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Original Paper

Formestane Versus Megestrol Acetate in Postmenopausal Breast Cancer Patients After Failure of Tamoxifen: a Phase III Prospective Randomised Cross Over Trial of Second-line Hormonal Treatment (SAKK 20/90)

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The aim of the study was to compare efficacy and tolerability of the new aromatase inhibitor formestane (Lentaron®) with megestrol acetate (Megestat®) (MGA) in postmenopausal patients with advanced breast cancer. 179 patients were randomised to receive either 250 mg formestane intramuscularly biweekly or MGA 160 mg orally daily. 51% of the patients had received tamoxifen as adjuvant treatment; 73% of the patients had positive and 16% unknown oestrogen receptor values. The response rate was 17% in both treatment arms (95% confidence interval 10–26% for formestane and 10–27% for MGA). Disease stabilisation ≥6 months was seen in 25% of the formestane and 22% of the MGA patients. Time to treament failure was 120 days in the formestane arm and 111 days in the MGA arm. There was no significant difference between the treatments with regard to response rate and time to treatment failure. Overall toxicity was similar in both arms, but weight gain >3 kg ($P = 0.081$) and severe cardiovascular toxicity ($P = 0.044$) were more frequently observed with MGA, e.g. deep vein thrombosis 0/90 formestane versus 5/81 MGA cases ($P = 0.022$). Formestane was associated with worsening of hot flushes/sleeping problems ($P = 0.051$) and mild leucopenia ($P = 0.004$). In our study, formestane and MGA showed similar antineoplastic activity as second-line hormonal treatment for advanced breast cancer. Both drugs have a specific toxicity profile. MGA was associated with significantly more severe cardiovascular toxicity and weight increase than formestane.

Key words: aromatase inhibitor, formestane, megestrol acetate, breast cancer

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INTRODUCTION

In 1990, approximately 325 000 women died of breast cancer worldwide, accounting for 16% of all cancer deaths among women in developed countries and 11% in developing countries [1]. In most industrialised countries, the disease affects more women than any other cancer and is the third most frequent cancer among the population as a whole. In Europe, breast cancer mortality shows a clear north–south gradient with the highest rate in the United Kingdom while Spain has the lowest [2]. Breast cancer incidence in Switzerland is higher than neighbouring countries—every year an estimated 3500 women are diagnosed with breast cancer in Switzerland and approximately 1600 will die of the disease [3]. One in every 12 Swiss women is expected to develop breast cancer during her lifetime and half will die from it. Although the overall mortality rate has remained fairly stable in recent periods and even decreased in younger age groups, it has increased in women

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over 65 years of age [3]. Breast cancer patients with advanced disease have received a variety of endocrine treatments for more than a century, when Beatson reported on the beneficial effect of ovarectomy in patients affected by breast cancer just 100 years ago [4]. Other ablative hormonal procedures, such as adrenalectomy or hypophysectomy, were replaced by endocrine drug therapy because of their significant morbidity. Tamoxifen is the agent that is most frequently used in the treatment of breast cancer, both in the adjuvant and in the palliative setting. Aromatase inhibitors and progestins have been widely used as second-line treatment after tamoxifen failure, mainly in patients who responded to first-line endocrine therapy. Aminogluthetamide, a non-steroidal aromatase inhibitor, is frequently used as second-line treatment in many countries, but is associated with some undesirable effects, i.e. skin rashes, but also lethargy and dizziness, especially when used at higher doses.

4-hydroxyandrostendione (formestane) was the first steroidal compound and the first second-generation aromatase inhibitor, developed in an attempt to reduce side-effects seen with aminogluthetimide while retaining its antineoplastic activity. The drug is 30–60 times more potent than aminogluthetamide. Because of its extensive first by-pass metabolism in the liver, the preferred route of administration is intramuscular injection, but formestane is also active when given orally. Intramuscular formestane has been shown to be effective and well tolerated as second-line treatment in phase I/II studies [5]. In a recently published randomised phase III study, comparing formestane with tamoxifen as first-line therapy in postmenopausal patients with advanced breast cancer, equivalent treatment efficacy, in terms of response rate and response duration, as well as side-effects were reported [6]. In 1990, the Swiss Group for Clinical Cancer Research (SAKK) started a prospective randomised study, investigating antineoplastic activity and tolerability of formestane 250 mg given intramuscularly every two weeks versus Megestrol acetate 160 mg orally daily as second-line treatment in postmenopausal patients with advanced breast cancer and disease progression while receiving tamoxifen treatment.

PATIENTS AND METHODS

Postmenopausal patients with objective evidence of histologically and/or cytologically proven advanced breast cancer and measurable or evaluable disease were eligible. Patients must have failed prior adjuvant and/or palliative treatment with tamoxifen, irrespective of patients' best response. Prior adjuvant chemotherapy was allowed, but had to be completed more than 12 months before enrolment in the trial. Further inclusion criteria were SAKK/ECOG performance status 0–2, indication for endocrine therapy as decided by the treating physician. Informed consent was obtained from all patients. Patients with previous or concurrent malignant disease, except for adequately treated *in situ* carcinoma of the cervix and basal cell or squamous cell carcinoma of the skin, were not eligible. Patients on tamoxifen treatment without progression or patients with exposure to other endocrine agents after tamoxifen failure were not eligible, nor were patients with a medical history of deep vein thrombosis and/or thromboembolic events. Patients on oral anticoagulation and significant renal (creatinine >180 μmol/l), hepatic (aspartate-aminotransferase AST, alanine-aminotransferase ALT, alkaline phosphatase AP >2 × upper institutional limit, bilirubin >25 μmol/l), cardiac or metabolic dysfunction, were not eligible. Concomitant anticancer treatment, e.g. biphosphonate therapy, except single dose for hypercalcaemia, biological response modifiers, chronic use of glucocorticoids, was also an exclusion criterion. Radiotherapy given to a non-indicator lesion was allowed. Patients were randomised centrally after being stratified for institution, type of treatment with tamoxifen (adjuvant versus palliative) and response to prior tamoxifen (partial response (PR)/complete response (CR) versus no change (NC)/progressive disease (PD) versus not applicable). In November 1992, the inclusion criteria were modified to allow pretreatment with one chemotherapy regime for advanced disease.

The trial was planned to test differences in time to treatment failure (TTF) and toxicity assuming the availability of 60 patients/year, an accrual duration of at least 4 years (target number = 240 patients) and one year follow-up after the last patient was randomised to achieve a power of 80–90% for clinically relevant differences between the two treatments, i.e. 20% less toxicity for the better treatment and 50% increase in median TTF (sample size calculation performed with computer package power 1.3, Epicenter Software, Pasadena, California, U.S.A.). As we anticipated differences in toxicity rather than in efficacy between the treatments, the documentation forms were prepared according to these needs. With the actual sample size of 177 patients, the power was approximately 93% for toxicity from a baseline of 30% and approximately 74% for TTF from a baseline of 4 months.

TTF was measured from date of randomisation to date of progression or unacceptable toxicity. The specific toxicity endpoint was defined as presence of any of the following: 3 kg or more weight gain, thromboembolism (superficial phlebitis, deep vein thrombosis or pulmonary embolism), hypertension (>150 mmHg systolic or >90 mmHg diastolic; for hypertensive patients, an increase in systolic pressure ≥30 mmHg or in diastolic pressure ≥15 mmHg), or any other treatment-related event leading to interruption of therapy. Other toxicity was graded according to WHO/UICC criteria. WHO/UICC criteria were used to categorise other toxicities and partial/complete response. All cases were reviewed by two medical oncologists. However no formal external review was performed.

The Chi-square or Fisher's exact tests were used for contingency tables, while the Wilcoxon rank sum test was applied for comparisons of continuous variables. TTF was analysed by the log-rank test and Cox regression. All tests were two-sided.

RESULTS

Patients' characteristics

179 patients were randomised between February 1991 and June 1995. 2 randomised patients were ineligible due to renal insufficiency and thrombosis. The characteristics of eligible patients are listed in Table 1. Approximately 11% (19/177) of the patients had negative oestrogen receptor status and 22% negative progesterone receptor status. Approximately half the patients had received tamoxifen as adjuvant and half as palliative treatment. The distribution of patients' characteristics between the two treatment arms was well balanced, the only significant difference occurring

Table 1. Patient characteristics

	Formestane		MGA	
	N	(%)	*N*	(%)
Prior TAM treatment				
Adjuvant	47	(52)	44	(51)
Palliative	44	(48)	42	(49)
Best response to prior TAM treatment				
CR	2	(2)	4	(5)
PR	13	(14)	13	(15)
NC	13	(14)	10	(12)
PD	11	(12)	10	(12)
Not assessable	4	(4)	4	(5)
Not applicable (adjuvant only)	47	(52)	44	(51)
Unknown	1	(1)	1	(1)
Prior chemotherapy for metastatic disease				
No	79	(87)	80	(93)
Yes	12	(13)	6	(7)
Performance status at study entry				
0	45	(49)	49	(57)
1	34	(37)	28	(33)
2	12	(13)	9	(10)
Oestrogen receptors				
<10 fmol/mg	7	(8)	12	(14)
≥10 fmol/mg	69	(76)	60	(70)
Unknown	15	(16)	14	(16)
Progesterone receptors				
<10 fmol/mg	15	(16)	24	(28)
≥10 fmol/mg	61	(67)	49	(57)
Unknown	15	(16)	13	(15)
Age (years)				
Median	64		66	
Range	45–84		43–87	
Weight (kg)* (Wilcoxon rank sum test $P = 0.011$)				
Median	67		61	
Range	42–103		39–101	
Total number of patients	91		86	

*One missing value in arm MGA.

in weight at study entry: patients in the formestane arm had a heavier mean weight than those in the MGA arm ($P = 0.011$). Median age was 65 years (range 43–87 years).

Most frequent tumour localisations were bone (68%), lymph nodes (34%), lung (27%) and pleura (18%). Liver metastases were present in 9% of patients treated with formestane and 21% of the patients treated with MGA (chi-square test $P = 0.023$). Patients were divided into two groups, those with predominantly visceral disease (including liver, lung, pleura, pericardium, peritoneum and abdomen) and those with predominantly soft tissue disease (including lymph nodes, skin, chest wall and axilla, subcutaneous and local recurrence). There was a trend for more visceral disease in the MGA arm, as compared to the formestane arm ($P = 0.087$) (Table 2).

Table 3. Efficacy results

	Formestane	MGA
	N	*N*
CR	5	2
PR	10	12
NC	41	32
TTF ≤6 months	18	14
TTF >6 months	23	18
PD	22	13
Not assessable	1	2
Early failure (≤8 weeks)	12	24
Due to PD	9	15
Due to toxicity	1	2
Due to death	1	4
Due to other reasons	1	3
Total	91	85

Efficacy

One patient in the MGA arm refused to start treatment and 1 patient in the formestane arm had received radiotherapy on the indicator lesions. 2 patients, one in each arm, refused further reassessment. This left 173 fully evaluable of 177 eligible patients.

The CR and PR rate (CR and PR) was 15/90 (17%, 95% confidence interval CI 10–26%) for formestane and 14/83 (17%, CI 10–27%) in the MGA arm. The difference between the two treatment arms was non-significant (Fisher's exact test $P = 1.00$). If disease stabilisation lasting at least 6 months was included in the objective response rate, the figures were 38/90 (42%, CI 32–53%) for formestane and 32/83 (39%, CI 28–50%) for MGA, which were also non-significantly different ($P = 0.64$). 34% of the patients in both arms had progressive disease as the best response. The early treatment failure rate was 13% (95% CI 7–22%) for formestane and 28% (CI 19–30%) for MGA. This difference reached statistical significance (Fisher's exact test $P = 0.015$). In patients with positive ER status, the response rate for formestane and MGA was 16% and 17%, respectively. Details are shown in Table 3. Median time to treatment failure was 120 days in the formestane

Table 2. Tumour localisation at study entry

	Formestane		MGA		Total	
	N	(%)	*N*	(%)	*N*	(%)
Bone	68	(75)	53	(62)	121	(68)
Liver	8	(9)	18	(21)	26	(15)
Lung	20	(22)	28	(33)	48	(27)
Pleura	17	(19)	15	(17)	32	(18)
Lymph nodes	32	(35)	29	(34)	61	(34)
Skin	12	(13)	12	(14)	24	(14)
Brain	0	(0)	2	(2)	2	(1)
Other	6	(7)	4	(5)	10	(6)
Viscera	37	(41)	46	(53)	83	(47)
Soft tissue	37	(41)	38	(44)	75	(42)
Total numbers of patients	91		86		177	

arm and 111 days in the MGA arm. The hazard ratio of MGA versus formestane was 1.2 ($P = 0.17$).

169 of the 176 treated patients had treatment failure at the time of analysis (August 15, 1996). The probability of treatment failure over time can be seen in Figure 1. The causes of treatment failures are summarised in Table 4. Progressive disease was the main reason for treatment failure in both arms. Toxicity as an exclusive cause of treatment failure was infrequent and there was no significant difference between the treatment arms (Fisher's exact test $P = 0.12$). If toxicity cases in the categories 'death due to other reasons' and 'other causes of treatment failure' were also taken into account, then the rate of treatment failure caused by toxicity in the formestane arm remained the same, i.e. 1 of 85 (1%, CI 0.03–6%), but became 12 of 84 (14%, CI 8–24%) in the MGA arm (Fisher's exact test $P = 0.0012$). Similarly, the rates of treatment failure caused by cardiovascular problems were 0 of 83 cases with formestane, but 9 of 84 cases for MGA (11%, CI 5–19%) ($P = 0.0012$) (Table 4). No toxicity at injection site for formestane i.m. administration was claimed for treatment failure.

Multivariate Cox regression analysis on time to treatment failure in 176 treated patients with treatment and tumour localisations at study entry as explanatory variables were investigated (Table 5). Although there were significantly more liver metastases in the MGA arm, it was not a significant factor for TTF in model 1 (Table 5). Other disease localisations and bone were most important for TTF. In model 2 bone was the most significant factor but visceral and soft tissue disease were also significant.

Toxicity

One patient in the MGA arm had refused to start treatment and was therefore not evaluable for toxicity. 5 patients died before the first follow-up and did, therefore, not contribute assessments between study entry and treatment failure. However, they were included in the analysis of TTF. The causes of their deaths were tumour progression in one case on formestane; and four cases, treated with MGA due to suspected lung embolism and tumour progression; sepsis; lung embolism; and acute cardiac failure (Table 4). This left 171 patients for toxicity analysis (Table 6). Approximately 40% of patients had no toxicity and approximately 30% had only mild toxicity. 30% of the patients had clinically relevant grade 2 and 3 toxicity. Overall, hot flushes and sleeping problems were the most frequent side-effects without significant differences between the treatment arms. Deep vein thrombosis was seen in 5 patients who received MGA and in none of the patients given formestane (Fisher's exact test $P = 0.022$). Pulmonary embolism was observed in 2 out of 81 patients treated with MGA and in 1 out of 90 patients treated with formestane. These results are summarised in Table 7.

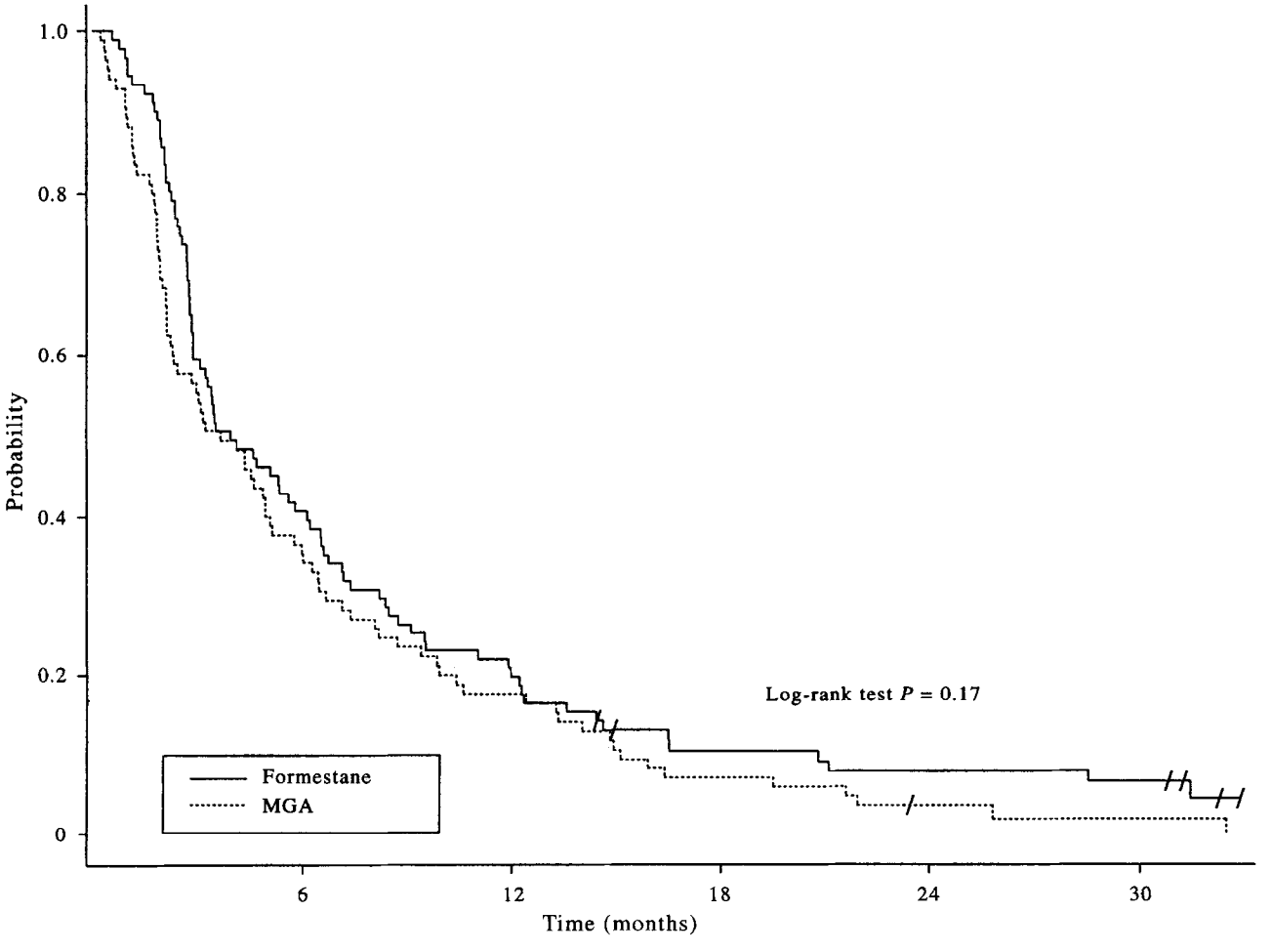

Figure 1. Time to treatment failure.

Table 4. Causes of treatment failure

	Formestane		MGA	
	n	(%)	*n*	(%)
PD	80*	(94)	67*	(80)
Bone	51		25	
Liver	16		15	
Lung	16		18	
Lymph nodes	16		15	
Pleura	13		7	
Skin	4		9	
Other localisation	14		9	
Toxicity	1	(1)	5*	(6)
Deep vein thrombosis	0		1	
Pulmonary embolism	0		2	
Weight gain	0		1	
Hot flushes	1		1	
Neurological disturbance	0		1	
Cerebral bleeding	0		1	
Cardiac failure	0		2	
Other toxicity	0		1	
Death	2	(2)	4	(5)
Due to tumour	2		0	
Due to other reasons	0		4	
Other cause of treatment failure	2	(2)	8	(10)
Due to patient refusal	1		2	
Due to other reasons	1		6	
Total	85		84	

*The numbers in the overall items are smaller than the sums of the corresponding subitems because some patients had contributions to multiple subitems.

Clinically relevant—grade 2 and 3—sleeping problems and/or hot flushes were more frequently seen in the formestane arm (24% versus 12%) and reached borderline statistical significance ($P = 0.051$). Cardiovascular problems of any grade were more frequently observed in the MGA group: 6/90 patients treated with formestane and in 13/81 patients treated with MGA (Fisher's exact test $P = 0.044$). Furthermore, moderate and severe life-threatening cardiovascular events were also significantly more frequent in patients treated with MGA (15% versus 3%: $P = 0.013$).

Specific toxicity at injection site of formestane was unusual. Only 6 patients ever had erythema, 2 patients had sterile lumps, 1 patient had a haematoma and 6 patients reported pain at injection site. 3 further patients reported complaints which were most probably not caused by formestane injections.

Weight gain and hypertension were assessed as differences from baseline values at study entry. Overall weight gain was more frequently seen in patients treated with MGA but was statistically non-significant ($P = 0.08$). This is especially true for the subcategory of clinically relevant weight gain (≥3 kg) which was seen in 32% of MGA-treated patients, but only in 20% of formestane-treated patients. There was no significant difference between the treatments regarding changes in the blood pressure, either newly developed arterial hypertension or clinically relevant increase of blood pressure as described in the protocol ($P = 0.25$). Selected laboratory parameters, haemoglobin, white blood cell count, platelets, alkaline phosphatase, AST, ALT, bilirubine and creatinine were documented at baseline and compared to the worst grade toxicity during treatment. No significant difference between the two treatment arms except for white blood cell count was seen. More formestane-treated patients experienced leucopenia than MGA-treated patients (27% versus 7%) ($P = 0.004$). However, 23% of the patients and 5% of the patients, respectively, had only WHO grade 1 leucopenia.

Overall, approximately 39% of the patients had no toxicity, 29% had only mild toxicity, and 32% had moderate, severe or life-threatening toxicity.

Crossover treatment

39 out of 85 (46%) patients randomised to the formestane arm and 36 out of 84 patients (43%) randomised to the MGA arm changed to the optional alternative compound after failure of the randomised treatment. To date, there are still 8 patients under the optional treatment whose responses and treatment duration are not yet available. None of the 33 patients in the formestane arm and 3 out of 33 patients (9–95% CI, 2–24%) in the MGA arm had a partial remission. Additionally, 13 patients reached disease stabilisation, 4 in the formestane arm and 9 in the MGA arm lasting ≥6 months. Partial response and/or long-term disease stabilisation was thus obtained in 4/33 (12%, 95% CI, 3–27%) of the formestane treated patients and in 12/33 (36%, 95% CI, 20–55%) of MGA treated patients. The main cause of treatment failure was again progressive disease in both arms: 88% in the formestane arm and 94% in the MGA arm. The median time to treatment failure was 84 days (range 16–880 days) with formestane and 104 days (20–525 days) with MGA.

Table 5. Results of multivariate Cox regressions on TTF

	Model 1		Model 2	
Explanatory variables	Hazard ratio	*P*-value	Hazard ratio	*P*-value
Treatment (MGA versus Formestane)	1.31	0.11	1.31	0.09
Bone (yes versus no)	1.79	0.002	1.94	0.004
Liver (yes versus no)	1.09	0.71		
Lung (yes versus no)	1.46	0.05		
Pleura (yes versus no)	0.92	0.68		
Lymph nodes (yes versus no)	1.39	0.06		
Skin (yes versus no)	0.95	0.84		
Other (yes versus no)	3.36	0.0001		
Viscera (yes versus no)			1.46	0.2
Soft tissue (yes versus no)			1.43	0.04

Table 6. Worst toxicity during treatment

	Formestane		MGA	
	n	(%)	*n*	(%)
Sleep problems (Fisher's exact test $P = 0.59$)				
Mild	26	(29)	21	(26)
Moderate	10	(11)	6	(7)
Hot flushes (Fisher's exact test $P = 0.38$)				
Mild	25	(28)	20	(25)
Moderate	13	(14)	7	(9)
Severe	1	(1)	0	(0)
Tremor (Fisher's exact test $P = 0.90$)				
Mild	5	(6)	6	(7)
Moderate	2	(2)	1	(1)
Neurological disturbance (Fisher's exact test $P = 0.47$)				
Mild	12	(13)	8	(10)
Moderate	3	(3)	4	(5)
Severe	0	(0)	2	(2)
Superficial phlebitis (Fisher's exact test $P = 0.42$)				
Yes	2	(2)	4	(5)
Deep vein thrombosis (Fisher's exact test $P = 0.022$)				
Yes	0	(0)	5	(6)
Pulmonary embolism (Fisher's exact test $P = 0.60$)				
Yes	1	(1)	2	(2)
Weight gain (Fisher's exact test $P = 0.08$)				
<3 kg	71	(79)	54	(67)
≥3 kg	18	(20)	26	(32)
Unknown	1	(1)	1	(1)
Hypertension (Fisher's exact test $P = 0.25$)				
Yes	33	(37)	23	(28)
Unknown	4	(4)	3	(4)
Other toxicity (Fisher's exact test $P = 0.12$)				
Mild	16	(18)	11	(14)
Moderate	3	(3)	9	(11)
Severe	0	(0)	1	(1)
Total number of patients	90		81	

Table 7. Worst toxicity in summary variables

	Formestane		MGA	
	n	(%)	*n*	(%)
Sleep problems and/or hot flushes (Fisher's exact test $P = 0.18$)				
Mild	28	(31)	30	(37)
Moderate	21	(23)	10	(12)
Severe	1	(1)	0	(0)
Tremor and/or neurological disturbance (Fisher's exact test $P = 0.63$)				
Mild	13	(14)	10	(12)
Moderate	5	(6)	5	(6)
Severe	0	(0)	2	(2)
Thromboembolism* (Fisher's exact test $P = 0.20$)				
Yes	3	(3)	7	(9)
Cardiovascular problems† (Fisher's exact test $P = 0.044$)				
Mild	3	(3)	1	(1)
Moderate	2	(2)	6	(7)
Severe	1	(1)	6	(7)
Any toxicity‡ (Fisher's exact test $P = 0.16$)				
Mild	29	(32)	21	(26)
Moderate	25	(28)	19	(23)
Severe	2	(2)	8	(10)
Total number of patients	90		81	

*Including superficial phlebitis, deep vein thrombosis and pulmonary embolism. †Including thromboembolism, oedema, cardiac failure, cerebral bleeding and lung embolism. ‡The worst grade of any toxicity in this table.

DISCUSSION

It is now a century since a response to endocrine manipulation in advanced breast cancer was first reported [4] and over 25 years since the first clinical use of tamoxifen [7]. Tamoxifen has now become the single most important endocrine therapy for early and advanced breast cancer. In patients with advanced disease, the selection of endocrine agents is mainly based on its toxicity profile. Tamoxifen has remained the agent of choice in the first-line treatment of advanced disease despite the fact that several studies have shown higher response rates for medroxyprogesterone acetate [8] or aminogluthetimide [9].

However, recently published studies have shown that second-generation aromatase inhibitors, without need for corticoid replacement, produce little toxicity, whereas clinically relevant toxicity, especially thromboembolic events and hot flushes, are more frequently seen with tamoxifen compared to fadrozole-treated patients [10, 11]. Thus, the development of non-toxic aromatase inhibitors in patients failing tamoxifen has become more and more important. Formestane was the first second-generation aromatase inhibitor developed and clinically tested. Our study confirmed that formestane is a non-toxic endocrine treatment in patients with advanced disease or disease progression following tamoxifen treatment.

In our study, the patients' characteristics with regard to known prognostic factors were well balanced between the treatment arms, with the exception of the presence of liver metastases which showed a small, but statistically significant imbalance in favour of patients randomised to formestane. Patients randomised to MGA had more liver metastases than patients randomised to formestane. However, this small imbalance did not affect the overall results of the study. Cox multivariate regression analysis showed that presence of liver metastases was not associated with response to treatment. Overall time to treatment failure and survival were not statistically significant between the two treatment arms, and comparable to results of recently published endocrine treatment for advanced breast cancer [10, 11]. Nevertheless, there is the possibility that the higher presence of liver metastases in the MGA arm might have contributed to the higher number of early failures in the MGA group.

Another difference was in body weight, which was significantly higher in the formestane arm but body weight is not a prognostic factor by itself, although adipose tissue is the main source of oestrogens in postmenopausal women. However, we cannot exclude the possibility that a higher body weight can favour the outcome of patients treated with an aromatase inhibitor such as formestane. The differences in body weight, in the proportion of patients with visceral dominant disease, and the higher frequency of ER and PgR negative tumours in the MGA arm, although not significant, might have precluded the possibility of perceiving a small difference in efficacy between the treatment groups.

The lower response rates than expected in both arms most probably reflects the inclusion of patients with less favourable prognosis, although the majority of patients had ER-positive disease. The high proportion of patients with bone metastases who frequently did not achieve an objective response, due to the lack of clear-cut remineralisation, also contributes to the observed results. Furthermore, the stricter application of response criteria and the inclusion of all patients with early failure in the analysis for efficacy results in a lower response rate compared to the reports of earlier

conducted trials. Nevertheless, aproximately 1 out of 4 patients treated with formestane and 1 out of 5 patients treated with MGA achieved disease stabilisation >6 month. The duration of response and survival for patients with advanced breast cancer who achieve disease stabilisation with endocrine treatment are similar to those women who have an objective partial remission. This category of patients can, therefore, be included in the objective response rate of a given (endocrine) treatment, as suggested by many oncologists [12, 13].

Comparing progressive disease in different sites (Table 4) with tumour localisation at study entry (Table 2), we observed a substantial higher rate of progression in bones in the formestane group (51/68) than in the MGA group (25/53). Progressive disease in the lung was more frequent in the formestane group (16/20) than in the MGA group (18/28). In the formestane group, progressive disease in the liver occurred in all 8 patients with liver metastases at study entry and in another 8 patients. In the MGA arm, 3 of the 8 patients with liver disease at study entry did not show progressive disease in the liver and no other patients developed liver metastases. These findings suggest that MGA could be more effective than formestane in these disease sites.

Both drugs were well tolerated and toxicity as the only reason for treatment failure was infrequently observed. 70% of the patients had no clinically relevant toxicity with either treatments. Overall, there was no difference between the frequency of side-effects with both treatments. However, MGA was associated with significantly more clinically relevant (WHO grade ≥ 2) toxicity. Deep vein thrombosis was disgnosed in 5 patients randomised to MGA, but no case was reported in patients randomised to formestane. Cardiovascular problems with moderate, severe or life-threatening toxicity were significantly more often observed in the MGA arm (15% versus 3%) than in the formestane arm ($P = 0.013$). Cardiovascular problems, such as deep vein thrombosis, pulmonary embolism, cerebral bleeding and cardiac failure, were the exclusive cause of treatment failure in 7 and contributed in at least 2 further cases to treatment failure in patients randomised to MGA. These events occurred in our study population despite the fact that patients with a prior history of thromboembolic event, cardiac comorbidity and patients on oral anticoagulation, irrespective of its indication, were excluded from the study. None of the patients randomised to formestane had treatment failure because of cardiovascular toxicity or problems at injection site. As expected, weight gain (≥ 3 kg) was more frequently seen in patients treated with MGA. Formestane was associated with little toxicity. Leucopenia, mostly of mild grade, was significantly associated with formestane treatment. Clinically relevant symptoms of oestrogen deprivation, such as hot flushes and associated sleeping problems, were more frequently seen with formestane. The difference between the treatment arms reached almost statistical significance ($P = 0.051$).

One out of 3 patients had at least one episode of moderate or severe toxicity. This figure might be regarded as high in postmenopausal patients on second-line hormonal treatment. We did not expect relevant differences in efficacy when the study was planned, but rather differences in the toxicity profile of the drugs. Therefore, toxicity was closely monitored and visit forms for documentation were especially designed to detect side-effects of the treatments. Recently available results from a European survey about living with advanced breast cancer hormone treatment showed that the side-effects of hormonal treatment are underestimated by physicians. Patients are often more willing to discuss these problems with the nurse which they would not raise with physicians because of embarrassment, fear, lack of time and relationship. The progestins and, to a lesser extent, the aromatase inhibitors aminogluthetimide and formestane, are perceived to be poorly tolerated, giving rise to side-effects such as weight gain, hot flushes, lethargy, tiredness, irritability, vaginal bleeding and dyspnoea [14]. These facts might, therefore, explain the relatively high rate of relevant toxicity reported in our study—the relatively low toxicity rates reported in other endocrine studies in advanced postmenopausal breast cancer.

Approximately half the patients changed to the alternative compound at the time of treatment failure, but only a few patients achieved a partial remission. Nevertheless, objective response and disease stabilisation of at least 6 months duration with third-line hormonal treatment was seen in 4/33 of the patients who crossed over to formestane and in 12/37 of those who crossed over to MGA. No statistical comparison between the two treatments has been attempted because conclusions drawn from such a comparison might be biased due to the lack of randomised assignment and the selection of patients who were crossed to the optional treatment.

The long median TTF seen with both drugs demonstrates that an interesting proportion of patients could benefit for a considerable time from both treatments. These results also confirmed our previous experiences of successful sequential endocrine treatment in advanced breast cancer [11, 15].

Our results are in accordance with results obtained in several phase II studies [16], involving 361 patients, yielding a response rate of 19% with disease stabilisation in a further 20% of the patients. Median duration of response in these studies ranged from 13 to 33 months, the median time to progression from 80 to 120 days [16]. Our results are also in accordance with a large multicentre study, involving 479 evaluable patients and comparing the same drug regimens as second-line endocrine therapy in postmenopausal patients with advanced breast cancer as in our study. There was also no statistically significant or clinically relevant difference in time to treatment failure, overall survival, response rate and response duration between formestane and megestrol acetate. As in our study, megestrol acetate was associated with significantly more cardiovascular events and weight gain [17].

Other aromatase inhibitors of the third generation cam be administered orally such as the non-steroidal compounds anastrozole and letrozole. Both drugs were compared to megestrol acetate in postmenopausal patients with advanced breast cancer as a second-line treatment: anastrozole at a dose of 1 mg or 10 mg daily, has been compared with megestrol acetate 160 mg daily in 378 patients. There was no statistically significant difference between either doses of anastrozole and megestrol acetate in terms of response rate or time to treatment failure in previous publications. The three treatments were well tolerated but more patients treated with megestrol acetate reported weight gain, oedema and dyspnoea compared to patients treated with anastrozole [18]. A recent update on these anastro-

zole trials showed a significant survival advantage for patients treated with anastrozole [19]. In a large multicentre study, letrozole was also compared to megestrol acetate as second-line treatment in postmenopausal patients with advanced disease. Five hundred and fifty-one patients were entered in the study and received, double-blind, either letrozole 0.5 mg or 2.5 mg daily, or megestrol acetate 160 mg daily. Results showed a dose effect of letrozole and superiority of 2.5 mg letrozole over megestrol acetate in terms of response rate (23.6% versus 16.4%) and the risk ratio of time to treatment failure (0.77, $P = 0.04$). Letrozole was also significantly better tolerated with respect to serious adverse experiences and discontinuation of treatment due to poor tolerability [20].

Formestane has also been tested as a first-line treatment and compared to tamoxifen in a multinational, randomised study, involving 409 postmenopausal women with advanced breast cancer [6]. No difference in terms of objective response rate was observed, but time to treatment failure and time to progression were of longer duration in the tamoxifen treated group. Median survival times were similar in both arms. Both therapies were generally well tolerated. Formestane, as third- or fourth-line endocrine treatment, achieved a response rate of 22% with a median duration of 10 months, and a further 20% of patients had disease stabilisation in 147 patients who failed multiple prior endocrine therapies. The investigators noted a particularly interesting activity of formestane in patients who failed prior treatment with the non-steroidal compound aminogluthetimide [21].

In conclusion, second-generation aromatase inhibitors, such as formestane, are effective endocrine agents in postmenopausal patients with advanced breast cancer. In our study, formestane was as effective as megestrol acetate. Both treatments have distinctive toxicity profiles, formestane being associated with more clinically relevant symptoms of oestrogen deprivation, such as hot flushes and sleeping problems, as well as with mild leucopenia. MGA was significantly associated with cardiovascular problems and weight increase. Clinically relevant or life-threatening toxicity was significantly more often observed in patients with MGA and more patients treated with the progestin had treatment failure because of toxicity. Thus, formestane was better tolerated than MGA. There is emerging evidence that aromatase inhibitors with low toxicity are preferable to progestins in the treatment of postmenopausal patients with advanced breast cancer failing tamoxifen treatment.

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