Randomized Trial of Low-Dose Chemotherapy Added to Tamoxifen in Patients With Receptor-Positive and Lymph Node–Positive Breast Cancer

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Purpose: **To evaluate the outcome in patients with stage II hormone receptor–positive breast cancer treated or not treated with low-dose, short-term chemotherapy in addition to tamoxifen in terms of disease-free and overall survival.**

Patients and Methods: **A total of 613 patients were randomized to receive either low-dose chemotherapy (doxorubicin 20 mg/m² and vincristine 1 mg/m² on day 1; cyclophosphamide 300 mg/m²; methotrexate 25 mg/m²; and fluorouracil 600 mg/m² on days 29 and 36 intravenously) or no chemotherapy in addition to 20 mg of tamoxifen orally for 2 years. A third group without any treatment (postmenopausal patients only) was terminated after the accrual of 79 patients due to ethical reasons.**

Results: **After a median follow-up period of 7.5 years, the addition of chemotherapy did not improve the outcome in patients as compared with those treated with tamoxifen alone, neither with respect to disease-free nor overall survival. Multivariate analysis of prognostic factors for disease-free survival revealed menopausal status, in addition to nodal status, progesterone receptor, and histologic grade as significant. Both untreated postmenopausal and tamoxifen-treated premenopausal patients showed identical prognoses significantly inferior to the tamoxifen-treated postmenopausal cohort. Prognostic factors for overall survival in the multivariate analysis showed nodal and tumor stage, tumor grade, and hormone receptor level as significant.**

Conclusion: **Low-dose chemotherapy in addition to tamoxifen does not improve the prognosis of stage II breast cancer patients with hormone-responsive tumors. Tamoxifen-treated postmenopausal patients show a significantly better prognosis than premenopausal patients, favoring the hypothesis of a more pronounced effect of tamoxifen in the older age groups.**

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ADJUVANT CHEMOTHERAPY and endocrine therapy are common standards in today's treatment of patients with breast cancer. However, it is still difficult to select for patients actually benefiting from therapy alone and not only suffering from side effects of the treatment.

At the time this trial was initiated in 1984, our knowledge concerning adjuvant systemic treatment of patients after operation for breast cancer was as follows: (1) adjuvant chemotherapy had been shown to be effective in improving disease-free survival (DFS) and overall survival (OS), especially in premenopausal patients[1]; and (2) adjuvant tamoxifen (TAM) had been shown to cause a significant reduction in recurrence rates, predominantly in postmenopausal patients.[2]

There were conflicting results, however, with regard to the age dependency of this TAM effect.[2,3] Neither tumor nor patient parameters had (and has as of yet) been identified to accurately predict responsiveness toward cytotoxic chemotherapy. For the efficacy of TAM action, however, corticosteroid hormone receptors have repeatedly proven to be predictive for response to endocrine treatment both in the adjuvant and metastatic states.

In 1984, we began a trial in node-positive, estrogen receptor (ER)– and/or progesteron receptor (PgR)–positive pre- and postmenopausal women after primary surgery with or without breast irradiation. Patients were randomly allocated to receive 20 mg of TAM daily for 2 years or TAM plus one cycle of low-dose, short-term chemotherapy consisting of one cycle of doxorubicin and vincristine (AV) and one cycle of cyclophosphamide, methotrexate, and fluorouracil (CMF). This treatment was chosen in order to test the hypothesis of whether such chemotherapy, showing virtually no side effects, could improve the prognosis of patients previously treated with TAM alone. We chose this type of chemotherapy because we were concerned about whether the observed benefit for chemotherapy would outweigh the costs in terms of toxic effects after the administration of systemic chemotherapy, such as CMF. In addition, an

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untreated control group was included in the postmenopausal group until 1989. After the publication of the 1988 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview,[4] we decided to terminate recruitment to this arm because of the overwhelmingly convincing results that OS in TAM-treated postmenopausal patients had improved significantly. The accrual time of this trial ended in December 1990. The results presented provide mature data with a median follow-up period of 7.5 years, a recurrence rate of 212 (41.1%) of 516 assessable treated patients, and a death rate of 193 (37.4%) of 516.

PATIENTS AND METHODS

Study Design

This study was performed by the Austrian Breast Cancer Study Group (ABC) and represents the second multicenter trial initiated in 1984. Separate trials were initiated for hormone receptor–negative patients. Randomization was performed at the study center in Vienna by telephone. Twenty-one clinics and hospitals in Austria participated in this trial. Data collection, protocol review, data monitoring, and quality control were performed centrally.

Patients were stratified according to tumor stage (< 2 cm, 2 to 5 cm, and > 5 cm), number of involved lymph nodes (one to three, four to nine, and $\geq 10+$), menopausal status (premenopausal or postmenopausal), type of surgery (breast preservation or modified radical mastectomy with or without irradiation), corticosteroid hormone receptor status[5] (ER ≤ 10, 11 to 100, ≥ 100 fmol/mg cytosol protein; PgR ≤ 10, 11 to 100, ≥ 100 fmol/mg cytosol protein), and tumor grade (grade 1/2, lobular; grade 3) according to Bloom and Richardson.[6] Adaptive randomization according to Pocock and Simon[7] was used.

After giving informed consent, patients were randomly allocated with equal probability to either TAM (2×10 mg daily orally for 2 years) or TAM plus chemotherapy, and in postmenopausal patients, additionally to an untreated control. Accrual into the third treatment arm was terminated by the steering committee after the first results of the EBCTCG became available in 1988, since we had considered it unethical because of the obvious benefit of TAM for postmenopausal patients. Out of all sample size calculations, 510 patients were calculated for the particular comparison of TAM with or without chemotherapy based on the following assumptions: potential increase of OS at 7-year follow-up from 60% to 69%, with 5 years of accrual, alpha = 0.05, power = 0.85, and one-sided test. This number would have been sufficient to detect an eventual difference in our trial.

Patient Eligibility

Women were required to be younger than 70 and older than 18 years of age and to show the following: (1) histologically confirmed complete removal of a unilateral carcinoma of the breast (clear margins) and level I and II axillary nodal dissection; (2) histologic examination of at least six axillary nodes with at least one being involved; (3) ER and/or PgR level ≥ 10 fmol/mg cytosol protein; and (4) no distant metastases, confirmed by lung x-ray, liver ultrasound, and bone scan or, if clinically indicated, computed tomography scan.

Patients were eligible with pathological tumor stages Ib to IIIa. Ineligibility criteria included previous malignancy, except for cured basal-cell or squamous cell carcinoma of the skin or early cervical cancer. Pregnancy or lactation were further exclusion criteria. No previous irradiation or preoperative antineoplastic treatment was allowed. All patients with breast conservation were treated with radiotherapy, which was optional in patients with mastectomy. Women were required to be in generally good health (Eastern Cooperative Oncology Group 0 and 1), to tolerate postoperative treatment, and to begin treatment within 4 weeks of surgery after having given informed consent.

Treatment Regimens

TAM was administered at a dose of 2×10 mg orally daily for 2 years, and chemotherapy was concomitantly given intravenously: on day 1, doxorubicin 20 mg/m^2 and 1 mg/m^2 vincristine; on days 29 and 36, cyclophosphamide 300 mg/m^2, methotrexate 25 mg/m^2, and fluorouracil 600 mg/m^2.

Patient Evaluation

All patients received follow-up examinations every 3 months for the first 3 years and then at 6-month intervals thereafter. Routine evaluation of the patients included clinical examination and laboratory analysis (including carcinoembryonic antigen and cancer antigen 15-3 tests). Chest x-ray, liver ultrasound, and mammography were performed annually, or more frequently if clinically indicated. Patients' first relapse (local, regional, distant, or combined) and death served as primary end points for OS and relapse-free survival, respectively. A local or regional relapse had to be confirmed histologically whenever possible.

Statistical Methods

All randomized and eligible patients were included in the analysis according to the intention-to-treat principle. The date of final analysis was September 1, 1997. All patient data were collected at the study group's central data office and processed and analyzed applying SAS software (SAS Institute Inc, Cary, NC).

Time to first relapse or death from randomization was estimated and graphically presented according to the method of Kaplan and Meier.[8] Differences between curves were assessed by Mantel's log-rank test[9] for censored survival data.

Furthermore, interactions between treatment and prognostic variables were investigated. The Cox proportional hazards model[10] was used to model the prognostic value of treatment, tumor grade, menopausal status, tumor stage, tumor histology, lymph node status, ER, and PgR on time to first relapse and survival time in a univariate and multiple manner. Interactions of treatment with prognostic variables were investigated by entering the product of individual hazards into the model. The proportional hazards assumptions were checked by including a time-dependent factor in the model. Patients who died because of reasons other than breast cancer were considered as censored with death. All *P* values given are two-sided.

RESULTS

Randomization and Eligibility

From January 1984 to December 1990, 613 patients were randomized. Of these, 17 (3%) proved ineligible because of the reasons outlined in Table 1. Of the remaining 596 patients, 261 were randomized to chemoendocrine treatment, 256 to endocrine therapy alone, and 79 to surgical control (postmenopausal patients only). These 79 patients were incorporated into the main analysis; however, they were analyzed for special purposes, as shown later. Seventy-five percent of the eligible patients were followed for more than 6 years. Fourteen patients were lost from follow-up and

Table 1. Trial Information

	No. of Patients	%
Randomized	613	
Eligible	596	97
Not eligible	17	3
Exclusion criteria obstacled during audit		
Tumor stage 4	8	
Age over 70 years	9	
Lost from follow-up	14	2
Untreated control group (terminated 3/18/89)	79	
Mean observation time, months	93	
75% quantile	76	
25% quantile	114	

regarded as censored. Eleven patients died because of other reasons. The number of 579 patients during an accrual time of 7 years represents roughly 13% of all patients in Austria who were theoretically suitable for participation in this trial, based on the outlined selection criteria.

Patient Characteristics

The two treatment arms were evenly distributed according to stratified patient characteristics (Table 2). Fifty percent of all patients were premenopausal, more than 60% comprised a lower-risk group with one to three involved nodes, and only 40 patients had a tumor larger than 5 cm in diameter. As expected, the majority of the patients had well- or moderately well-differentiated tumors. At that time, only 20% underwent breast conservation, and a minority of patients with mastectomy received irradiation of the operation field. With respect to corticosteroid hormone receptor levels, 43 patients showed ER-negative and 96 patients showed PgR-negative tumors. One hundred sixty patients (31%) had an ER content larger than 100 fmol/mg cytosol protein, and 215 (41%) showed a PgR level higher than 100 fmol.

Recurrence-free Survival

There were 212 recurrences of disease: 112 (33.1%) in the AV-CMF group and 100 (29.1%) in the TAM group. This difference is statistically insignificant. The 5-year recurrence-free survival rates for AV-CMF and TAM alone were 60% and 62%, respectively. Kaplan-Meier curves for recurrence-free survival are virtually superimposable (Fig 1). We tested our hypothesis of additional chemotherapy for several treatment interactions (age, lymph node stage, and receptor status) and failed to show any meaningful significance. The patterns of sites of first recurrence are listed in Table 3.

The local recurrence rate in patients treated with breast conservation and radiotherapy was 4.3%; among patients with mastectomy, only five were irradiated and the local recurrence rate was 17%. One hundred thirty-five patients (26%) developed distant metastases: 75 in the combination arm and 60 in the TAM endocrine arm. As expected, the predominant sites were bone, liver, and lung. In 52 patients, metastases developed in more than one organ simultaneously as the first sign of relapse.

Univariate analysis for prognostic factors of DFS showed nodal status, tumor stage, ER, PgR, tumor grade, and menopausal status to be significant; of these, nodal status, PgR, menopausal stage, and tumor grade showed an independent prognostic value in multivariate analysis (Table 4).

Because of the unexpected finding that age, in multivariate analysis, was an independent prognostic factor, we then compared the recurrence rates of TAM-treated pre- and postmenopausal patients with those of the surgical control group.

Table 2. Patient Characteristics

	Treatment Group		
	AV-CMF-TAM (n)	TAM (n)	Control (n)
No. of patients	261	256	79
Menopausal status			
Premenopausal	130	128	
Postmenopausal	131	128	79
No. of involved nodes			
1-3	164	157	51
4-10	76	77	23
> 10	21	22	5
Tumor stage			
T1	91	99	30
T2	147	140	42
T3	23	17	7
Tumor grade			
1, 2×	182	168	57
3	72	78	22
Histology			
Lobular	23	25	4
Ductal	151	143	48
Miscellaneous	87	88	27
Age			
≤< 50 years	119	118	2
> 50 years	142	138	77
Type of surgery			
Breast conservation	54	62	16
Modified radical mastectomy	207	194	63
Corticosteroid hormone-receptor status			
ER, fmol/mg cytosol protein			
0-9	23	20	6
10-100	159	155	37
> 100	79	81	36
PgR, fmol/mg cytosol protein			
0-9	50	46	19
10-100	106	100	34
> 100	105	110	26
ER^+PgR^+	188	190	54
ER^+PgR^-	50	46	19
ER^-PgR^+	23	20	6
Irradiation			
Yes	58	63	23
No	203	193	56

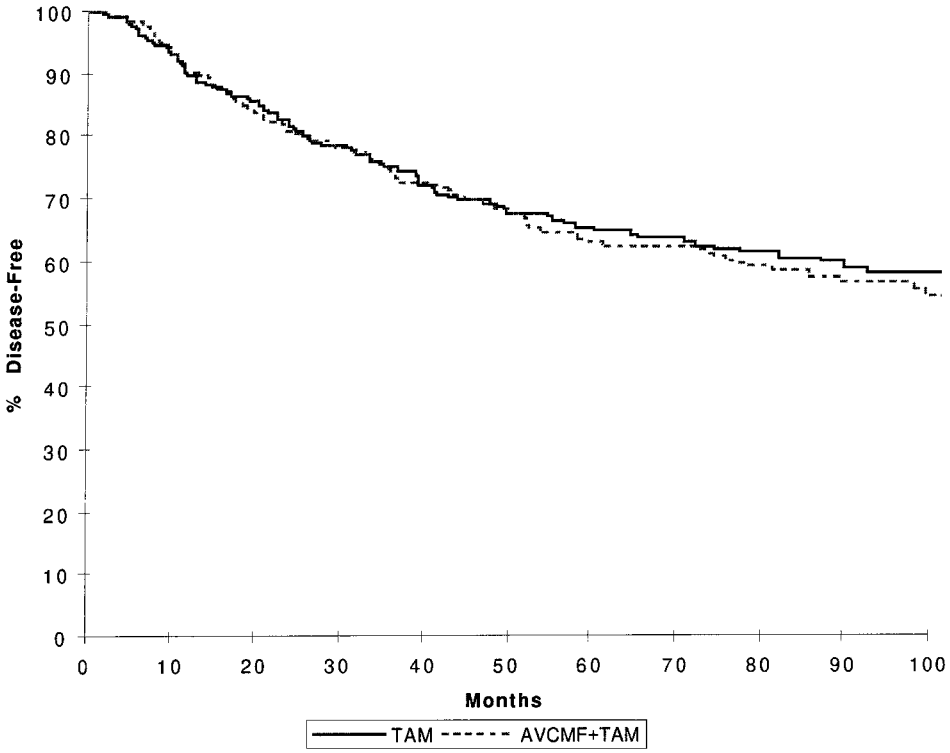

Fig 1. Kaplan-Meier curves of DFS in patients with TAM and AV-CMF + TAM ($P = .48$).

Figure 2 shows the Kaplan-Maier plots of treated pre- and postmenopausal patients compared with the untreated control group. Postmenopausal TAM-treated patients showed significantly improved DFS. The curves of the premenopausal and untreated postmenopausal patients indicate a virtual overlap. We then compared the number of recurrences among the postmenopausal patients of both TAM-treated groups with that of the untreated patient cohort and found a significantly higher recurrence rate in the surgery-only group (Table 5). Those data are compatible with the hypothesis that TAM given at 20 mg for 2 years increases DFS predominantly in the postmenopausal group and has little effect in premenopausal patients. However, this result was gained by an indirect comparison.

Table 3. Number and Sites of Recurrence and Secondary Malignancy

	Treatment Group		
	AV-CMF-TAM (n)	TAM (n)	Control (n)
No. of recurrences			
Total	108	100	35
Local	26	32	10
Local + distant	7	8	1
Distant only	75	60	24
Sites of distant metastases only			
Lung	5	6	1
Pleura	0	3	0
Bone	23	20	14
Liver	14	10	1
CNS	1	0	0
Combination	29	21	
Secondary malignancy	12	15	

Overall Survival

Within a median follow-up period of 7.5 years, 193 patients died (93 in the TAM group and 100 in the AV-CMF–TAM group). The OS rate amounted to 62%. The Kaplan-Meier curves in Fig 3 demonstrate no statistical difference between the curves.

Prognostic relevance was demonstrated in univariate analysis for the number of involved nodes and tumor stage,

Table 4. Recurrence-Free Survival: Univariate and Multivariate Analyses of Prognostic Factors at 7.5-Year Follow-Up Without Untreated Control Group

	Univariate Analysis			Multivariate Analysis		
	Relative Risk	Confidence Limit	*P*	Relative Risk	Confidence Limit	*P*
Treatment	1.1		.48			
Tumor grade	1.41	1.06-1.89	.02	1.34	1.00-1.79	.05
Menopausal status	0.71	0.55-0.94	.02	0.71	0.54-0.94	.02
Tumor stage	1.38	1.11-1.73	.003			
Tumor histology	1.04		.35			
Nodal status	1.86	1.54-2.25	.0001	1.74	1.43-2.11	.0001
ER	0.73	0.58-0.92	.0009			
PgR	0.83	0.69-0.99	.04	0.78	0.65-0.94	.01

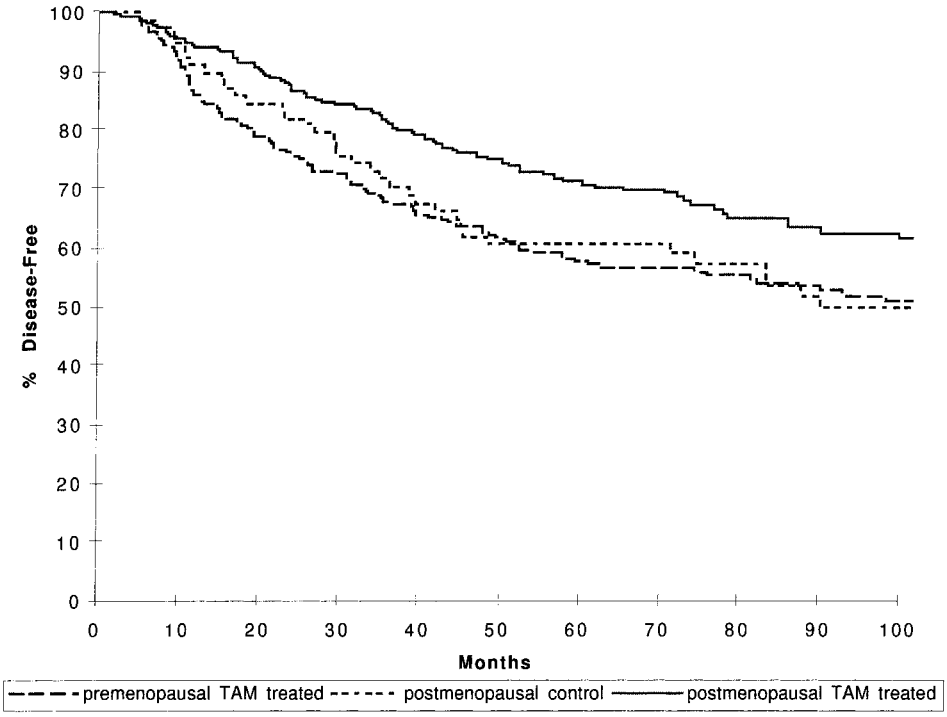

Fig 2. Kaplan-Meier curves of DFS in all patients including postmenopausal untreated patients.

ER, PgR, and tumor grade; the final outcome in the multivariate analysis indicated that all of these factors also make a significant independent contribution (Table 6). The most important prognostic factors are nodal status and PgR; yet tumor stage, tumor grade, and ER status are also independent prognostic variables.

DISCUSSION

Beginning in the mid-1980s, we chose to prospectively evaluate the hypothesis of whether it is possible to achieve beneficial effects with chemotherapy as compared with conventional regimens by lowering the dose and shortening the length of cytotoxic drug administration. We have randomized more than 1,100 patients and tested this hypothesis in the following three different patient cohorts stratified according to nodal and corticosteroid hormone receptor status: (1) ER-negative, PgR-negative, node-negative patients; a comparison of AV-CMF with an untreated control group showed no beneficial effect of the chemotherapy regimen (ABC-01)[11]; (2) ER-negative, PgR-negative, node-positive patients; AV-CMF was compared with 6 × CMF (ABC-03, data under evaluation); and (3) ER-positive, PgR-positive, node-positive patients. Overall, we showed that low-dose, short-term chemotherapy had no beneficial effect when given in addition to TAM in pre- and postmenopausal patients. In view of our results, we failed to support our hypothesis with the presented data. The low-dose, short-term chemotherapy we gave was insufficient to cause a significant beneficial effect when given postoperatively in an adjuvant fashion.

Table 5. DFS of Postmenopausal Patients Treated With TAM or Serving as Untreated Control Group ($P = 0.07$ Mantel-Cox, $P = 0.06$ Breslow)

		Recurrences	
	No. of Patients	No.	%
Control	79	36	45.5
TAM-treated	128	41	32

However, we believe it is still a valid, important, albeit unanswered question whether full-dose chemotherapy is necessary to achieve significant beneficial effects in terms of improvement of DFS and OS. The standard chemotherapy regimen (6 × CMF) is still associated with severe side effects showing significant and serious toxicity, including leukopenia, nausea, vomiting, and thromboembolic events, as well as significantly milder toxicity, including thrombocytopenia, anemia, infections, mucositis, diarrhea, and neurologic toxicity, as pointed out by Pritchard et al.[12] Even deaths have been reported.

In a recent National Surgical Adjuvant Breast and Bowel Project (NSABP) trial,[13] 17% to 25% grade III and IV toxicity was observed after combined chemoendocrine treatment (TAM + CMF) in patients with stage I hormone-responsive breast cancer; this trial also recorded treatment-related death. It is noteworthy in this context that patients are

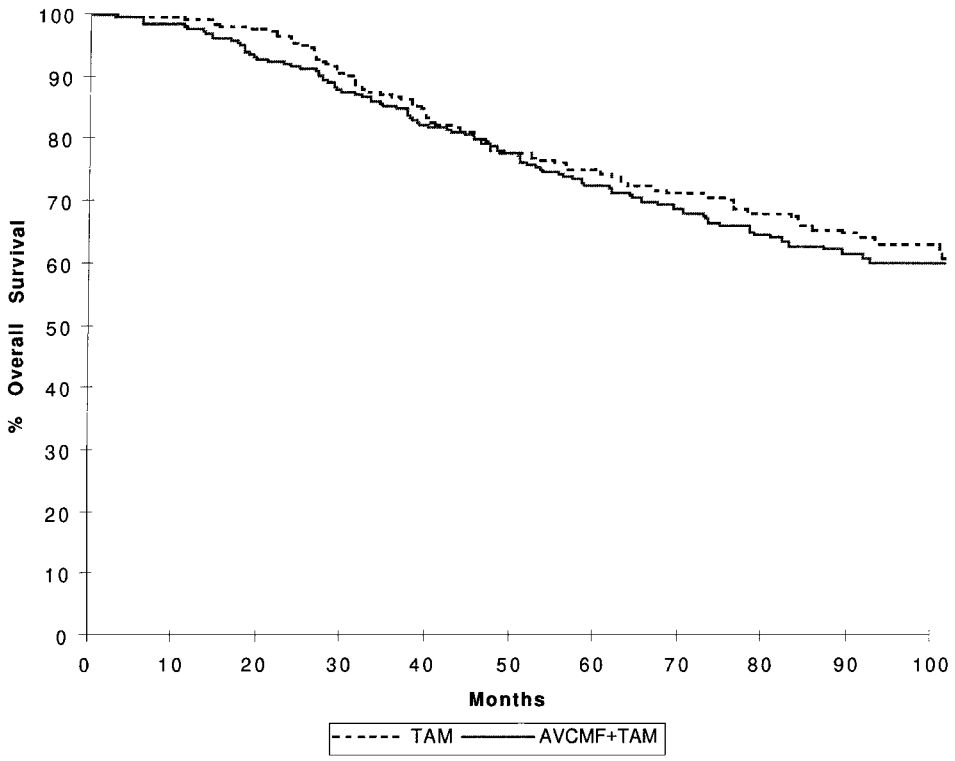

Fig 3. Kaplan-Meier curves of OS in TAM- and AV-CMF + TAM–treated patients (*P* = .71).

prepared to accept even serious toxicity to achieve as little as 1% improvement in survival.[14] Seventy-seven percent of all patients accept serious side effects for a 12-month prolongation of life, and 89% of them for a 24-month prolongation.[15] Adjuvant chemotherapy with no measurable benefit, however, is meaningless and should be avoided.

TAM is still the first choice for adjuvant therapy in postmenopausal patients with hormone-responsive breast cancer. In premenopausal stage II patients with hormone-responsive tumors, CMF is still standard therapy. Trials with a direct comparison between CMF and TAM and incorporating luteinizing hormone–releasing hormone analogs are ongoing and will further clarify this problem. The overview of 1992 has indicated beyond any doubt that TAM, given for at least 2 years, profoundly alters the prognosis of these patients, translating into a 30% reduction in the odds of recurrence and a 19% reduction in the odds of death.[16] In stage II disease, however, the DFS and OS rates at 10 years are only 51.2% and 58.8%, respectively. Obviously, there is ample space for improvement.

Table 6. OS: Univariate and Multivariate Analyses of Prognostic Factors at 7.5-Year Follow-Up Without Untreated Control Group

	Univariate Analysis			Multivariate Analysis		
	Relative Risk	Confidence Limit	*P*	Relative Risk	Confidence Limit	*P*
Treatment	1.05		.71			
Tumor grade	1.51	1.12-2.04	.007	1.40	1.03-1.89	.03
Menopausal status	0.92		.57			
Tumor stage	1.62	1.29-2.03	.0001	1.37	1.08-1.74	.01
Tumor histology	0.94		.53			
Lymph node status	2.0	1.65-2.42	.0001	1.80	1.46-2.2	.0001
ER	0.72	0.56-0.92	.008	0.71	0.54-0.93	.01
PgR	0.79	0.66-0.95	.01	0.78	0.63-0.94	.008

There are at last two different options for improving TAM-based results. One option is to combine two different endocrine-active drugs (eg, antiestrogen and aromatase inhibitor) simultaneously or concomitantly, an option our group is currently pursuing with more than 3,000 randomized postmenopausal patients with hormone-responsive tumors in two different randomized trials. Another option is to combine TAM with cytotoxic drugs. Several trials have been performed in this context, based either on chemotherapy with additional TAM[17-20] or the reverse.[21,22] The 1992 overview[16] showed a 27% reduction in the odds of recurrence in trials consisting of chemotherapy added to TAM as compared with TAM alone, but no survival advantage.

The results produced by individual trials have been heterogeneous. Some found no benefit in DFS or OS,[23-25] some found a benefit for DFS alone,[17,26,27] and still others found a significant advantage for both DFS and OS.[21,22,28] A

recent survey by Goldhirsch et al[29] indicated that trials applying original CMF showed a significant benefit, whereas others did not.

Another recent overview, by Gelber et al,[15] showed that adjuvant chemotherapy did not provide more quality-adjusted survival time than TAM alone for 3,920 women ≥ 50 years old with involved nodes. Overview data from 1998 for polychemotherapy in early breast cancer[30] indicate that the addition of polychemotherapy to TAM produces some benefits. This difference was not significant in premenopausal patients; however, patient numbers are small. In postmenopausal women, the addition of polychemotherapy showed a 19% reduction in the odds of recurrence and an 11% reduction in the odds of death.

Recently published results from the NSABP B20 trial,[13] comparing TAM with two different regimens of chemotherapy in addition to TAM, found a significant 5% improvement in DFS and a 3% improvement in OS in 2,306 stage I breast cancer patients with hormone-responsive tumors. These results led the authors to the conclusion that all patients with breast cancer should be candidates for chemotherapy, with the possible exception of patients with tumors smaller than 1 cm. It must be borne in mind, however, that 94% of all patients in stage I with hormone-responsive tumors survive for 5 years on TAM alone and that only a small but significant number of patients draws an additional benefit from chemotherapy. On the basis of these results, it would therefore prove crucial to gain insights into the predictive factors for response to additional chemotherapy. It seems as though specific patient characteristics would predict for better response to chemotherapy (young age, PgR 0 to 9 fmol/mg cytosol protein). However, the statistical test for interaction between these factors and treatment failed to show clear significant variation in the response to chemotherapy, possibly because of a far too low number of events. It is a matter of judgment whether to recommend adjuvant chemotherapy for all patients with breast cancer—even those with a very low chance of benefiting from additional chemotherapy—or to select a group of patients (age < 49 years, ER+, PgR 0 to 9 fmol/mg cytosol protein) to prospectively evaluate the same question with larger numbers of patients.

As was shown by the Cancer and Leukemia Group B,[31] it is absolutely critical to administer chemotherapy in full dose. Wood et al showed that going below some critical dose of an anthracycline-based regimen in stage II breast cancer patients leads to inferior results. Re-evaluation of this trial after a follow-up period of 9 years still shows that a higher dose is associated with better DFS and OS.[32]

One question that was not fully clarified in the 1992 overview[16] was the value of TAM in premenopausal patients depending on hormone receptor values. The reason was the relatively small number of premenopausal patients treated with TAM in randomized trials. In women under 50 years old, recurrence was significantly reduced. Mortality, on the other hand, has not significantly decreased. In the 1998 overview[33] with more mature data, the DFS risk reduction with 2 years of TAM in premenopausal patients was significant, yet only 14%, compared with 32% in younger postmenopausal patients and 42% in patients older than 70. This clear difference of TAM benefit in younger and older patients corresponds well with our presented data and is obviously only true after 2 years of TAM administration. In patients treated for 5 years with TAM, the beneficial effect is identical for all age groups with respect to DFS and OS. Therefore, length of administration of TAM also seems to be a critical factor, especially for younger women. The data from our patient cohort for OS at 5 years corresponds well with the OS of 74.3% for women with receptor-positive, node-positive breast cancer who took 2 years of adjuvant TAM described in the overview.[33] Considering the fact of a 2-year administration in our trial, DFS differs significantly in pre- versus postmenopausal patients, as shown in Fig 2. Furthermore, multivariate analysis for DFS (Table 3) did indicate menopausal status as a significant, independent prognostic factor. Postmenopausal patients in the terminated control group and premenopausal patients showed virtually identical Kaplan-Meier curves for DFS. The receptor status of postmenopausal patients in the treated and the nontreated group were identical, with the receptor status of premenopausal patients being lower, as was shown by other groups as well.

Altogether, this trial shows that a single cycle of chemotherapy, although including an anthracycline in addition to TAM, has no beneficial effect in patients with hormone-responsive stage II breast cancer. These data are in agreement with the data of the overview of 1992,[16] showing only a minimal effect from a single cycle of perioperative chemotherapy. We have explained our results with the inferior dose-intensity. However, it seems to be critical to select for factors predictive for chemotherapy response in addition to TAM. Future trials must be based on tumor and/or host characteristics (tumor grade, corticosteroid receptor content, age, *HER-2/neu*) in order to avoid chemotherapy in resistant patients. We are currently conducting a trial of an anthracycline-containing chemotherapy regimen in addition to TAM in breast cancer patients with grade 3 tumors. Future clinical trials should formulate more specific questions to obtain more specific answers.

APPENDIX
Other Members of the Austrian Breast Cancer Study Group

The other members of the Austrian Breast Cancer Study Group are: G. Reiner, A. Reiner, P. Götzinger, T. Grünberger, S. Taucher, B. Gebhard, M. Rudas, D. Kandioler, M. Djavanmard, and C. Zielinski (University of Vienna, Departments of Surgery, Pathology, and Internal Medicine); M. Smola, G. Rosanelli, H. Hauser, L. Kronberger, M. Hoff, H. Stöger, A. Kasparek, M. Schmid, T. Bauernhofer, R. Moser, E. Andritsch, P. Wagner, S. Reinisch, and M. Wehrschütz (University of Graz, Departments of Surgery and Medicine); M. Seifert, R. Obwegeser, C. Kurz, A. Obermair, K. Czerwenka, J. Spona, N. Vavra, C. Dadak, C. Kainz, and B. Hartmann (University of Vienna, Department of Gynecology and Obstetrics); K. Mach (Oberwart); H. Spoula and M. Hanak (Hanusch Krankenhaus); V. Wette and G. Jatzko (St. Veit an der Glan); G. Michlmayr, D. Nitsche, and C. Tausch (Linz); F. Hofbauer and M. Lang (Oberpullendorf); G. Wahl (Linz); M. Schemper (University of Vienna); H. Ludwig (Wilhelminen Spital); O. Böckl, R. Menzel, E. Moritz, C. Papp, H. Luschnik, P. Mayer, C. Rass, G. Russ, R. Schandalik, M. Umlauf, and E. Hell (Salzburg, Departments of Internal Medicine and Surgery); and D. Depisch, W. Kwasny, and R. Pointner (Wiener Neustadt).

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