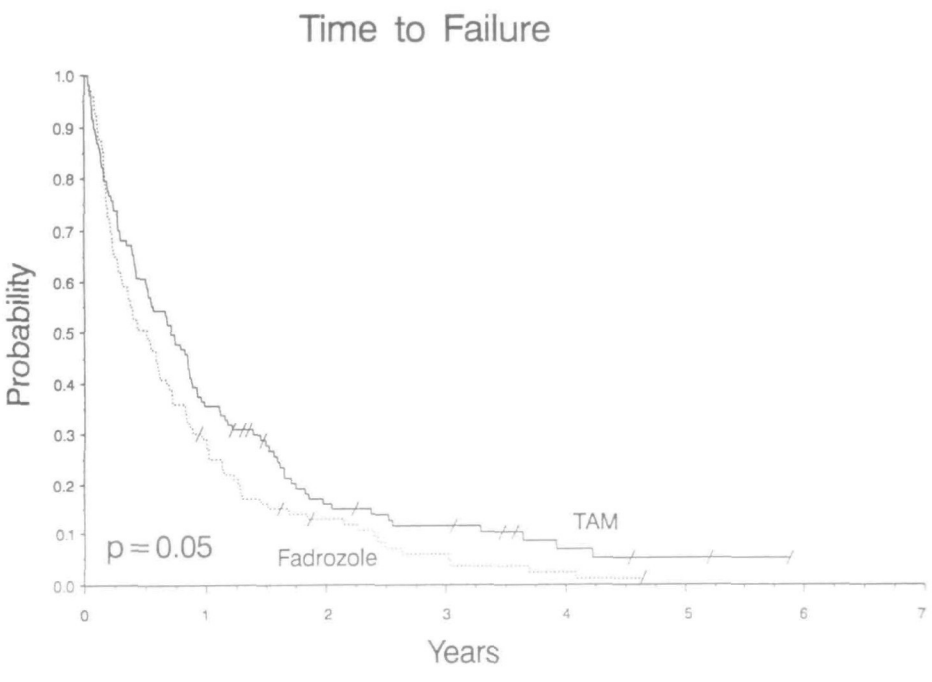

Figure 1. Time to failure (TTF) for patients 105 patients who received fadrozole and 107 patients who received tamoxifen.

status, or presence of bone or liver lesions. The hazard ratio for fadrozole was 1.30 compared to TAM as reference (95% CL: 0.96–1.75, $P = 0.09$).

An additional evaluation of time to progression (TTP) was performed. In TTP calculations, patients failing without progression (early crossover or treatment stop, refusal, death, etc.) are 'censored' at the time of occurrence and not considered as failures. Because of the difference in censoring mechanism, TTP is significantly longer in the TAM group (log-rank $P = 0.01$). The median response duration is 19.8 months in the TAM group and 15 months in the fadrozole group (log-rank $P = 0.35$) (Figure 2).

OS is similar in the two arms (log-rank $P = 0.90$) (Figure 3). Cox regression showed that neither initial treatment adjusted for performance status, dominant disease site in soft tissue, number of localizations, receptor status, presence of bone and liver lesions, were significantly associated with OS. The hazard ratio for fadrozole is 0.91 compared to TAM as reference (95% CL: 0.63–1.32, $P = 0.63$). OS with more than 25% of patients alive at 5 years is unexpectedly high in our study population with a substantial proportion of unfavourable patient characteristics.

Table 5. First treatment: patients worst toxicity (WHO grade).[a]

	TAM no. (%)	Fadrozole no. (%)	*P*-value
Thromboembolic disease			
2	1 (1%)	0	0.12
Death while on treatment	3 (3%)	0	
Hot flushes			
1	9 (8%)	14 (13%)	
2	11 (10%)	9 (9%)	0.76
3	4 (4%)	2 (2%)	
4	2 (2%)	0	
Insomnia			
1	1 (1%)	2 (2%)	0.42
2	3 (3%)	0	
Nausea/vomiting			
1	1 (1%)	3 (3%)	0.16
2	0	1 (1%)	
Skin			
1	0	1 (1%)	0.49
Other			
Yes	12 (11%)	6 (5%)	0.22
Any toxic effect			
Yes	37 (35%)	31 (30%)	0.47
Clinical relevant toxicity (any WHO ≥ 2)			
Yes	29 (27%)	13 (13%)	0.009
Total patients	107	104	

[a] Toxicities = 0 are not reported.

First treatment: Side effects

Two hundred eleven eligible patients were considered assessable for toxic effects of the first treatment. One patient refused follow-up and examinations. Details with worst toxicity per patient attributed to the randomised treatment are presented in Table 5. There was significantly more clinically relevant toxicity (any WHO > 2) in patients randomized to TAM. Cardiovascular events, including three fatalities, were observed only in patients treated with TAM. One patient died of autoptically confirmed bilateral pulmonary embolism 9 days after starting the treatment with TAM (early toxic death). Another patient with no known pre-existing cardiopathy died of a cardiovascular event 5 weeks after onset of treatment with TAM. A pulmonary embolism as possible cause of death was suspected, but no autopsy was performed. A further patient died at home of a cardiovascular event 10 days after treatment onset with TAM. A TAM effect was suspected but not

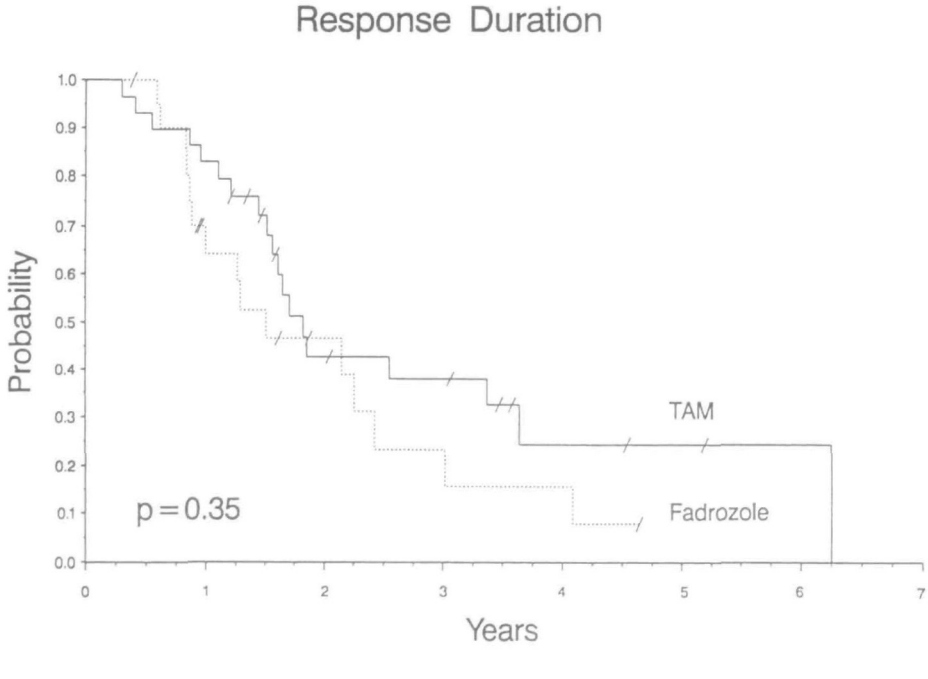

Figure 2. Duration of response for patients 105 patients who received fadrozole and 107 patients who received tamoxifen.

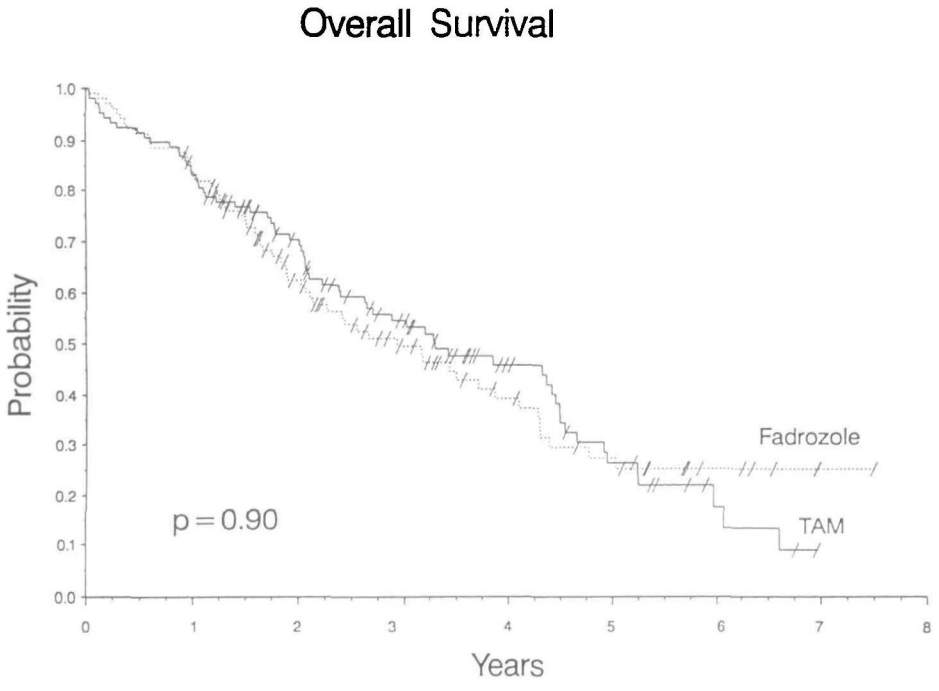

Figure 3. Overall survival for patients 105 patients who received fadrozole and 107 patients who received tamoxifen.

proven by autopsy. Additional TAM side effects were: depression, headache, increased bone pain, inappetence, gastric pain, fatigue, vaginal flora, hypercalcemia and hyperuricemia (with acute renal failure); for fadrozole: fatigue, flare in bone scan, inappetence, weakness and somnolence.

Nine patients (8 TAM and 1 fadrozole) discontinued the first treatment because of side effects; for TAM: thromboembolic disease in three cases, hypercalcemia, increased bone pain, hot flushes, headache and malaise, gastric pain with inappetence and nausea, and for fadrozole: weakness and dizziness in one case each.

Second treatment (cross-over) efficacy

One hundred ninety-five patients stopped (93%) the first treatment (96 after tamoxifen, 99 after fadrozole). One hundred forty-eight patients (76%) crossed over to TAM or fadrozole (82 to TAM and 66 to fadrozole). The rate of crossover to fadrozole was significantly lower than the one to TAM ($P = 0.006$). Since treatment selection after first failure is not random, further statistical comparisons of TAM and fadrozole as second treatment are biased and have therefore not been performed.

Response and early failure according to cross-over treatment are summarized in Table 6. For 2 patients on fadrozole it was too early to assess response. Twenty-four of 82 patients (29%) who crossed to TAM and 6 of 64 patients (9%) who crossed to fadrozole had an objective response. Thirty-four patients treated with TAM and 29 patients treated with fadrozole as cross-over treatment achieved stabilisation of their disease after having failed first-line endocrine therapy for advanced breast cancer. The median duration of cross-over treatment was 254 days for TAM and 112 days for fadrozole. The median duration of CR, PR and stable disease was 12 months for TAM and 10 months for fadrozole.

Response to cross-over treatment by initial response is shown in Tables 9 and 10.

Second treatment (cross-over) toxicity

One hundred forty-eight patients were considered assessable for the toxicity of their crossover treatment. Patterns and grades of toxicites with TAM and fadrozole as randomised treatments were similar. Toxicity > WHO grade 2 was more frequently observed in patients crossed to TAM (23%) than in those crossed to fadrozole (17%). An additional thromboembolic event, but no further fatalities, was observed among the TAM-treated patients. Five patients (2 on TAM and 3 on fadrozole) stopped the second treatment because of toxicity. The reasons for discontinuation of TAM were hypercalcemia, and severe dyspnea 2–4-hours after

Table 6. Response and early failure according to cross over treatment.

	TAM no. (%)	Fadrozole no. (%)
CR/PR	24 (29%)	6 (9%)
CR	7	2
PR	17	4
NC	34	29
PD	17	17
ENTD	1	2
Early stop of treatment	6	10
Total	82	64
Early failure (occurring in the first 12 weeks)	23 (28%)	29 (45%)

ingestion of tamoxifen with a positive rechallenge test after 2 weeks; for fadrozole they were conjunctivitis and headache, headache and malaise, and skin reaction in the form of acute angioedema of the face and neck without visceral involvement.

One patient received fadrozole for 9 months and TAM for 18 months before diagnosis of a second tumor (ovarian cancer).

A total of 189 patients were exposed to TAM and 170 to fadrozole and all were considered assessable for 'overall toxicity' defined as the sum of all toxicities observed during randomized and cross-over treatments. Twenty-five percent of all TAM-exposed patients, but only 14% of all fadrozole-exposed patients, experienced clinically relevant side effects. The 95% CL were: 19%–31% for TAM and 9%–19% for fadrozole.

Discussion

The choice of the agent to be used in postmenopausal patients with advanced breast cancer and the indication for hormonal treatment is mainly based on the agent's toxicity profile. TAM remained the standard treatment despite the fact that several studies have shown considerably higher response rates for medroxyprogesterone acetate MPA [6] or AG [7] when used as first-line treatment and compared in randomized studies to TAM. However, the higher response rate did not translate into a longer time to treatment failure, and toxicity was usually greater with AG 1000 mg daily plus glucocorticoid replacement therapy or MPA 1000 mg daily.Two previously published studies also compared TAM to AG. Response rate, response duration and time to treatment failure were similar in TAM- and AG-treated patients [5, 25].

Another study compared the new selective non-reversible steroidal aromatase inhibitor formestane with TAM as first-line treatment in postmenopausal women with advanced breast cancer. Of the 348 patients evaluable for response, 33% had objective responses to formestane and 37% to TAM. Time to progression and time to treatment failure were significantly longer in TAM-treated patients [26].

Our study was closed in December 1994 after 6.5 years of accrual. The trend of the response rate in favour of TAM, seen in a previous interim report, was confirmed in the current evaluation, but did not attain statistical significance [21].

The difference in TTF between the treatment arms is borderline-significant.

Patient characteristics were well balanced between the treatment arms with respect to performance status, estrogen receptor status and disease-free interval from diagnosis to first relapse, and prior adjuvant hormonal and chemo-therapy. However, there was a statistically significant difference between the treatment arms with regard to predominant localisation of disease at study entry. The fadrozole-treated patients had significantly more pleura ($P = 0.03$) and liver ($P = 0.009$) localisations. There was also a trend toward more lung involvement, resulting in more unfavourable visceral and less bone-dominant disease site for patients randomised to fadrozole.

This disparity in patient characteristics has probably caused the slightly lower response rate (which, however, did not reach statistical significance) of patients randomized to fadrozole. We assume that the borderline-significantly shorter TTF of patients randomized to fadrozole is due to the imbalance as well. The observed difference in TTF might also be due to physician reluctance to use a new drug (fadrozole) as first-line treatment when a widely accepted, well known and usually well tolerated standard treatment is available. Our hypothesis is supported by the fact that more patients receiving fadrozole were crossed to TAM than vice versa ($P = 0.006$). A double blind trial design could have averted this source of bias. In an attempt to correct for the imbalance, Cox regression analysis was used to asses the treatment effect on TTF after adjustment for other covariates. The non-statistically-significant hazard ratio for patients treated with fadrozole was 1.30 compared to the ratio for TAM-treated patients ($P = 0.09$). Thus far this imbalance has not affected overall survival which was similar in the two arms. Interestingly, the TTF for patients with lung metastases and bone metastases were identical. Patients with visceral-predominant disease had an almost identical TTF to that of patients with bone-predominant disease.

Responses to crossover treatments have been observed in both directions, but conclusions might be biased due to the lack of randomized assignment and to the fact that fewer patients received fadrozole as second-line treatment. Overall, early failure was seen in 36% of the patients after crossover, showing that the majority of patients did benefit from the second hormonal treatment for considerable periods of time (median duration of CR, PR and stable disease between 10 and 12 months). One of 9 patients with initial progression on tamoxifen had a partial remission on fadrozole and an additional 3 of the 9 had disease stabilization as best response to fadrozole. One of 16 patients with initial progression on fadrozole responded to tamoxifen and another 6 of these had disease stabilization when treated with fadrozole. It appears that about half of the patients with straightforward disease progression on first-line hormonal treatment might have experienced a palliative effect when they were exposed to a second endocrine treatment. Although there were few objective responses, the long median duration of CR, PR and stable disease shows that many patients probably derived a beneficial effect from disease stabilization.

The two treatments had only a few toxic effects, with hot flushes, as expected, being the most frequently toxicity observed. Skin reactions, seen in up to 15% of patients treated with the previously-used non-steroidal aromatase inihibitor AG, were present in only 3 of 170 patients exposed to fadrozole. The reasons for cessa-

tion of treatment may reflect not only objective toxicity but also the treatment-associated subjective experience of the patients. Physicians participating in this study appeared reluctant to continue using fadrozole. This fact, as mentioned above, could have contributed not only to the shorter time to treatment failure in patients randomized to fadrozole but also to a closer observation of patients with regard to expected (skin reactions) and unexpected toxic effects. Cardiovascular incidents have been observed only in the TAM- treated group. Thromboembolic events, including 3 treatment-associated deaths, were seen in 4 patients randomized to TAM. A further instance of pulmonary embolism was observed in 82 patients receiving TAM as crossover treatment. Significantly more patients randomised to TAM (27%) had clinically relevant toxicity than patients randomized to fadrozole (13%).

The results obtained in our study with regard to response rate and time to treatment failure are somewhat inferior to the ones expected when the study was planned, and as compared to the literature. In patients with recurrent or metastatic breast cancer, TAM is the most frequently chosen agent for initial endocrine therapy with an expected overall complete and partial response rate of 30%–40% [3, 22].

However, in recently published multicenter trials using TAM 20 mg daily orally in a randomized comparison to MPA or AG as initial endocrine therapy for patients with metastatic breast cancer, response rates for TAM were considerably lower than expected – 17% and 27%, respectively [6, 7]. The time to treatment failure for TAM-treated patients was brief in both studies: 5.5 months and 3.5 months, respectively. Response rate and median time to treatment failure in our multicenter trial were comparable to the ones in these recently published trials. The lower response rate and shorter TTF are probably due to the inclusion of patients with more unfavorable prognosis and to the strict application of response criteria (e.g., evaluation by two chair persons, inclusion of all patients in the analysis, etc.). In recently reported phase II studies of fadrozole in pretreated postmenopausal patients with advanced breast cancer, relatively low response rates of 23% (95% CL: 12%–34%) in a single-institution study and of 16% (95% CL: 12%–20%) in a large multicenter study with external peer review were observed, with a TTF of approximately 4 months in both studies [23, 24]. The median overall survival in our study was higher than in both of the above-cited studies despite the fact that our study population included a considerable number of patients with visceral tumour lesions as predominate site of disease and involvement of multiple organ sites. Other factors of patient selection and treatment modalities after failure of study treatment may have contributed to these favorable results.

Conclusion

Fadrozole is a new non-steroidal aromatase inhibitor without need of glucocorticoid replacement and with little toxicity. In our experience both drugs were similarly effective, and fadrozole was associated with significantly less clinically-relevant toxicity. It may be considered as an alternative to TAM, especially for patients with a predisposition to thromboembolic events.

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References

1. Levi F, La Vecchia C, Lucchini F, Randimbison L. Epidemiology of Cancer in Switzerland. Lausanne, Switzerland, Association of Swiss Cancer Registries 1994.
2. Early Breast Cancer Trialist Collaborative Group. Systemic treatment of early breast cancer by hormonal cytotoxic or immune therapy: 133 Randomised trials involving 31,000 recurrences and 24,000 deaths among 75 000 women. Lancet 1992; 339: 1–15, 71–85.
3. Henderson IC. Endocrine therapy of metastatic breast cancer. In Harris JR, Hellmann S, Henderson IC et al. (eds): Breast Diseases. Philadelphia, PA: Lippincott Publishers 1991; 559–603.
4. Paterson AHG, Hanson J, Pritchard KI et al. Comparison of antiestrogen and progestogen. Therapy for initial treatment and consequences of their combination for second-line treatment of recurrent breast cancer. Semin Oncol 1990; 17 (Suppl 9): 52–67.
5. Smith J, Harris AL, Morgan M et al. Tamoxifen *versus* aminoglutethimide in advanced breast carcinoma: A randomised cross over trial. BMJ 1991; 283: 1432–4.
6. Muss BH, Case LD, Atkins JN et al. Tamoxifen *versus* high dose medroxyprogesterone acetate as an initial endocrine therapy for patients with metastatic breast cancer. Piedmont Association Study. J Clin Oncol 1994; 12: 1630–8.
7. Gale KE, Anderson JW, Tormey DC et al. Hormonal treatment for metastatic breast cancer an Eastern Cooperative Oncology Group phase III trial comparing aminoglutethimide to tamoxifen. Cancer 1994; 73(2): 354–61.
8. Poortman J, Thijssen JHH, Schwarz F. Androgen production and conversion to estrogens in normal postmenopausal women and in selected breast cancer patients. J Clin Endocrinol Metab 1973; 37: 101–9.
9. Fishman J. Biochemical mechanism of aromatization. Cancer Res 1982; 42 (Suppl): 3277S-3280S.
10. Nimrod A, Ryan K. Aromatization of androgens by human abdominal and breast fat tissue. J Clin Endocrinol Metab 1975; 40: 362–72.
11. Schteingrad GE, Cash R, Conn JW. Aminoglutethimide and metastatic adrenal cancer. J Am Med Assoc 1966; 198: 1007–10.
12. Gale KE. Treatment of advanced breast cancer with aminoglutethimide: A 14-year experience. Cancer Res 1982; 42 (Suppl): 3389S–3396S.
13. Harvey HA, Lipton A, Santen RJ et al. Clinical trial with the aromatase inhibitors CGS 16949A in advanced breast cancer. Preliminary results. In Jonat W, Santen RJ (eds): Aromatase Inhibition Present and Future. Symposium 15th UICC International Cancer Kongress Hamburg. New Jersey: Parthenon Publishing Group 1991; 89–96.

14. Beretta KR, Höffken K, Kvinnsland S et al. CGS 16949A, a new aromatase inhibitor in the treatment of breast cancer – a phase I study. Ann Oncol 1990; 1: 421–6.
15. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trials. Biometrics 1975; 31: 103–15.
16. WHO Handbook for Reporting Results of Cancer Treatment. Geneva: World Health Organization 1979.
17. StatXact. Statistical Software for Exact Nonparametric Inference. User Manual Version 2. Cambridge MA: Cytel Corporation.
18. Cox DR, Snell EJ. Analysis of Binary Data. Second ed. London: Chapman and Hall 1988.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Ass 1958; 53: 457–81.
20. Cox DR. Regression models and life tables. J R Statist Soc B 1972; 34: 187–220.
21. Thürlimann B, Beretta K, Bacchi M et al. First line fadrozole HCI (CGS 16949A) *versus* tamoxifen in advanced breast cancer: Prospective randomised Study SAKK 20/88. Proc ASCO 1995; 14: 98 (Abstr 90).
22. Petru E, Schmahl D. On the role of additive hormon monotherapy with tamoxifen, medroxyprogesterone acetate and aminoglutethimide in advanced breast cancer. Klin Wochenschr 1978; 65: 959–66.
23. Raats J, Falkson HC, Falkson CI. A study of fadrozole, a new aromatase inhibitor, in postmenopausal women with advanced metastatic breast cancer. J Clin Oncol 1992; 10(1): 111–6.
24. Höffken K, Chacon R, Dombernowsky P et al. Fadrozole hydrocloride (CGS 16949A). Double blind dose-finding study in postmenopausal patients with advanced breast cancer. Ann Oncol 1992; 3 (Suppl 5): 76 (Abstr 294).
25. Harvey HA, Lipton A, White DS. Crossover comparison of tamoxifen and aminoglutethimide in advanced breast cancer. Cancer Res 1982; 42 (Suppl 8): 3451S–3453S.
26. Perez Carrion R, Alberola Clandel V, Clandel V et al. Comparison of the selective aromatase inhibitor formestane with tamoxifen as first line hormonal therapy in postmenopausal women with advanced breast cancer. Ann Oncol 1994; 5 (Suppl 7): 519–24.

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