Randomized Adjuvant Trial of Tamoxifen and Goserelin Versus Cyclophosphamide, Methotrexate, and Fluorouracil: Evidence for the Superiority of Treatment With Endocrine Blockade in Premenopausal Patients With Hormone-Responsive Breast Cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5

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Purpose: **Effective adjuvant treatment modalities in premenopausal breast cancer patients today include chemotherapy, ovariectomy, and tamoxifen administration. The purpose of Austrian Breast and Colorectal Cancer Study Group Trial 5 was to compare the efficacy of a combination endocrine treatment with standard chemotherapy.**

Patients and Methods: **Assessable trial subjects (N = 1,034) presenting with hormone-responsive disease were randomized to receive either 3 years of goserelin plus 5 years of tamoxifen or six cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF). Stratification criteria included tumor stage and grade, number of involved nodes, type of surgery, and steroid hormone receptor content. Relapse-free survival (RFS) was defined as time from randomization to first relapse, local recurrence, or contralateral incidence, and overall survival (OS) as time to date of death.**

Results: **With a 60-month median follow-up, 17.2% of patients in the endocrine group and 20.8% undergoing chemotherapy developed relapses. Local recurrences emerged in 4.7% and 8.0%, respectively. RFS and local recurrence-free survival differed significantly in favor of endocrine therapy (*P* = .037 and *P* = .015), with a similar trend observed in OS (*P* = .195).**

Conclusion: **Overall, our data suggest that the goserelin-tamoxifen combination is significantly more effective than CMF in the adjuvant treatment of premenopausal patients with stage I and II breast cancer.**

J Clin Oncol 20:4621-4627.

THE ADJUVANT treatment of premenopausal patients with breast cancer is currently thought to be a domain of adjuvant chemotherapy. Above all, Bonadonna et al[1] have argued that premenopausal patients show a better response to adjuvant chemotherapy than postmenopausal women. Several overviews carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have furthermore indicated a 35% relative risk reduction for relapse, and 27% for death, in patients under 50 years of age, as compared with risks for relapse reduced by a mere 20%, and for death by 11%, in older trial participants. These results would support the hypothesis that cytotoxic treatments in premenopausal patients may act predominantly by way of endocrine manipulation rather than direct cytostatic action.[2] It has been demonstrated that patients undergoing an amenorrheic process induced by chemotherapy have a far better prognosis than those retaining their menstrual cycle.

It is interesting to note that—and currently not well understood why—premenopausal women with estrogen receptor (ER)–positive tumors, who should benefit from medical castration, in fact gain a lesser, insignificant benefit with respect to mortality reduction (20% ± 10%) than those showing tumors of lower ER levels (35% ± 9%).[3] We would argue that this observation can be explained by a direct cytotoxic effect of chemotherapy on all patients with ER-negative tumors (regardless of age), while the endocrine effects of chemotherapy are available only to those women in whom medical castration is achieved.

Apart from chemotherapy, two other modalities have proven important in the adjuvant treatment of premenopausal patients with breast cancer: tamoxifen administration and ovarian ablation. Tamoxifen given for 5 years produces a 40% (± 3%) reduction of relapse and a 23% (± 4%) reduction of death from any cause.[4,5] In turn, ovarian ablation has translated into absolute relapse-free survival (RFS) and overall survival (OS) rates improved by 6% and 6.3%, respectively, at least in the absence of chemotherapy.[6]

The following report presents information from an analysis of Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 5, at 5-year follow-up, randomizing premenopausal receptor-positive breast cancer patients with stage I and II disease to adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) compared with a combination endocrine treatment with goserelin and tamoxifen.

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Submitted September 24, 2001; accepted March 19, 2002.

Other members of the Austrian Breast and Colorectal Cancer Study Group are listed in the Appendix, available online at www.jco.org.

This article was published ahead of print at www.jco.org.

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0732-183X/02/2024-4621/$20.00

PATIENTS AND METHODS

Study Design

Initiated in 1990, this randomized, multicenter study was the fifth to be implemented by the ABCSG. As reported for previously launched ABCSG investigations, a large number of clinics and hospitals throughout Austria participated in Trial 5, while data collection, protocol review, monitoring of toxicity (scored according to World Health Organization recommendations) and events, and quality control procedures were performed centrally.[7,8] Premenopausal status was defined on the basis of ascertainable menses or an interval of no longer than 12 months since last menstruation. In clinically perimenopausal patients, follicle-stimulating hormone and luteinizing hormone serum levels were to correspond to those shown by premenopausal patients.

The trial subjects were stratified according to their tumor stage (< 2 cm, 2 to 5 cm, and > 5 cm), number of involved nodes, type of curative surgery, tumor grade according to Bloom and Richardson,[9] and steroid hormone receptor content established by biochemical and/or immunocytochemical means. In trial centers exclusively using the latter method to assay receptor status, the tumor tissue obtained was to show a minimum of 10% positively stained tumor cells to score as positive. Strongly positive ("double-plus") ER and/or progesterone receptor (PgR) status was diagnosed in the presence of either medium-range stain intensity and more than 70% positive cells or strong intensity and more than 30% positive cells.[10] Ninety percent of the receptor assays were done by immunocytochemistry.

Adaptive randomization was implemented according to Pocock and Simon.[11] After giving informed consent, patients were randomly allocated to receive either CMF or tamoxifen (Nolvadex; AstraZeneca Pharmaceuticals, Wilmington, DE) plus goserelin (Zoladex; AstraZeneca Pharmaceuticals). Trial 5 was not designed to test the role of combined chemoendocrine therapy, and no trial participant was administered tamoxifen after CMF treatment. Before initiation, Trial 5 was approved by the relevant medical ethics committees in Austria.

Patient Eligibility

Patients eligible for entry presented with stage I or II disease and complied with the following inclusion criteria: histologically confirmed complete removal of a unilateral carcinoma of the breast, pathologically clear margins, and level I and II axillary node dissection; pathologic examination of at least eight axillary nodes; ER and/or PgR levels ≥ 10 fmol/mg cytosol protein or immunocytochemically positive ER and/or PgR; and absence of metastases, confirmed by lung x-ray, liver ultrasound, and bone scan, or (if clinically indicated) computed tomography scan.

Exclusions

Patients were deemed unsuitable for participation in ABCSG Trial 5 if the following exclusion criteria could be applied: presence of noninvasive tumors; previous malignancy, with the exception of cured basal cell or squamous cell carcinoma of the skin or early cervical cancer; pregnancy or lactation; previous irradiation or preoperative antineoplastic or antihormonal treatment; lack of willingness to continue treatment; deficient contraception or further pregnancy desired; or mental or physical unsuitability for entry.

All trial subjects undergoing breast conservation were mandatorily administered radiotherapy, which was optional in those treated with mastectomy. In the chemotherapy arm, the sandwich technique was used with irradiation conducted after the first three cycles of CMF. Participants were required to be in good general health (Eastern Cooperative Oncology Group scale, level 0 or 1), to tolerate postoperative therapy, and to begin treatment within 4 weeks of surgery after submitting informed consent.

Treatment Regimens

CMF was administered intravenously for six cycles, on days 1 and 8, recycled on day 28, at the following doses: cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and fluorouracil 600 mg/m^2. Goserelin 3.6 mg per injection was given subcutaneously every 28 days for 3 years (39 injections). Tamoxifen 20 mg was administered orally once a day for 5 years.

Patient Evaluation

All patients received follow-up examinations every 3 months for the first 3 years and at 6-month intervals thereafter. Subjects were evaluated clinically and blood was drawn for laboratory analyses, including carbohydrate antigen 15-3 and carcinoembryonic antigen. Chest x-rays and liver ultrasounds were conducted twice a year and mammograms were performed annually. Gynecologic examinations were carried out every 6 months. Patients' first relapse, local recurrence, cancer in the opposite breast, and death served as primary end points for OS and RFS. Recurrences on the chest wall or in the axilla or the ipsilateral breast were defined as local recurrences; regional recurrences (supraclavicular) were classified as distant metastases. Second (non–breast cancer) malignancies and deaths without relapses were not included as events for calculating RFS. Whenever possible, local or regional relapses and contralateral incidences required histologic confirmation.

Statistical Analysis

This intent-to-treat analysis included all eligible patients whose baseline data were fully available for evaluation. Based on clinical measurements, the trial was originally designed to detect a difference in 5-year survival rates between the groups treated with combination endocrine treatment and chemotherapy. An original sample size of 660 patients, with 330 patients on each treatment arm, was considered adequate to detect a difference of 10% (65% to 75%) between the arms at a 5% significance level (two-sided log-rank test) and 90% power, when recruiting for a total of 4 years with a 5-year follow-up period. As to nodal status, the initial sample size was based on a distribution between two thirds lymph node–positive versus one third node-negative patients. The target sample size was increased to 1,050 on account of an unexpectedly large proportion of accrued patients presenting with lymph node–negative disease and a thus improved overall prognosis. The date of final analysis was October 12, 2000. All patient data, including information on administered treatment, assessed side effects and toxicity, controls, and the emergence of local relapses and/or distant metastases, were collected at the ABCSG's central data office and processed and analyzed by SAS software (SAS Institute, Cary, NC). Time to first relapse or death from randomization was estimated and graphically presented according to the method of Kaplan and Meier.[12] Differences between curves were assessed by the Mantel log-rank test for censored survival data.[13] The Cox proportional hazards model[14] was used to establish the prognostic value of treatment, tumor grade, tumor stage, lymph node status, ER and PgR, and age on the time of first relapse and survival time by the agency of univariate and multiple analyses. A trend test was performed for such ordered factors as tumor stage, lymph node status, ER and PgR content, and age on the assumption that the relative risk between two successive categories would remain the same. The Cox proportional hazards model was also applied to assess interactions between treatment and the other covariates. Amenorrhea was defined as having no menstrual bleeding for a minimum of 12 months and evaluated as a time-dependent explanatory covariate. Relapse was defined as the first reappearance of breast cancer at any local, distant, or contralateral site; patients who died because of reasons other than breast cancer were considered as censored with death. All *P* values are given from two-sided tests.

RESULTS

A total of 1,099 breast cancer patients were randomized between December 1990 and June 1999 (Table 1), representing one fourth of all eligible trial subjects in Austria. Thirty-three patients were found to be ineligible due to reasons that included previous antineoplastic/antihormonal treatment, delay of therapy

Table 1. Trial Information

	No.	%
Randomized patients	1,099	
Ineligible patients		
Did not fulfill eligibility criteria	33	
Lack of basic information	32	
Patients assessable for final analysis	1,034	
Median follow-up, months	60	
Deaths	96	9
Breast cancer-specific deaths	92	9
Relapses	197	19
Local recurrences	66	6

Table 2. Patient Characteristics According to Allocated Treatment

Characteristic	Endocrine Therapy Group (n = 511) (%)	Chemotherapy Group (n = 523) (%)
Pathologic tumor stage		
T1	57	58
T2	40	39
T3	4	4
Age		
< 35 years	7	7
≥ 35 years	93	93
Nodal status		
Negative	51	50
Positive: 1-10 nodes	46	48
Positive: > 10 nodes	3	2
Grading		
G1, G2, Gx	72	72
G3	28	28
Type of surgery		
Breast conservation	64	65
Mastectomy	36	35
Receptor status		
ER-negative	6	7
ER-positive	68	69
Strongly ER-positive	25	24
PgR-negative	9	11
PgR-positive	48	54
Strongly PgR-positive	43	34

onset, and deficient compliance with therapy as intended. Baseline data of relevance for evaluation, particularly with respect to prognostic factors, were deficient in another 32 of 1,066 women. Therefore, 1,034 assessable trial subjects, having completed a 60-month median follow-up, served as the basis for this analysis. Within this observation period, 197 patients (19%) experienced a relapse and 96 subjects died (92 from a cause associated with their malignancy).

As depicted in Table 2, patient characteristics were equally balanced between the endocrine and chemotherapy groups, with 511 and 523 trial participants, respectively. Seven percent were younger than 35 years of age. Close to two thirds of all trial subjects received breast conservation plus postoperative irradiation. The indication for radiotherapy in these patients was left to the discretion of the treating physician. Yet another small minority presented with an ER-negative tumor, 25% with a strongly ER-positive tumor, and 39% showed a strongly PgR-positive tumor.

After a median follow-up of 5 years, 92 out of 1,034 patients had died, 41 of whom had been treated in the endocrine arm and 51 in the chemotherapy arm (Table 3). A total of 197 women experienced a relapse, 88 and 109 in the hormonal and cytotoxic

Table 3. Five-Year Analysis of 1,034 Patients Randomized to Endocrine Therapy or Chemotherapy

Deaths and Relapses	Total	Endocrine Therapy Group (n = 511) No.	%	Chemotherapy Group (n = 523) No.	%	P Mantel	P Breslow
Breast-cancer specific deaths	92	41	8	51	10	.1900	.0900
Relapses	197	88	17	109	21	.0367	.0176
Local recurrences	66	24	5	42	8	.0135	.0029
Cancer of opposite breast	15	3	1	12	3	.0001	.0001

Table 4. Five-Year Analysis of Side Effects According to Allocated Treatment

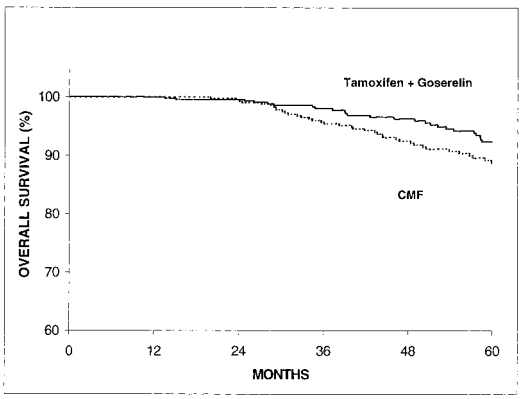
Side Effect	Endocrine Therapy Group (n = 511) (%)	Chemotherapy Group (n = 523) (%)
Hot flushes	91	54
Nausea	12	81
Alopecia	10	55
Depression	34	28
Vertigo	33	27
Pruritus	18	10
Stomatitis	4	23
Diarrhea	3	15
Fever	4	10

treatment groups, respectively. Local recurrences emerged in 66 patients (24 and 42, respectively). Fifteen patients developed a cancer in the opposite breast; three of them underwent hormonal treatment and 12 received CMF chemotherapy.

Table 4 lists side effects experienced in the course of the study. No treatment-related death was reported during follow-up. As expected, hot flushes were the major side effect arising from endocrine therapy and were experienced at least once by 91% of the patients in this group. On the other hand, such chemotherapy-typical side effects as nausea, alopecia, and hot flushes were encountered in the CMF therapy arm. Again, the latter side effect was identified as a predominant symptom, especially in amenorrheic patients.

Overall, treatment as intended was completed by 86% of the trial subjects after 3 years of combination endocrine therapy and by 83% of patients undergoing 6-month chemotherapy.

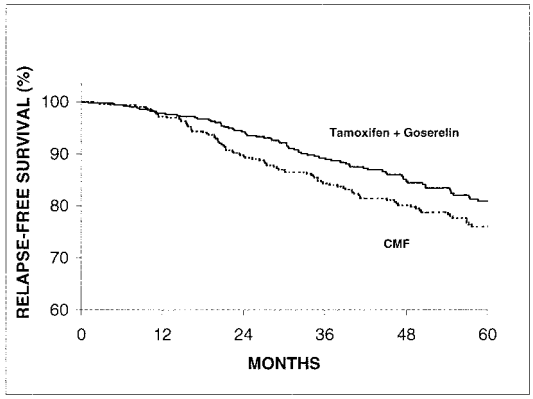
The main treatment analyses of Trial 5 are summarized in Figs 1, 2, and 3, including the numbers of patients at risk at 12, 24, 36, 48, and 60 months. Figure 1 shows the Kaplan-Meier plot of an OS analysis in patients treated with endocrine therapy as compared with those allocated to CMF. Although the data for survival are inevitably less mature than those for RFS, the hazard ratio estimate is in favor of endocrine treatment with tamoxifen and goserelin ($P = .195$). Table 5 gives the results of univariate and multivariate analyses of prognostic factors for OS. Multi-



Patients at risk

Endocrine therapy	511	485	430	356	304	235
Chemotherapy	523	478	424	358	291	217

Fig 1. Kaplan-Meier estimates of OS in the group assigned to endocrine therapy (tamoxifen and goserelin) and the group assigned to chemotherapy (CMF). Differences between groups were not significant ($P = .093$, generalized Wilcoxon test; $P = .195$, log-rank test). Figures of patients at risk are included.

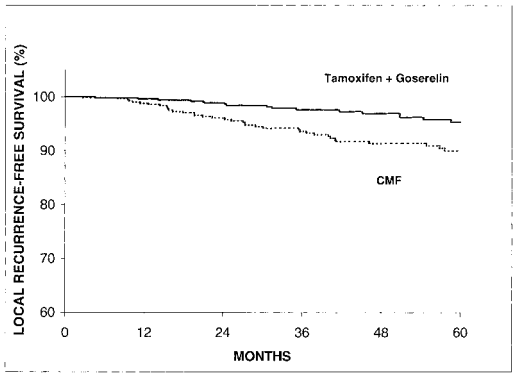


Patients at risk						
Endocrine therapy	511	476	410	329	272	207
Chemotherapy	523	464	379	309	244	179

Fig 2. Kaplan-Meier estimates of RFS in the group assigned to endocrine therapy (tamoxifen and goserelin) and the group assigned to chemotherapy (CMF). Differences between groups were significant (*P* = .017, generalized Wilcoxon test; *P* = .037, log-rank test). Figures of patients at risk are included.

variate analysis identified four independent factors significantly influencing survival: nodal status, tumor stage, PgR, and age.

Figure 2 presents Kaplan-Meier curves for RFS showing that patients treated with tamoxifen and goserelin benefit from statistically significantly improved RFS over those treated with CMF. The rate at 5 years was 81% in the endocrine therapy group as compared with 76% of patients administered polychemotherapy ($P = .037$). Univariate and multivariate analyses for 5-year RFS identified five prognostic factors, ie, nodal status, tumor stage, PgR, treatment, and grading (Table 6). The independent prognostic variables were nodal status, age, tumor stage, PgR, and treatment. This analysis indicated a 40% increase in the relative risk of experiencing a relapse for patients treated with CMF compared with those who received tamoxifen plus goserelin (RR, 1.4; 95% confidence interval, 1.06 to 1.87). Interestingly, and as for OS, independent prognostic relevance was again attached to the PgR—not the ER—in terms of RFS.



Patients at risk						
Endocrine therapy	511	478	411	330	273	208
Chemotherapy	523	464	381	314	248	182

Fig 3. Kaplan-Meier estimates of local recurrence-free survival in the group assigned to endocrine therapy (tamoxifen and goserelin) and in the group assigned to chemotherapy (CMF). Differences between groups were significant (*P* = .002, generalized Wilcoxon test; *P* = .015, log-rank test).

Table 5. Overall Survival: Univariate and Multivariate Analyses of Prognostic Factors at 5-Year Follow-Up (N = 1,034)

	Univariate Analysis			Multivariate Analysis		
Factor	RR	95% CI	*P*	RR	95% CI	*P*
Nodal status	2.26	1.81-2.82	.0001	1.87	1.47-2.38	.0001
Tumor stage	2.43	1.77-3.36	.0001	1.65	1.18-2.30	.0034
PgR	0.60	0.45-0.81	.0008	0.69	0.51-0.93	.0153
Age	0.40	0.23-0.71	.0017	0.48	0.27-0.87	.0155
Grading	1.92	1.27-2.90	.0021	1.40	0.91-2.16	.1232
Treatment	1.32	0.87-1.99	.1948	1.27	0.83-1.93	.2674
ER	0.95	0.65-1.39	.7945	0.93	0.61-1.41	.7227

NOTE. Variables were coded as follows: Nodal status: 0, 1-3, 4-10, or ≥ 11 axillary lymph node metastases; tumor stage: pT1, pT2, or pT3; PgR: negative, positive, or strongly positive; grading: G1, 2, x, or G3; treatment: endocrine therapy or chemotherapy; age: < 35 years or ≥ 35 years; ER: negative, positive, or strongly positive.

Abbreviations: RR, risk ratio; CI, confidence interval.

Figure 3 demonstrates a highly significant improvement in local recurrence-free survival among patients treated with endocrine therapy as compared with those administered cytotoxics ($P = .015$). In this regard, Table 7 shows nodal status and age to be the only independent, prognostically significant variables in addition to treatment. Trial subjects treated with CMF ran a two-fold risk of developing a local recurrence as compared with those undergoing endocrine combination therapy.

An evidence-based analysis revealed no significant interaction between age and treatment in the Cox model. The induction of amenorrhea in the group treated with chemotherapy was seen to depend on patients' age (data not shown). We conclude that the positive effect of amenorrhea on RFS in CMF patients is attributable to age. When considering age in this patient group, the induction of amenorrhea was seen to serve as a prognostic surrogate parameter for age, but it showed no additional significant explanatory value.

Table 8 depicts the number and sites of recurrences and secondary malignancies in the entire patient population. As shown in our analysis of local recurrence-free survival, local recurrences were very much reduced in the endocrine treatment group, and exclusively distant metastases were equally distributed between the two groups. The arms did not differ as to sites of distant recurrences only. In some patients, multiple sites were present at first recurrence, thus accounting for some mismatch of figures in Table 8. Secondary malignancies in the opposite breast were again strongly reduced in the endocrine treatment group. The numbers of other malignancies showed neither differences between patients treated with endocrine and chemotherapy nor, in particular, an increase in terms of endometrial cancer.

Table 6. Relapse-Free Survival: Univariate and Multivariate Analyses of Prognostic Factors at 5-Year Follow-Up (N = 1,034)

	Univariate Analysis			Multivariate Analysis		
Factor	RR	95% CI	*P*	RR	95% CI	*P*
Nodal status	2.10	1.80-2.46	.0001	1.87	1.58-2.21	.0001
Age	0.28	0.19-0.40	.0001	0.29	0.20-0.43	.0001
Tumor stage	1.99	1.58-2.50	.0001	1.49	1.18-1.88	.0008
PgR	0.73	0.59-0.89	.0025	0.74	0.60-0.92	.0056
Treatment	1.35	1.02-1.79	.0374	1.40	1.06-1.87	.0193
Grading	1.58	1.18-2.11	.0019	1.31	0.98-1.76	.0728
ER	0.96	0.74-1.25	.7713	0.91	0.69-1.20	.5137

Table 7. Local Recurrence-Free Survival: Univariate and Multivariate Analyses of Prognostic Factors at 5-Year Follow-Up (N = 1,034)

Factor	Univariate Analysis			Multivariate Analysis		
	RR	95% CI	P	RR	95% CI	P
Nodal status	2.23	1.70-2.92	.0001	2.00	1.50-2.67	.0001
Age	0.22	0.12-0.40	.0001	0.23	0.12-0.43	.0001
Treatment	1.86	1.13-3.08	.0150	1.98	1.19-3.29	.0083
Tumor stage	2.00	1.34-2.97	.0006	1.44	0.97-2.14	.0733
PgR	0.74	0.51-1.06	.0975	0.75	0.52-1.09	.1306
Grading	1.61	0.98-2.66	.0609	1.32	0.79-2.19	.2873
ER	1.04	0.66-1.63	.8700	0.97	0.60-1.57	.9021

DISCUSSION

Based on the present nationwide Austrian trial, we argue that complete endocrine blockade involving goserelin for 3 years and tamoxifen for 5 years is superior to standard chemotherapy in the adjuvant treatment of premenopausal women with stage I and II breast cancer.

Although adjuvant endocrine treatment approaches are proven effective in patients over 50 years of age, their value in the premenopausal setting is currently defined in less precise terms.[15] Chemotherapy in premenopausal breast cancer patients decreases the rate of relapses and deaths and, overall, has clearly been shown to be highly effective as an adjuvant treatment modality, serving to change the natural biology of this disease. The benefit, however, is gained by taking into account a number of—at times—serious side effects and infrequent treatment-related deaths, in addition to a permanent rate of amenorrhea in roughly 70% to 100% of premenopausal women, depending on the chemotherapeutic regimen administered and the patient's age.

Amenorrhea has been shown to be a major constituent of the action of chemotherapy. Patients who develop amenorrhea produce a significantly better prognosis than those whose menses persist after chemotherapy.[16,17] As shown above, however, age and induction of amenorrhea proved to be closely related factors in ABCSG Trial 5. Amenorrhea was induced in 55% of CMF patients at 12 months—and in 77% at 3 months—in the course of this trial. In turn, the percentage expectedly amounted to 100% in the endocrine therapy group, in which 68 patients regained menses after goserelin administration was discontinued. Currently, it is not known which of the two activities—the direct cytotoxic effect or the "indirect" endocrine manipulation—is more important and whether or not they diverge in different tumor cells, such as in hormone-responsive and -unresponsive breast cancer cells.[18]

Table 8. Number and Sites of Recurrences and Secondary Malignancies

Site	Endocrine Therapy Group (n = 511) (n)	Chemotherapy Group (n = 523) (n)
Recurrence		
Local	17	30
Local + distant	7	12
Distant only	55	54
Distant recurrence only		
Lung	13	16
Pleura	10	21
Bone	27	33
Liver	22	10
CNS	1	1
Secondary malignancy		
Opposite breast	3	12
Large intestine	4	4
Uterus	2	1
Skin	1	1
Lung	0	1
Others	6	5

NOTE. Of 15 cases of deficient relapse documentation, eight patients were treated in the endocrine therapy group and seven patients in the chemotherapy group.

The adjuvant setting has shown that permanent induction of amenorrhea, by way of surgical or radiologic castration, is a highly effective tool in breast cancer patients younger than 50 years of age. Overview data have argued in favor of a long-term beneficial effect arising from ovariectomy, yet direct comparisons between adjuvant chemotherapy (CMF) and ovariectomy have suggested no difference in long-term outcomes.[19-21]

The EBCTCG overview showed in several ways that the issue of adjuvant endocrine therapy remains incompletely resolved.[6] Although ovariectomy-versus-nil comparisons seem to evidence the high therapeutic impact of ovarian ablation, the former method seems to add little or nothing to the benefits of chemotherapy in the framework of trials applying chemotherapy with or without ovariectomy. The data are also substantiated by results from the Eastern Cooperative Oncology Group, according to which the addition of goserelin to cyclophosphamide, doxorubicin, and fluorouracil (CAF) failed to show a significantly beneficial effect.[22]

In the metastatic situation, outcomes have not differed between ovariectomy by surgery or radiotherapy and medically induced amenorrhea with luteinizing hormone–releasing hormone analogs. However, the addition of tamoxifen to such analogs was shown to be superior to either non–drug-based intervention.[23,24]

When ABCSG Trial 5 was launched in 1990, the above data were largely unknown. It was well established that adjuvant chemotherapy and ovariectomy represented effective adjuvant treatment modalities. Likewise, tamoxifen was recognized as adjuvant treatment in postmenopausal women with hormone-responsive breast cancer, but at that time it showed a limited effect, if any at all, in premenopausal patients. This was partly explained by high endogenous estradiol serum blood levels, which occupy the steroid hormone receptor and render tumor cells resistant to antiestrogens. The hypothesis guiding Trial 5 was that decrease of estrogen serum blood levels by the agency of goserelin administration should facilitate antiestrogenic (tamoxifen) action. We therefore chose to compare this combination with CMF, the chemotherapeutic regimen of choice at that time. Arguing in favor of the predictive value of the steroid hormone receptor, we furthermore decided to limit patient selection to women with hormone-responsive tumors.

Two other clinical trials have been based on similar designs, one using the same polychemotherapy[25] and the other restricted to node-positive tumors treated with fluorouracil, epirubicin, and cyclophosphamide.[26] Hampered by a somewhat small number of participants, the former trial failed to detect a statistically significant difference between combination endocrine treatment and CMF. The latter showed a clear yet insignificant trend in favor of endocrine treatment. Moreover, the combination of goserelin and tamoxifen has more recently been assessed, in addition to CAF, by an intergroup investigation in node-positive, receptor-positive patients.[22] As mentioned above, it was shown that the addition of goserelin to CAF failed to improve the rate of disease-free survival at 5 years, whereas tamoxifen added to goserelin and CAF significantly improved the outcome in pa-

tients undergoing such treatment. Another preliminary joint analysis of several heterogeneous individual trials indicated the general value of adding goserelin either to tamoxifen or chemotherapy.[27] This seems to be independent of additional treatments used.

As mentioned above, patients treated with surgical or irradiation ovariectomy present a prognosis that is identical to that of CMF-treated patients. Recently published data indicate that 2 years of goserelin produces the same disease-free survival rate as CMF in ER-positive, stage II breast cancer patients.[28] By adding tamoxifen administration to ovarian suppression, premenopausal women should benefit approximately in the magnitude of a "net" tamoxifen effect. This is exactly what has been observed in the present trial: The 40% increase in relative risk associated with chemotherapy may represent the benefit of tamoxifen in the premenopausal patient according to the 1998 Overview, adding substantially to the plausibility of the above hypothesis.

Recent reports have indicated a high level of false-positive receptor determinations among patients who were enrolled onto a trial of neoadjuvant endocrine therapy. For example, Ellis et al[29] have recently observed a large percentage (12%) of study tumor specimens submitted as ER- or PgR-positive on local laboratory results to be ER-negative on central analysis. Moreover, most of these were also PgR-negative. The authors concluded that this difference is seemingly related to false-positive results in the institutions of origin. There is no doubt that only improved quality control in the measurement of ER and PgR status, as traditional predictive factors subjected to comprehensive quality control in the framework of Trial 5, may serve to avoid such misclassification. In this country, various series of quality control determinations of steroid hormone receptor status have in recent years been implemented throughout all departments of pathology.

Questions remaining unresolved include whether results may be improved by different schedules and durations of CMF or combination chemoendocrine therapy, as well as whether using other cytotoxic regimens, ie, anthracyclines or taxanes, would provide superior results in the cytotoxic arm of a given comparison. No data are currently available to indicate that this is in fact the case in premenopausal patients with hormone-responsive tumors. In any case, if ovarian suppression together with tamoxifen is capable of effectively reducing relapse and death, then only a potentially directly cytotoxic effect deriving from cytostatic treatments would further enhance prognosis. Moreover, the increased level of toxicity must outweigh the improved efficacy of anthracycline or taxane combinations.

It is interesting to note that while distant recurrences were equally frequent in this Trial's endocrine and chemotherapy groups, almost twice as many local recurrences were identified in the CMF arm, substantially adding to the overall superiority of the goserelin plus tamoxifen combination. Other investigations have similarly indicated that different systemic treatment modalities influence the localization of primary relapse.[30]

An imbalance of episodes was identified with respect to side effects and patients' compliance and adherence to treatment. Expectedly, the pattern of side effects in the endocrine treatment group resembles the effects of complete endocrine blockade, mostly showing typical menopausal symptoms, whereas the applied cytotoxics bring about such chemotherapy-specific side effects as hot flushes, nausea, and alopecia, as expected from well-known data in the literature. With 86% of the patients completing 3 years of therapy with goserelin, this treatment can be considered as well tolerated and accepted by the trial subjects despite the longer course of administration.

In summary, ABCSG Trial 5 has shown complete endocrine blockade with goserelin and tamoxifen to be superior to standard chemotherapy in premenopausal women with hormone-responsive stage I and II breast cancer. On the basis of the presented findings, we conclude that combination goserelin-tamoxifen therapy is a rational treatment for early-stage disease in the premenopausal patient and that this combination potentially improves prognosis in younger women with breast cancer.

ACKNOWLEDGMENT

We thank Irene Agstner, Martina Mittlböck, Prof Richard Pötter, Prof Michael Schemper, and Karl Thomanek, Vienna University, for their biometrical and editorial expertise. We are also grateful to AstraZeneca Pharmaceuticals for their esteemed assistance in monitoring the patient data, and to all the patients who participated in ABCSG Trial 5.

APPENDIX

The appendix listing other members of the Austrian Breast and Colorectal Cancer Study Group is available online at www.jco.org.

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