Combined Treatment With Buserelin and Tamoxifen in Premenopausal Metastatic Breast Cancer: a Randomized Study

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Background: **Surgical or medical castration and antiestrogenic treatment with tamoxifen are common endocrine treatments for premenopausal women with breast cancer. However, tamoxifen therapy induces high levels of plasma estradiol, with unknown long-term effects. In this study, we investigated the effect of combining estrogen suppression with the luteinizing hormone-releasing hormone agonist buserelin and estradiol receptor blockade with tamoxifen to determine whether the high estradiol levels induced by tamoxifen could be reduced and whether the antitumor effects would be better.** ***Methods:*** **In a three-arm, randomized, prospective trial, from 1988 through 1995, a total of 161 premenopausal patients with advanced breast cancer were randomly assigned to treatment with buserelin, tamoxifen, or both. Patients with steroid receptor-negative tumors or with tumors of unknown receptor status who had a disease-free interval of less than 2 years were excluded. The median follow-up was 7.3 years, during which 76% of the patients died, all of breast cancer. Patient and tumor characteristics were well balanced among treatment groups. All *P* values are from two-sided tests.** ***Results:*** **Combined treatment with buserelin and tamoxifen was superior to treatment with buserelin or tamoxifen alone by objective response rate (48%, 34%, and 28% of patients who could be evaluated, respectively; *P* = .11 [χ^2 test]), median progression-free survival (9.7 months, 6.3 months, and 5.6 months; *P* = .03), and overall survival (3.7 years, 2.5 years, and 2.9 years; *P* = .01). Actuarial 5-year survival percentages were 34.2% (95% confidence interval [CI] = 20.4%–48.0%), 14.9% (95% CI = 3.9%–25.9%), and 18.4% (95% CI = 7.0%–29.8%), respectively. No differences in antitumor effects were observed between single-agent treatment groups. During combined treatment or treatment with buserelin alone, plasma estradiol levels were suppressed equally; in contrast, during treatment with tamoxifen alone, plasma estradiol levels increased threefold to fourfold over pretreatment levels.** ***Conclusion:*** **Combined treatment with buserelin and tamoxifen was more effective and resulted in longer overall survival than treatment with either drug alone. [J Natl Cancer Inst 2000;92: 903–11]**

Many steroid and peptide hormones, growth factors, and other trophic substances are involved in the growth regulation of breast cancer *(1–4).* Endocrine treatment of breast cancer is designed to decrease plasma concentrations of one or more of these hormones and growth factors or to inhibit the biologic effects of these trophic substances directly in the tumor cell. Deprivation or antagonism of estradiol, a growth-stimulating hormone for estrogen-dependent breast cancers, is especially important. Endocrine therapy for breast cancer consists of a variety of medical and surgical ablative treatments *(2,5–10).* For premenopausal patients with metastatic breast cancer, the classic treatment is ovariectomy *(11).* After DeSombre et al. *(12)* showed that a luteinizing hormone-releasing hormone (LHRH) analogue could induce tumor regression in an experimental tumor model system, the results of the first clinical study with an LHRH analogue were reported by Klijn and de Jong *(13).* Since then, a series of more than 13 phase II studies with various LHRH agonists, such as goserelin, buserelin, and others, have shown an objective response in 161 (38%) of 419 patients *(14).* Overall, the objective response rate in estrogen receptor-positive tumors was 50%.

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See "Notes" following "References."

See "Appendix" section for list of other members participating in the study.

Although direct antitumor effects of LHRH analogues have been demonstrated *in vitro* and specific LHRH-binding sites have been found in 52%–67% of primary human breast cancers [for review, *see (15)*], the main mechanism of action of LHRH analogues is medical castration. The application of depot formulations (long-acting subcutaneous or intramuscular implants) of various LHRH agonists caused long-term suppression of ovarian estrogen secretion *(14,16–18).* A recent randomized study of 138 premenopausal patients with estrogen receptor-positive and progesterone receptor-positive metastatic breast cancer *(19)* showed that treatment with the LHRH agonist goserelin resulted in failure-free survival and overall survival similar to those observed after ovariectomy.

Tamoxifen is now the standard first-line therapy for postmenopausal metastatic breast cancer and is also accepted as an alternative to ovariectomy in premenopausal patients *(5–10).* Based on eight phase II and two phase III clinical studies involving a total of 348 premenopausal patients treated with tamoxifen *(5),* an objective response was observed in 103 patients (30%). However, the group of premenopausal women treated with tamoxifen had very high levels of plasma estradiol, sometimes for many years, because of the tamoxifen-induced stimulation of pituitary–ovarian functions *(2,5,9,20,21).* The possible deleterious effects of these high levels of plasma estradiol, which can compete with tamoxifen for binding to estrogen receptors, have been debated for many years *(20).* Furthermore, only two relatively small studies *(22,23)* have compared the effectiveness of surgical castration with that of tamoxifen and showed no major differences in results. However, no definite conclusions can be reached from these studies [*(22,23),* but *see also (5,9,19)*] because the power of each was very low. In contrast, for hormone-dependent breast cancer cells, *in vitro* studies *(24)* have shown that long-term withdrawal of estrogens increased the sensitivity of these cells to estradiol, suggesting that the addition of an antiestrogen might be valuable.

Combined treatment with LHRH analogues and other endocrine agents, such as tamoxifen, therefore, is of great interest *(2,25–29).* Endocrine studies *(2,26–29)* showed that an LHRH agonist given subcutaneously completely suppressed the tamoxifen stimulation of pituitary and ovarian functions and resulted in plasma estrogen levels that were comparable to normal postmenopausal levels. Thus, combination treatment with an LHRH agonist and tamoxifen can induce a so-called "complete estrogen blockade," which is the suppression of plasma estradiol levels by the LHRH agonist and blockade of the estrogen receptor by the antiestrogen. Previously, Klijn and Foekens *(26)* and Nicholson et al. *(29)* reported, in small nonrandomized studies, that a combined treatment of buserelin or goserelin with an antisteroidal agent increased the duration of response.

To test the hypothesis further, we designed a three-arm study to assess the antitumor and endocrine effects of long-term first-line combined endocrine treatment with buserelin (an LHRH agonist) and tamoxifen compared with treatment with each drug alone. To our knowledge, this study is the only three-arm, randomized study to investigate these treatments for metastatic breast cancer in premenopausal women.

PATIENTS AND METHODS

Patients and Treatment

During the period from 1988 through 1995, a total of 161 patients were recruited by 17 centers from nine countries. The patients were premenopausal and had metastatic or locally advanced breast cancer. They were equally and randomly assigned to one of three treatment groups according to European Organization for Research and Treatment of Cancer (EORTC) protocol 10881 approved by the Protocol Review Committee of the EORTC (Table 1). Stratification factors for the randomization included centers, receptor status, disease-free interval, and stage of disease (metastatic or locally advanced). All patients entered in this study were informed of the investigational nature of the study and provided informed consent in accordance with institutional guidelines. A premenopausal woman was defined as a woman who had a menstrual period less than 3 months before randomization. All patients had histologically proved breast cancer with at least one measurable lesion or a lesion that could be evaluated at the start of treatment. Eligibility criteria also included a positive estrogen receptor and/or progesterone receptor status ($\geq$10 fmol/mg of protein), irrespective of the duration of the disease-free interval, or an unknown steroid receptor status and a disease-free interval of at least 2 years or longer.

The following patients were excluded from the study: those with tumors that were both estrogen receptor negative and progesterone receptor negative, those with a poor performance status (World Health Organization [WHO] status of >3), those with rapidly progressing life-threatening disease (including extensive liver metastases, carcinomatous lymphangitic disease of the lungs, or central nervous system metastases), those with increased concentrations of plasma bilirubin (>30 μmol/L) or creatinine (>150 μmol/L), those with other concurrent or past malignancies (with the exception of adequately treated basal or squamous cell cancer of the skin and *in situ* carcinoma of the cervix), and those who were pregnant. Patients with previous systemic endocrine or chemotherapeutic treatment for advanced disease were not eligible. However, patients with previous adjuvant treatment with tamoxifen and/or chemotherapy were allowed if they had received no adjuvant chemotherapy for at least 6 months, if they had received no treatment with tamoxifen for more than 1 year before entry, and if amenorrhea had not occurred. Patients were randomly assigned by the EORTC Data Center to receive one of three first-line treatments (Table 1). These treatments were 1) buserelin implants (6.6 mg implanted subcutaneously every 8 weeks; during the first 12 weeks, every 6 weeks), 2) a daily dose of tamoxifen (40 mg administered orally), or 3) a combination of both drugs at the same dosages. When disease progression was detected, a crossover of drugs (tamoxifen after buserelin or buserelin after tamoxifen) in the single-treatment arms was advised but was not mandatory. Second-line treatment was left to the discretion of the local investigator in view of the highly heterogeneous conditions of individual patients during the course of metastatic disease, which required individually designed treatments. However, to be informed about the course of the disease from the time of tumor progression, survival curves from time to failure of first-line treatment were constructed.

Methods and Follow-up

Patients were clinically evaluated every 6 weeks for the first 12 weeks and every 8 weeks thereafter until disease progression. At each visit, all complaints, vaginal bleeding, hot flashes, and other side effects were recorded, in addition to medications taken and performance status. At each visit, a physical examination, measurement of palpable lesions, and limited blood tests (alkaline phosphatase

Table 1. Patient population and study design: European Organization for Research and Treatment of Cancer protocol 10881*

	Total	LHRH-A	TAM	LHRH-A + TAM
No. of patients registered	161			
No. of patients randomly assigned to treatment group	161	54	54	53
No. of patients ineligible and/or not assessable	16	7	4	5
No. of patients assessable for response	145	47	50	48
Median follow-up, y	7.3			
No. of patients with DP	149	49	51	49
No. of deceased patients	122	43	44	35

*LHRH-A = buserelin, a luteinizing hormone-releasing hormone agonist; TAM = tamoxifen; DP = disease progression during treatment irrespective of type of response.

and γ-glutamyltransferase) were also carried out. Complete routine hematology and blood chemistry were done every 16 weeks. Objective clinical assessment included specific x-rays, computed tomography scans of liver lesions, and photographs of skin metastasis every 8–16 weeks, as appropriate, and bone scans every 6 months. In nearly all centers, plasma estradiol levels were measured every 6–8 weeks during the first year and every 16 weeks thereafter by institutional standard assays. Values below the detection level of the respective estradiol assays were given the limiting value of the assay. Between centers, the upper levels of normal postmenopausal plasma concentrations varied from 19 pg/mL to 38 pg/mL. For a patient treated longer than 1 year and who had more than one plasma estradiol determination per year, the average estradiol value per year for that patient was used. Steroid receptor determinations were performed by a ligand-binding assay according to guidelines of the EORTC Biomarker Study Group *(30)*, by enzyme immunoassays *(31)*, or infrequently by immunohistochemistry. Response to treatment was assessed by use of standard criteria of the International Union Against Cancer *(32)*. For patients with bone metastases and a complete response, complete remineralization of lytic lesions in the bone was required, or, for a partial response, a clear improvement accompanied by a decrease in pain was required. Bisphosphonates were not used in this study. The Data Center and the study coordinator reviewed all forms.

Statistical Analysis

The study was designed to compare the objective response rate of the combined treatment with the objective response rate of the single-drug arms and to detect an increase from 40% to 60% in this rate. Therefore, the aim was to accrue 116 patients in each arm to reach a power of 80% for a two-sided test with an α value of .05. Accrual to the study was slower than expected and, because of the decreasing accrual and the rapidly increasing application and duration of systemic adjuvant therapy, the EORTC Breast Cancer Cooperative Group decided to terminate the study prematurely after 7 years.

In our analysis of the three treatment arms, we compared two time-to-event end points, progression-free survival and overall survival, as well as one ordered categorical end point, objective response rate, which consisted of four categories (i.e., complete remission, partial remission, no change, and progressive disease).

For the time-to-event end points, an overall test for the difference among the three treatment groups was based on the log-rank test *(33)* of data from all patients (intent-to-treat principle). The three treatment arms were also compared pairwise by the log-rank test. With the use of an overall statistical significance level of 5%, each pairwise comparison was tested at the 2% level according to Tukey's multiple comparisons method *(34)*. Survival curves for the three treatment groups were estimated by the Kaplan–Meier technique *(35)*. In addition, stratified analyses were done for the time-to-event end points, based on the Cox proportional hazards model *(36)* with the use of patient characteristics for which there appeared to be an imbalance as stratification factors (e.g., WHO performance status). If the stratified and unstratified analyses led to similar results, results of the more simple unstratified analysis are shown.

Furthermore, the effect of four prognostic factors—i.e., disease-free interval (<2 years or ⩾2 years), age (⩽40 years or >40 years), dominant site of disease (soft tissue, bone, or visceral), and adjuvant chemotherapy (yes or no)—on progression-free survival was studied and tested by the log-rank test. For the prognostic factors that statistically significantly influenced progression-free survival, a Cox proportional hazards model was fitted with and without the interaction between the treatment and the prognostic factor. A test for interaction used the likelihood ratio test to compare these two models *(37)*.

The test for the objective response rate was based on the Kruskal–Wallis test *(38)*. All patients who could be evaluated for response were used. In addition, the four categories were combined into two categories—i.e., responders (containing the categories complete remission and partial remission) and nonresponders (containing the categories no change and progressive disease)—and a χ^2 test was done on this binary variable *(39)*. The three treatment arms were also compared pairwise by the χ^2 test. Again, each pairwise comparison was tested at the statistical significance level of .02. A separate but similar analysis was performed after adding data from patients who had had stable disease for more than 6 months to the objective response category (complete remission, partial remission, and no change for >6 months). The same four prognostic factors were studied for the binary response variable and were tested with a χ^2 test. If a statistically significant effect was obtained, a logistic regression model with and without the interaction term was fitted, and the two models were again compared by the likelihood ratio test corresponding to a test for interaction. All *P* values are from two-sided tests.

Results

Patient and Tumor Characteristics

During the period from 1988 through 1995, a total of 161 patients were recruited by 17 centers from nine countries as follows: 64 patients from The Netherlands, 39 from France, 23 from Belgium, 16 from South Africa, eight from Poland, six from Spain, three from Austria, one from Germany, and one from Hungary. Nine patients were ineligible and were not evaluated, and seven additional eligible patients could not be evaluated. These 16 patients could not be evaluated because of missing information (eight patients) or protocol violations (eight patients). The protocol violations included incorrect receptor status (three patients), postmenopausal status (one patient), neoadjuvant chemotherapy (one patient), brain metastasis (one patient), treatment refusal (one patient), and early termination of tamoxifen after 3 days because of hot flashes (one patient). Thus, data from 145 patients could be evaluated for response (Table 1). The median follow-up of all 161 patients was 7.3 years. In total, 149 patients showed disease progression and 122 (76%) of the 161 patients died, all of breast cancer. The patient and tumor characteristics were well balanced over the three treatment groups (Table 2). A statistically significant difference was observed only for performance status, showing a slightly more favorable distribution in the group treated with tamoxifen. In addition, there was a trend to less visceral disease in the group treated with buserelin alone.

Antitumor Efficacy and Survival

Excluding patients who could not be evaluated, the objective response rate (complete remission and partial remission) was better in the group treated with the combination therapy (23 of 48 patients; 48%) than in the groups treated with buserelin alone (16 of 47 patients; 34%) or tamoxifen alone (14 of 50 patients; 28%) (Table 3). Taking all four types of response into account, there was a statistically significant difference in the objective response between the three treatment groups by the Kruskal–Wallis test ($P = .031$). If the four categories of response were combined into two categories (complete remission and partial remission versus no change and progressive disease), the difference in the response rate between the three treatment groups was not statistically significant (χ^2 test; $P = .11$). When we include the data from the 16 patients who could not be evaluated in the second category (no change and progressive disease), the same *P* values (both $P = .13$) resulted. However, when data from patients with stable disease for more than 6 months were added to the objective response category (complete remission, partial remission, and no change for >6 months), the objective response rate was statistically significantly better ($P = .007$) in the group with combination therapy (36 of 48 patients; 75%) than in the groups treated with buserelin alone (29 of 47 patients; 62%) or tamoxifen alone (22 of 50 patients; 44%).

Compared with patients in the combined-treatment arm, patients treated with buserelin alone or tamoxifen alone had a lower chance of having an objective response (complete remission and partial remission; odds ratios of 0.56 and 0.42, respectively). Response rates in patients in the single-treatment arms compared with those in the combined-treatment arm were different and led to unadjusted *P* values of .169 for buserelin and .042 for tamoxifen. In contrast, the response rates in patients

Table 2. Patient and tumor characteristics: all patients at entry in the study*

Characteristic	LHRH-A (n = 54)	Tamoxifen (n = 54)	LHRH-A + tamoxifen (n = 53)
Age, y			
Median	43	42	43
Range	28–58	24–51	31–50
Weight, kg			
Median	64	60	61
Range	45–89	46–90	43–84
World Health Organization performance status, No. (%)			
0	24 (53)	37 (79)	31 (61)
1	16 (36)	10 (21)	14 (27)
2	5 (11)	0 (0)	5 (10)
3	0 (0)	0 (0)	1 (2)
Disease stage, No. (%)			
Locally advanced	1 (2)	3 (6)	0 (0)
Metastases	49 (98)	50 (94)	51 (100)
Disease-free interval, No. (%)			
<2 y	18 (36)	21 (40)	20 (38)
⩾2 y	32 (64)	32 (60)	32 (62)
Surgery, No. (%)			
Yes	43 (86)	49 (92)	46 (88)
No	7 (14)	4 (8)	6 (12)
Adjuvant tamoxifen, No. (%)			
Yes	3 (6)	0 (0)	1 (2)
No	47 (94)	53 (100)	51 (98)
Adjuvant chemotherapy, No. (%)			
Yes	18 (36)	16 (30)	15 (29)
No	32 (64)	37 (70)	37 (71)
Dominant site, No. (%)			
Soft tissue	10 (21)	8 (15)	8 (16)
Bone	24 (50)	19 (37)	22 (43)
Visceral	14 (29)	25 (48)	21 (41)
Receptor status			
ER- and/or PgR-positive	35 (65)	40 (74)	40 (75)
Unknown	18 (33)	14 (26)	13 (25)
ER- and PgR-negative	1 (2)	— (—)	— (—)

*Because of missing data, the patient numbers with respect to different characteristics do not always add up to the same total number of patients. LHRH-A = luteinizing hormone-releasing hormone agonist (i.e., buserelin); ER = estrogen receptor; PgR = progesterone receptor.

treated with buserelin alone and in patients treated with tamoxifen alone were much more similar ($P = .52$).

The three treatment arms differed statistically significantly from each other with regard to progression-free survival (Table 3), with the median times to disease progression being 9.7 months for patients in the combined-treatment group, 6.3 months for patients treated with buserelin alone, and 5.6 months for patients treated with tamoxifen alone ($P = .03$; overall log-rank test) (Fig. 1). Presently, the longest duration of response and the longest duration of administration of combined treatment are more than 11 years. Compared with patients in the combined-treatment arm, patients treated with buserelin or tamoxifen alone showed poor progression-free survival, with hazard ratios of 1.65 (95% confidence interval [CI] = 1.09–2.49) and 1.50 (95% CI = 1.01–2.24), respectively (Table 3). Separate comparisons of the single-treatment arms to the combined-treatment arm showed differences in progression-free survival for both single-treatment arms and led to unadjusted P values of .008 for buserelin and .047 for tamoxifen. Progression-free survival values for patients treated with buserelin alone and for patients treated with tamoxifen alone were very similar ($P = .71$).

Thirty-five (66%) of the 53 patients in the combined-treatment group died, 43 (80%) of the 54 patients in the group treated with buserelin alone died, and 44 (81%) of the 54 patients in the group treated with tamoxifen alone died. The overall log-rank test for overall survival showed that these values were statistically significantly different ($P = .01$) (Fig. 2). Separate comparisons of overall survival among patients in the single-treatment arms and in the combined-treatment arm showed that these values were statistically significantly different, with unadjusted P values of .006 for buserelin and .029 for tamoxifen. Overall survival values in the groups treated with buserelin alone and tamoxifen alone were again similar ($P = .33$). The median overall survival was longer in patients after combined treatment (3.7 years) than in patients after treatment with buserelin alone (2.5 years) or tamoxifen alone (2.9 years) ($P = .01$) (Table 3). The death hazard ratios for patients treated with buserelin alone or tamoxifen alone were 1.95 (95% CI = 1.23–3.10) and 1.63 (95% CI = 1.03–2.59), respectively, when compared with patients receiving the combined treatment. The 5-year actuarial survival was higher for patients in

Table 3. Summary of results*

Parameter	LHRH-A (n = 54) No.	LHRH-A (n = 54) %	TAM (n = 54) No.	TAM (n = 54) %	LHRH-A + TAM (n = 53) No.	LHRH-A + TAM (n = 53) %	OR and/or HR† for LHRH-A versus combined	OR and/or HR† for TAM versus combined
Complete remission (CR)	2	4	2	4	3	6		
Partial remission (PR)	14	30	12	24	20	42		
No change (NC)	17	36	13	26	15	31	0.56 (0.24–1.30)	0.42 (0.17–1.06)
Progressive disease	14	30	23	46	10	21		
Could not be evaluated	7		4		5			
CR + PR + NC > 6 mo	29/47	62	22/50	44	36/48	75		
Median progression-free survival (95% confidence interval)	6.3 mo (4.7–8.3)		5.6 mo (4.5–8.5)		9.7 mo (7.8–14)		1.65 (1.09–2.49)	1.50 (1.01–2.24)
Median overall survival (95% confidence interval)	2.5 y (1.7–3.5)		2.9 y (2.2–3.8)		3.7 y (2.5–4.8)		1.95 (1.23–3.10)	1.63 (1.03–2.59)
Actuarial survival at 5 y	14.9%		18.4%		34.2%			
Actuarial survival at 7 y	5%		10%		30%			

*LHRH-A = luteinizing hormone-releasing hormone agonist (i.e., buserelin); TAM = tamoxifen. NC > 6 months = stable disease > 6 months.

†OR = odds ratio of having objective response (complete remission + partial remission versus no change + progressive disease); HR = hazard ratio for progression-free and overall survival (with 95% confidence intervals in parentheses).

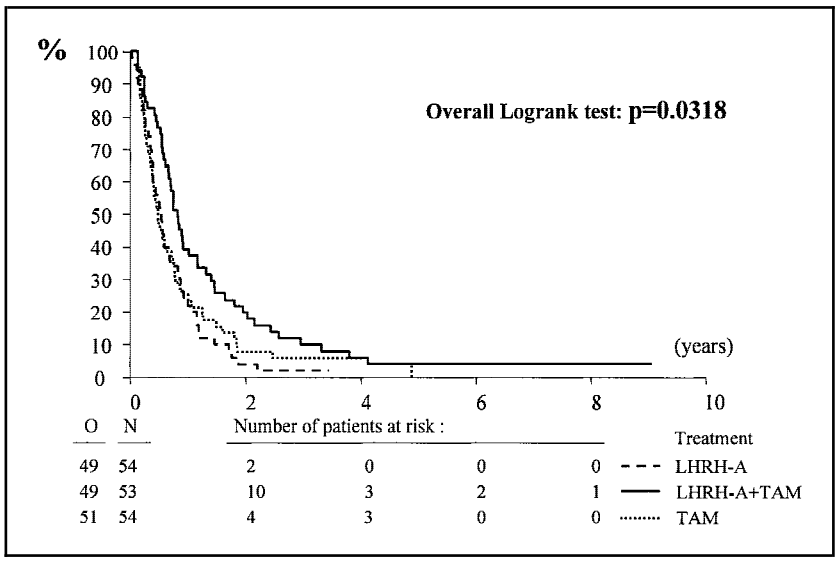

Fig. 1. Progression-free survival of all 161 patients. O = number of observed events; N = number of patients randomly assigned. LHRH-A = luteinizing hormone-releasing hormone agonist (i.e., buserelin); TAM = tamoxifen. *P* value is from a two-sided test. For more data, *see* Table 3.

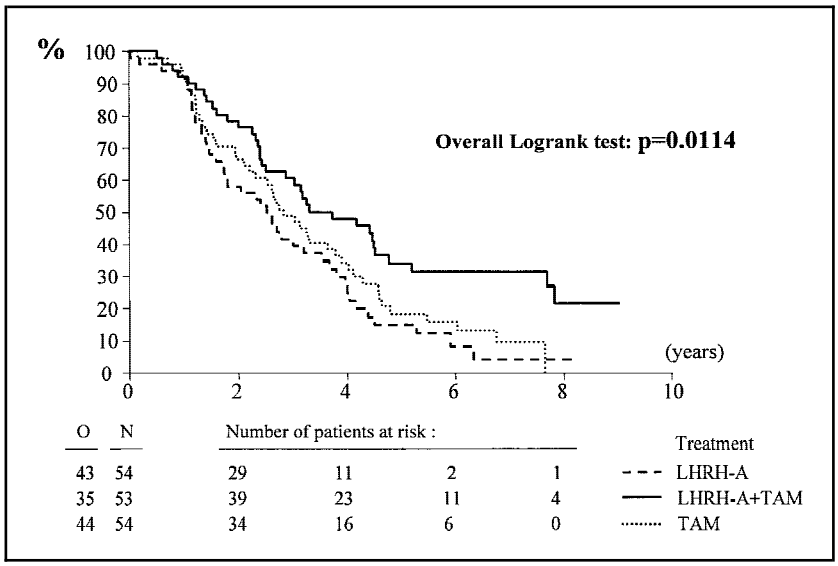

Fig. 2. Overall survival of all 161 patients. O = number of observed events; N = number of patients randomly assigned. LHRH-A = luteinizing hormone-releasing hormone agonist (i.e., buserelin); TAM = tamoxifen. *P* value is from a two-sided test. For more data, *see* Table 3.

the combined-treatment group (34.2%; 95% CI = 20.4%–48.0%), with a difference of 15.8%–19.3% in comparison to that for patients treated with buserelin alone (14.9%; 95% CI = 3.9%–25.9%) or tamoxifen alone (18.4%; 95% CI = 7.0%–29.8%) (Table 3).

Even when additional stratified log-rank tests were done, because of a slight imbalance in performance status (in favor of the tamoxifen treatment group), the results and conclusions did not change, indicating that the combined treatment was always better than the single-drug treatments.

For survival after disease progression, there was a borderline statistically significant difference among the three treatment arms ($P = .06$), with the median time to death from disease progression being 29 months for patients in the combined-treatment group, 18.3 months for patients treated with buserelin alone, and 27.1 months for patients treated with tamoxifen alone (Fig. 3). Compared with patients receiving combined treatment, patients treated with buserelin alone or tamoxifen alone showed hazard ratios of 1.7–1.45 for survival after disease progression. For survival after disease progression, comparison of the single-treatment arms with the combined-treatment arm showed differences, with unadjusted *P* values of .03 for buserelin alone and .088 for tamoxifen alone. Survival values for the group treated with buserelin alone and for the group treated with tamoxifen alone were very similar ($P = .41$).

Prognostic Factors

The disease-free interval was the only prognostic factor that had a statistically significant effect on progression-free survival ($P = .011$) and overall survival ($P = .02$). Patients with a disease-free interval of 2 years or longer had a median time to disease progression of 8.3 months, and patients with a disease-free interval of less than 2 years had a median time to disease progression of 6.4 months. The median time to death was 39.9 months for patients with a disease-free interval of 2 or more years; it was 32 months for patients with a disease-free interval of less than 2 years. The interaction between treatment and disease-free interval, however, was not statistically significant for progression-free survival ($P = .43$) and overall survival ($P = .93$).

The dominant site of disease was the only prognostic factor that had a statistically significant effect on the objective response rate ($P = .021$). The objective response rate was 59% for patients with soft-tissue disease, 27% for patients with bone metastases, and 39% for patients with visceral metastases. The interaction between treatment and dominant site, however, was not statistically significant ($P = .078$), although this interaction test is not powerful and is based on a restricted number of patients in each subgroup.

Endocrine Effects on Plasma Estradiol Levels and Menstrual Cycle and Side Effects

All patients with at least one estradiol measurement result before and/or during treatment were included in the endocrine study. Because of missing data and the decreasing number of patients without progressive disease, the number of patients evaluated decreased during follow-up (Table 4). In the two groups of patients treated with buserelin alone or buserelin with tamoxifen, both the median and the mean levels of plasma estradiol dropped to normal postmenopausal values within 6 weeks and remained suppressed throughout treatment in all patients (Table 4 and Fig. 4). In the group treated with tamoxifen alone, however, plasma estradiol levels increased on average threefold to fourfold in nearly all patients. In the same patients, this increase fluctuated widely during treatment but persisted for years throughout treatment with values of 1000 pg/mL or more (Table 4).

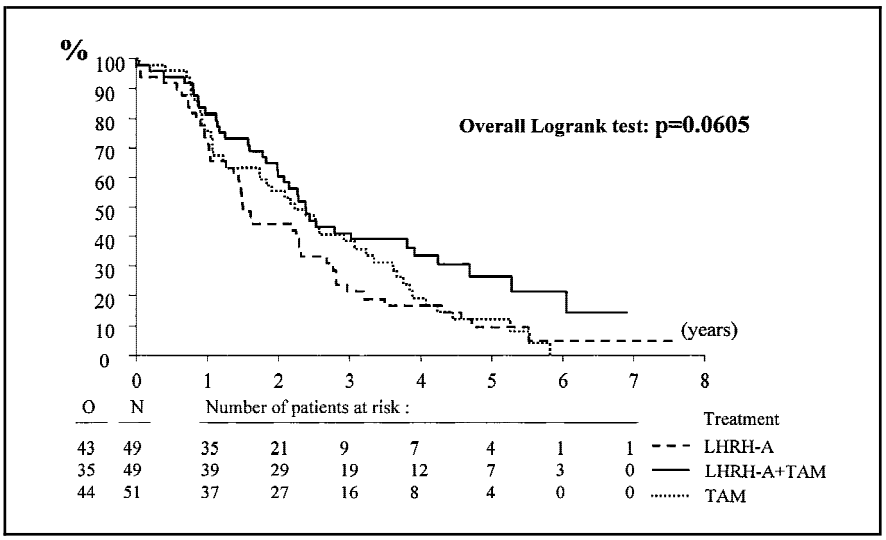

Fig. 3. Survival from detection of disease progression of all 161 patients from time to failure of first-line treatment. O = number of observed events; N = number of patients randomly assigned. LHRH-A = luteinizing hormone-releasing hormone agonist (i.e., buserelin); TAM = tamoxifen. *P* value is from a two-sided test. For more data, *see* Table 3.

Some patients could not be evaluated for amenorrhea and/or hot flashes because of a short period of treatment caused by early progressive disease, a prior hysterectomy without ovariectomy, or missing data. Hot flashes occurred less frequently ($P<.001$) during treatment with tamoxifen alone (17 of 43 patients; 40%) than during treatment with buserelin alone (38 of 43 patients; 88%) or during the combination treatment (41 of 47 patients; 87%). Amenorrhea also developed less often ($P<.001$) during treatment with tamoxifen (nine of 38 patients; 24%) than during treatment with buserelin alone (39 of 40 patients; 98%) or combined treatment (44 of 44 patients; 100%). Nausea was reported by five patients (three with WHO grade 1 and two with WHO grade 2; 12%) treated with tamoxifen alone, one patient (grade 1) receiving combined treatment, and no patients treated with buserelin alone. Nausea in the group treated with tamoxifen alone might have been partly related to the high plasma levels of estradiol that were comparable to those observed during pregnancy. Three patients in the group treated with tamoxifen alone experienced abdominal pain and discomfort caused by ovarian cysts (one underwent ovariectomy for that reason), one reported menometrorrhagia, and one reported visual disturbances. No endometrial carcinoma was reported. Overall, only two (1.2%) of 161 patients, both (i.e., two [3.7%] of 54) treated with tamoxifen alone, stopped treatment because of side effects (severe hot flashes).

DISCUSSION

Surgical ovariectomy has been used for the last 100 years as treatment for advanced breast cancer in premenopausal patients *(11)*. Phase II studies of medical treatment with tamoxifen *(5)* or LHRH agonists *(14)* showed response rates that were similar to those observed after surgical castration. Two randomized studies comparing surgical ovariectomy with tamoxifen *(22,23)* and two other randomized studies comparing surgical ovariectomy with the LHRH agonist goserelin *(19,40)* have been reported. Those studies showed that medical treatment and surgical ablation are equally effective. Therefore, it was not surprising that, in our three-arm randomized study, we did not find statistically significant differences in any of the three end points tested between groups treated with tamoxifen alone or buserelin alone. However, most reported randomized studies had a relatively low power. Therefore, the possibility of minor differences cannot be excluded. To detect such small differences, very large studies are required.

From an endocrine point of view, treatment with tamoxifen and buserelin resulted in important differences. Patients treated

Table 4. Plasma estradiol concentrations (pg/mL) before and during treatment*

	Follow-up										
Treatment	Baseline	6 wk	12 wk	20 wk	28 wk	36–44 wk	1 y	2 y	3 y	4 y	5–9 y
LHRH-A											
Median, pg/mL	114	20	20	11	15	16	22	7	9		
Mean, pg/mL	123	23	23	21	21	20	21	19	9		
No. of patients	37	30	32	27	19	15	9	3	1		
Range, pg/mL											
Lowest value	5	4	5	5	8	5	8	6			
Highest value	316	109	79	91	54	42	<38	45			
TAM											
Median, pg/mL	80	256	212	482	346	439	390	208	231	923	
Mean, pg/mL	123	425	451	481	339	537	338	149	245	923	
No. of patients	32	31	21	13	14	10	10	5	3	2	
Range, pg/mL											
Lowest value	4	5	33	5	65	35	8	8	131	269	
Highest value	544	1523	1632	1034	890	1438	653	269	374	1578	
LHRH-A + TAM											
Median, pg/mL	68	19	15	16	16	17	15	20	12	17	10
Mean, pg/mL	116	23	18	19	18	18	19	18	13	17	10
No. of patients	34	29	30	25	24	18	17	9	5	4	2
Range, pg/mL											
Lowest value	17	5	5	5	5	7	8	8	8	8	8
Highest value	750	107	63	71	56	42	49	34	24	26	11

*LHRH-A = luteinizing hormone-releasing hormone (i.e., buserelin); TAM = tamoxifen.

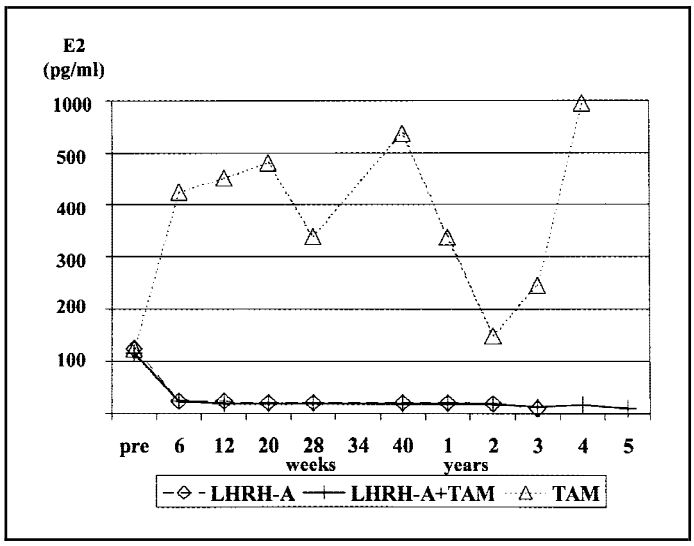

Fig. 4. Mean plasma estradiol levels before and during therapy with the three treatment regimens (*see* Table 4 for numbers of patients, median and mean values, and ranges). LHRH-A = luteinizing hormone-releasing hormone agonist (i.e., buserelin); TAM = tamoxifen; E2 = estradiol.

with tamoxifen alone had levels of plasma estradiol that were threefold to fourfold higher than pretreatment values, and the elevated levels persisted for several years. In contrast, patients treated with buserelin alone had postmenopausal levels of estradiol. Plasma estradiol levels induced by treatment with buserelin alone were similar to those reported for (short-term) treatment with goserelin [i.e., mean values of 20–23 pg/mL *(19,28)*]. Our combined-treatment regimen of buserelin and tamoxifen completely suppressed the tamoxifen-stimulated pituitary–ovarian axis and resulted in plasma estrogen levels that were similar to those observed during treatment with buserelin alone. In our trial, progression-free survival ($P = .03$) and overall survival ($P = .01$) in the group receiving combined treatment were statistically significantly superior to those in the groups receiving single-drug treatment (Figs. 1 and 2). Combined treatment also had a 14%–20% higher objective response rate, although the difference in response rate was not statistically significant ($P = .11$; Table 3). However, when disease that was stable for more than 6 months was included in the objective response category, the differences in clinical benefit in terms of response rate were highly statistically significant ($P = .007$).

Thus far, only two randomized studies *(40,41)* that compared a combined treatment (LHRH agonist and tamoxifen) and treatment with a single LHRH agonist (goserelin) have been reported, and one study in Japan is ongoing. However, none of these three studies included a third arm with tamoxifen alone. An arm for treatment with tamoxifen alone is desirable from a scientific point of view because it can be used to prove that the benefit of combined treatment is not simply caused by tamoxifen. A small Italian study *(40)* of 85 patients that had a two-by-two factorial study design and 18–24 patients per treatment group demonstrated a higher response rate in patients treated with goserelin plus tamoxifen (45%) than in patients treated with goserelin alone (27%). Although this difference of 18% is comparable to the results of our study, it was not statistically significant because of the low number of patients in the study. In addition, no differences with respect to survival and the results of surgical castration were observed. A second, larger international study *(41)* of 318 patients showed, in concordance with our study, a statistically significantly improved progression-free survival after combined treatment compared with that after a single treatment with goserelin ($P = .03$) but no statistically significant improvement in the survival or objective response rate (38% versus 31%). However, patients with estrogen receptor-negative tumors or an unknown estrogen receptor status, irrespective of the length of the disease-free interval, were also included in this study, which "diluted" the patient population with patients who had hormone-resistant breast cancer. However, within the subgroup of 115 patients with skeletal metastases only, statistically significant differences in favor of combination therapy were seen for the objective response rate, time to disease progression, and survival. Furthermore, preliminary results of a recent meta-analysis *(42)* of 506 patients treated in four randomized trials (including this study) showed that, for all three efficacy parameters (i.e., response rate, progression-free survival, and overall survival), combined treatment with an LHRH agonist plus tamoxifen was superior to treatment with an LHRH agonist alone. Unfortunately, a meta-analysis on comparisons between a combined-treatment arm and treatment with tamoxifen alone is not possible because of the lack of such studies.

In our study, there appeared to be no interaction between clinical prognostic factors and treatment. In unselected patients with visceral disease, endocrine treatment is generally less effective, which, however, is mainly due to the association with negative steroid receptor status *(43)*. Probably because we excluded steroid receptor-negative patients, visceral metastasis was not an important prognostic factor for progression-free survival and overall survival, but a relative high overall response rate of 39% for all treatment groups together was found (even about 60% during combined treatment).

The overall survival of patients with metastatic breast cancer is commonly comparable for combined endocrine treatment and sequential treatment *(9,10)*. In our study, we did not include a mandatory crossover for the single-treatment groups because crossover studies are difficult to conduct well *(19)*. The highly heterogeneous conditions of individual patients during the course of metastatic disease require various treatment approaches. However, we believe that there should be no major difference among the three arms of our study with regard to subsequent treatment regimens because the patients were randomly assigned according to individual center and were treated during the same study period with the same type of chemotherapeutic and endocrine agents. Thus, the most striking observation in our study is the highly statistically significant improvement in overall survival of patients receiving the combination treatment. This improvement could be the result of a higher response rate and longer progression-free survival after reduction to a substantially lower tumor load. The greater reduction in tumor load might have increased the sensitivity of the tumor to other types of subsequent treatment because of the general relationship between tumor load and resistance to treatment. Thus, our unexpected observation that patients receiving the combined first-line endocrine treatment tended to survive longer after disease progression (Fig. 3) is important—this in spite of the fact that fewer optional endocrine treatments were available for this group from the time of detection of progressive disease during first-line endocrine therapy.

The results of our study may also aid in the interpretation of results from published and ongoing (adjuvant) studies on standard-dose and high-dose chemotherapy. Adjuvant chemotherapy is more effective in premenopausal women than in postmenopausal women *(44)*, and this effect is positively associated with chemotherapeutically induced castration in nearly all trials *(45–49)*. Ablation of functioning ovaries and combination chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) have similar effects on disease-free survival and overall survival *(50)*. High-dose chemotherapy induces chemical castration in nearly 100% of the patients, in contrast to standard-dose chemotherapy, and high-dose chemotherapy is followed by adjuvant tamoxifen therapy in nearly all trials. Thus, the combination of high-dose chemotherapy and tamoxifen can also indirectly result in "complete estrogen blockade" in (nearly) all patients, in contrast to standard treatment *(51)*. Consequently, a small difference in survival in favor of high-dose chemotherapy can (at least partly) be explained by differences in indirect endocrine effects. This hypothesis is supported by the results of two randomized trials that show that adjuvant endocrine therapy, consisting of surgical or medical castration and treatment with tamoxifen, was statistically significantly superior to standard chemotherapy with FAC (5-fluorouracil, doxorubicin [i.e., Adriamycin], and cyclophosphamide) *(52)* or CMF *(49)*, although preliminary results of a third adjuvant study *(53)* did not reveal a difference between the results of treatment with CMF and the results of treatment with the LHRH agonist goserelin and tamoxifen. Recently, in addition to combination chemotherapy with cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF), combined treatment with goserelin and tamoxifen was shown to statistically significantly improve the disease-free survival (from 67% to 78%), but treatment with goserelin alone did not *(54)*. Therefore, it is important to determine whether the additional beneficial effect of combined endocrine therapy was reached, especially in women without chemotherapy-induced castration.

In conclusion, our unique three-arm, randomized study clearly showed that combined treatment with an LHRH agonist plus tamoxifen is superior to treatment with each drug alone, with respect to response rate, progression-free survival, and overall survival among premenopausal patients with metastatic breast cancer. Therefore, the results of our study are important for daily standard clinical practice, not only for patients with metastatic disease but also for patients with steroid receptor-positive primary tumors. We suggest that future studies also add aromatase inhibitors to the combined-treatment regimen; this treatment should further suppress plasma estradiol levels *(55,56)*.

APPENDIX

Other participating members of the European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group are as follows: R. Sylvester/EORTC Data Center, Brussels, Belgium; M. Namer, Centre Antoine Lacassagne, Nice, France; J. P. Julien, Centre Henri Becquerel, Rouen, France; J. Garcia Conde, Hospital Clinico Universitario, Valencia, Spain; M. Dünser and R. Margreiter, University Hospital, Innsbruck, Austria; T. Tjabbes, Sophia Hospital, Zwolle, The Netherlands; K. J. Roozendaal, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands; P. C. van der Velden, Stichting het van Weel-Bethesda Hospital, Dirksland, The Netherlands; J. W. R. Nortier, Diakonessenhuis, Utrecht, The Netherlands.

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NOTES

The authors are the writing committee of the European Organization for Research and Treatment of Cancer—Breast Cancer Cooperative Group.

We thank Hoechst AG, Frankfurt, Germany, for their support and for the free supply of buserelin. We also thank Petra Bos for typing the manuscript.

Manuscript received June 8, 1999; revised March 28, 2000; accepted March 30, 2000.