Randomized Trial of Tamoxifen Versus Tamoxifen Plus Aminoglutethimide as Adjuvant Treatment in Postmenopausal Breast Cancer Patients With Hormone Receptor-Positive Disease: Austrian Breast and Colorectal Cancer Study Group Trial 6

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Purpose: **To determine whether the addition of aminoglutethimide to tamoxifen is able to improve the outcome in postmenopausal patients with hormone receptor–positive, early-stage breast cancer.**

Patients and Methods: **A total of 2,021 postmenopausal women were randomly assigned to receive either tamoxifen for 5 years alone or tamoxifen in combination with aminoglutethimide (500 mg/d) for the first 2 years of treatment. Tamoxifen was administered at 40 mg/d for the first 2 years and at 20 mg/d for 3 years.**

Results: **All randomized and eligible patients were included in the analysis according to the intention-to-treat principle. After a median follow-up of 5.3 years, the 5-year disease-free survival in the aminoglutethimide plus tamoxifen group was 83.6% versus 83.7% in the monotherapy group ($P = .89$). The corresponding data for overall survival at 5 years were 91.4% and 91.2%, respectively ($P = .74$). More patients failed to complete combination treatment (13.7%) because of side effects as compared to tamoxifen alone (5.2%; $P = .0001$).**

Conclusion: **Aminoglutethimide given for 2 years in addition to tamoxifen for 5 years does not improve the prognosis of postmenopausal patients with receptor-positive, lymph node-negative or lymph node-positive breast cancer.**

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THE CRUCIAL value of adjuvant endocrine treatment in early breast cancer has been illustrated most extensively with the antiestrogen tamoxifen. The first clinical trials for adjuvant therapy with tamoxifen were started as early as the late 1970s. The first investigation to demonstrate a definite survival advantage with adjuvant tamoxifen versus no adjuvant treatment was the Nolvadex Adjuvant Trial Organization study.[1] Subsequently, the benefit of adjuvant tamoxifen was confirmed by the results of additional large, randomized trials, especially in patients presenting with strongly estrogen receptor (ER)–positive tumors.[2-8] Thus, treatment with tamoxifen became standard care in postmenopausal hormone-responsive breast cancer. However, it has been hypothesized that the results of adjuvant tamoxifen may be improved by addition of other endocrine drugs. Not only may the antiestrogen fail to target tamoxifen-resistant cell clones, but the partially agonist action shown by this agent also raised certain concerns, particularly after its effect on the endometrium was disclosed some 10 years ago.[9,10] The focus on tamoxifen in recent years has therefore been to understand its toxicity, to identify patients more likely to benefit from the drug, and to optimize duration of use.

For these reasons, addition of other antiestrogenic agents is now of interest in the search for a meaningful complement to, or perhaps substitution for, tamoxifen in the adjuvant treatment of breast cancer. By virtue of their peripheral mode of action, aromatase inhibitors are considered a particularly attractive class of drugs. They have been shown to effectively inhibit estrogen synthesis in such peripheral tissues as muscle, fat, and skin; normal breast stromal tissue; and breast tumor tissue.

Aminoglutethimide was one of the first aromatase inhibitors to become available for clinical use. It has been proven to effectively block estrogen production in the adrenal cortex, extraglandular peripheral tissues containing aromatase, and breast carcinoma tissue. Moreover, this first-generation agent has been proven to be effective in the treatment of postmenopausal women with advanced breast cancer.[11-13] Approximately 30% of patients respond to aminoglutethimide treatment, a response rate similar to that obtained using tamoxifen. ER status was shown to be useful in predicting response to this form of treatment in metastatic disease.[14]

On the basis of promising preliminary reports,[15] the Austrian Breast and Colorectal Cancer Study Group (ABCSG) initiated a prospective, randomized clinical study (ABCSG Trial 6) in 1990 for postmenopausal patients with hormone receptor–positive breast cancer, comparing adjuvant tamoxifen plus aminoglute-

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thimide with tamoxifen alone to determine the relative efficacy of the combined approach.

PATIENTS AND METHODS

Study Design

After receiving approval by the relevant institutional review boards and ethics committees, the central data center in Vienna coordinated patients' random assignment by telephone. In total, 52 departments and hospitals participated in this trial. Data collection, protocol review, data monitoring, and quality control were performed centrally.

Inclusion criteria were stage I or II breast cancer, postmenopausal status, ER and or progesterone receptor (PgR) positivity, confirmed either by biochemical or immunohistochemical analyses. Patients were stratified by age (50 to 60, 61 to 70, and 71 to 80 years), tumor stage ($\leq$ 2, 2.1 to 5, and $\geq$ 5.1 cm), nodal involvement (none, 1 to 3, 4 to 10, and $\geq$ 11), histological tumor grading,[16] surgical procedure used (breast-conserving treatment [BCT] or modified radical mastectomy [MRM], with or without radiotherapy), hormone receptor status (ER-positive/PgR-positive, ER-positive/PgR-negative, ER-negative/PgR-positive), and participating center. Adaptive randomization was applied according to Pocock and Simon.[17]

When patients' written informed consent was obtained, trial participants were randomly assigned with equal probability to receive either tamoxifen alone for 5 years or aminoglutethimide (125 mg twice daily for the first week, 125 mg in the morning and 250 mg in the evening for the second week, and 250 mg twice daily thereafter) for the first 2 years of therapy in addition to tamoxifen for 5 years. For the first 2 years, tamoxifen was given twice daily at 20 mg. Increased tamoxifen dosage was chosen after reports that simultaneous administration with aromatase inhibitors may impair its level of bioavailability,[18] with the objective of avoiding undertreatment in the combination arm. Tamoxifen administration was reduced to 20 mg/d after 2 years, taking into account a potentially increased risk for endometrial cancer.[9,10]

Patients

Postmenopausal patients with histologically confirmed primary unilateral breast cancer (pT1 to pT3a) with negative or positive axillary nodes (pT1a exclusively in the presence of positive ipsilateral axillary nodes) were enrolled on Trial 6. Patients were classified as postmenopausal following at least a 1-year interval since the last menstrual period. Otherwise, if menopausal status was not clearly determinable, gonadotropins, follicle-stimulating hormone, and luteinizing hormone had to be in the postmenopausal range. Surgical treatment consisted either of BCT or MRM with obligatory negative margins plus complete axillary clearance, which included complete level I and II dissection. Patients were required to present a minimum of six axillary nodes on histology, whereas our recommendation was to histologically investigate at least 10 nodes. ER and/or PgR levels had to be $\geq$ 10 fmol/mg cytosol protein when performed biochemically or positive (+ or ++) when performed immunohistochemically.

Ineligibility criteria included evidence of distant metastases, premenopausal status, preoperative antineoplastic treatment and irradiation, previous malignancy (except cured squamous cell carcinoma of the skin or early cervical cancer), negative or unknown hormone receptor status, bilateral oophorectomy or radiation castration, and serious medical or emotional problems. Patients were required to begin treatment within 6 weeks after surgery.

Most patients undergoing BCT were treated with radiotherapy, which was optional in mastectomized patients and left to the discretion of the individual investigator.

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

Statistical Methods

All patient data were collected at the ABCSG Trial Center and processed and analyzed applying SAS software (SAS Institute Inc., Cary, NC).

When the required trial size was prospectively calculated, OS was estimated to be 70% for these patients on the basis of available data at that time. To detect a 5-year survival difference of 10% (65% to 75%) 5 years after termination of recruitment, with a two-sided test of significance of .05 and a power of 80%, we initially planned to recruit 666 trial participants over a period of 4 years. Because interim analyses revealed that overall prognosis was markedly better than expected in these patients, and thus that maintaining the initially planned trial size would yield an insufficient number of events, we subsequently increased target accrual three-fold.

OS was expressed as the number of months from the date of randomization until death. DFS was defined as the interval between the day of surgery and the first evidence of recurrent breast cancer. Patients who died because of confirmed reasons other than breast disease, without having experienced breast cancer recurrence, were considered as censored for all analyses. Time to first relapse or death was estimated and graphically presented according to the method of Kaplan and Meier.[19] Differences between curves were assessed by Mantel's log-rank test[20] for censored survival data.

Furthermore, interactions were investigated between treatment and prognostic variables. The Cox proportional hazards model[21] was applied in a univariate and multivariate manner to model the prognostic value of treatment, tumor grade, tumor stage, lymph node status, age, ER, PgR, surgical procedures, and radiotherapy on time to first relapse and survival time. Interactions of treatment with prognostic variables were investigated by including the product of individual hazards into the model. The proportional hazards assumptions were checked by integrating a time-dependent factor. All given *P* values are from two-sided analyses.

Toxicity was analyzed by comparing the patients' highest grades of side effects experienced in each group within the first 2 years and the remaining 3 years of therapy.

All randomized and eligible patients with checklists were included in the analyses according to the intention-to-treat principle. The date of final analysis was March 30, 2000.

RESULTS

Patient Characteristics

From December 1990 to December 1995, a total of 2,021 patients were randomly assigned to ABCSG Trial 6. Nine were subsequently found to be ineligible after central source data verification by the Trial Center and were excluded from all analyses. The reasons for exclusion were the presence of distant metastases (two patients), presence of a second malignancy (one patient), and missing evaluation of hormone receptor content (two patients). Although premenopausal status was the reason for two exclusions, another particularly young patient was withdrawn from our study despite having undergone bilateral salpingo-oophorectomy and, thus, induction of postmenopausality. Finally, one woman was excluded because of decreased prothrombin time. Six of these ineligible patients had been randomly assigned to receive tamoxifen plus aminoglutethimide, and three had been assigned to receive tamoxifen alone. Of the remaining 2,012 patients, 1,008 were randomly assigned to receive combination endocrine treatment and 1,004 were randomly assigned to tamoxifen monotherapy. No follow-up results were available for 26 of 2,012 patients (1.3%). These patients were excluded from the analyses. Detailed radiotherapy documentation was available for 1,929 patients.

Population characteristics, such as age, tumor size, and primary treatment (type of surgery, radiotherapy), were well balanced between the two treatment arms (Table 1). In

Table 1. Patient Characteristics

Characteristic	No. of Patients (%)	
	T	T+AG
Age, years	n = 996	n = 990
< 51	24 (2.4)	22 (2.2)
51-60	291 (29.2)	302 (30.5)
61-70	411 (41.3)	395 (40.0)
71-80	270 (27.1)	271 (27.4)
Tumor size, cm	n = 996	n - 990
≤ 2	576 (57.8)	578 (58.4)
> 2 ≤ 5	391 (39.3)	381 (38.5)
> 5	29 (2.9)	31 (3.1)
No. of nodes involved	n = 996	n = 990
None	620 (62.2)	615 (62.1)
1-3	252 (25.3)	261 (26.4)
4-10	92 (9.2)	85 (8.6)
≥ 11	32 (3.2)	29 (2.9)
Estrogen receptors	n = 996	n = 969
Negative	20 (2.0)	26 (2.6)
Positive	976 (98.0)	963 (97.4)
Progesterone receptors	n = 995	n = 989
Negative	194 (19.5)	171 (17.3)
Positive	801 (80.5)	818 (82.7)
Grading	n = 996	n = 990
Grade 1, 2, or unknown	779 (78.2)	773 (78.1)
Grade 3	217 (21.8)	217 (21.9)
Type of surgery	n = 996	n = 990
Breast conservation	545 (54.7)	538 (54.3)
Mastectomy	451 (45.3)	452 (45.7)

Abbreviations: T, tamoxifen; T+AG, tamoxifen plus aminoglutethimide.

particular, no significant differences were identified between the groups for the number of pathological lymph nodes and ER and/or PgR status. The median duration of follow-up was 5.3 years for all patients.

DFS

Among the 1,986 evaluated patients, 330 (16.6%) relapses occurred during the observation period, 165 in each of the treatment groups (Table 2). No significant difference in the probability of recurrence was found between the two groups (P = .89; Fig 1). Similarly, no significant difference was seen with respect to the type of recurrence (locoregional *v* distant metastases). A trend was observed in increasingly experienced bone metastases in the group undergoing combination treatment. In turn, liver metastases were slightly more frequent in the group treated with tamoxifen alone.

Table 2. Number of First Recurrences, Second Primary Tumors, and Deaths

	No. of Patients (%)	
	T (n = 996)	T+AG (n = 990)
Recurrence (locoregional and/or distant metastases)	165 (16.6)	165 (16.7)
Locoregional recurrence	31 (3.1)	35 (3.5)
Distant metastases	100 (10.0)	98 (9.9)
Lymph nodes supraclavicular	14 (1.4)	10 (1.0)
Bone	34 (3.4)	47 (4.7)
Liver	24 (2.4)	13 (1.3)
Lung	18 (1.8)	20 (2.0)
Others	10 (1.0)	8 (0.8)
Other malignant diseases	51 (5.1)	44 (4.4)
Colon cancer	13 (1.3)	13 (1.3)
Contralateral breast cancer	15 (1.5)	12 (1.2)
Endometrial cancer	8 (0.8)	6 (0.6)
Others	15 (1.5)	13 (1.3)
Death	94 (9.4)	100 (10.1)
Breast cancer–related	89 (8.9)	93 (9.4)
Breast cancer–unrelated	5 (0.5)	7 (0.7)

Abbreviations: T, tamoxifen; T+AG, tamoxifen plus aminoglutethimide.

The local recurrence rate in patients treated with BCT and radiotherapy was 1.9%. Seven patients among the 155 (4.5%) who underwent MRM and irradiation therapy experienced a local recurrence (data not shown).

Survival

Ninety-three (9.4%) of the trial subjects in the group given tamoxifen plus aminoglutethimide died of breast cancer, compared with 89 (8.9%) of the group administered tamoxifen alone. OS at the time of analysis was 91.4% for patients assigned to combination endocrine therapy and 91.2% for patients assigned to tamoxifen alone. No statistically significant difference was found between the two treatment groups (P = .74; Fig 2). Twelve patients died from reasons other than breast cancer (seven in the tamoxifen plus aminoglutethimide group and five in the tamoxifen group).

Prognostic Factors

Cox multiple regression analysis showed that the size of the tumor, PgR status, and axillary node status represented significant prognostic factors for DFS and OS (data not shown). Grading was an independent significant prognostic factor for DFS only. The relative risk of recurrence was reduced in patients with grade 3 tumors treated with combination therapy as compared with tamoxifen alone. If we take the relative risk for tamoxifen plus aminoglutethimide as 1, the relative risk in the tamoxifen-alone group was 1.36 for grade 3 tumors and 0.85 for grades 1, 2, and unknown. These findings are statistically significant (P = .04).

Second Primary Tumors and Side Effects

Forty-four secondary cancers (4.4%) occurred in the group treated with tamoxifen and aminoglutethimide, and 51 (5.1%) in the group treated with tamoxifen alone. Various types were found in both arms, with a similar distribution and a prevalence of colon and contralateral breast disease (Table 2). Similarly, no significant difference of endometrial cancer was found between the study groups.

There were no treatment-related deaths. Forty-nine patients (5.0%) in the tamoxifen plus aminoglutethimide group experienced major grade 3 and 4 side effects, as compared with 21 (2.2%) in the group treated with tamoxifen alone (Table 3; P = .0008). As expected, major side effects occurred more frequently in the group given combination endocrine treatment than in the group treated exclusively with tamoxifen, and more frequently in both groups during the first 2 years of treatment compared with the following 3 years.

In contrast, hot flashes, headache, and depressive discharges were experienced more often in patients treated with tamoxifen alone than in those undergoing combination treatment. Side effects were the reason for withdrawal from treatment in 136 patients (14.0%) of the tamoxifen plus aminoglutethimide group

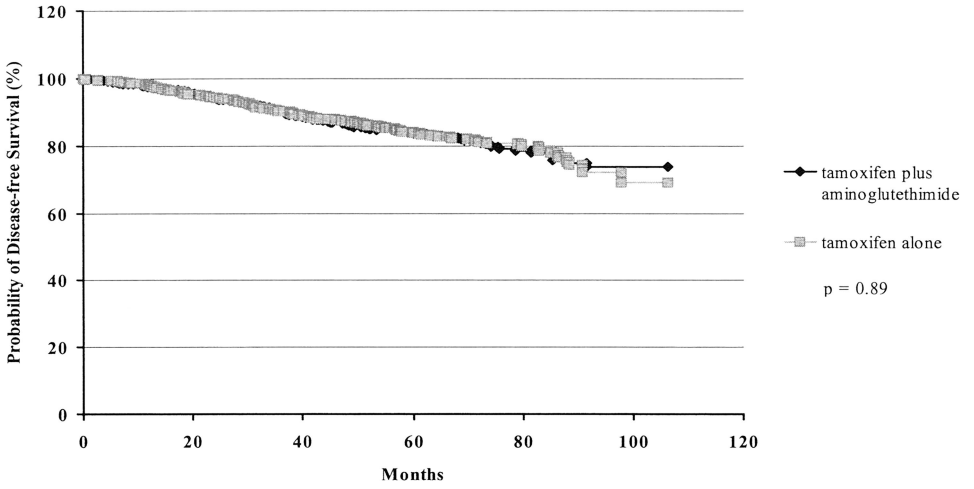

Fig. 1 Kaplan and Meier[19] estimate of disease-free survival (%).

and in 51 patients (5.2%) of the tamoxifen group ($P = .0001$; Table 3).

DISCUSSION

The objective of this randomized trial was to evaluate the efficacy of the nonselective aromatase inhibitor aminoglutethimide combined with tamoxifen as compared with exclusive standard tamoxifen administration. Trial 6 investigated these adjuvant therapy modalities and showed that combination endocrine treatment is not superior to tamoxifen in postmenopausal patients with primary, hormone receptor–positive breast cancer. The foremost rationale for implementing combination endocrine treatment was our hypothesis that reduction of peripheral serum estradiol by the agency of an aromatase inhibitor should increase the efficacy of tamoxifen. Our results clearly fail to support this idea and, rather, indicate conclusively that the reduction of peripheral serum estradiol in postmenopausal patients does not enhance the efficacy of tamoxifen.

Adjuvant tamoxifen given for 5 years currently represents the standard of care for postmenopausal patients with endocrine-responsive breast cancer. The most recent update of results emerging from the Scottish Adjuvant Tamoxifen Trial after a median follow-up of 15 years confirms that if adjuvant tamoxifen is given to women with operable breast cancer, it need not be for more than 5 years.[22] One explanation for the limited efficacy is that breast cancer cells, at least in an experimental design, develop to depend on tamoxifen, and that the late failure of, or the de novo resistance to, adjuvant tamoxifen may theoretically be related to these observations.[23,24]

Several theoretical approaches have been established to improve treatment results in this group of patients, encompassing the majority of primary breast cancer patients. First, increasing the tamoxifen dose has been investigated. In terms of both recurrence and mortality, the benefits associated with tamoxifen 20 mg/d were seen to be as large as with 30 to 40 mg/d. Unfortunately, high-dose regimens have resulted in some additional toxicity and side effects and have been abandoned in most centers worldwide after the effect of tamoxifen on the endometrium was established.[9,10,25] Second, the duration of tamoxifen treatment can also be increased. Although more data have become available in recent years, the optimum duration of drug administration is still undetermined. The results of randomized trials[26-28] indicate that the optimum duration of tamoxifen treatment is at least 5 years. Its fair level of tolerability is well recognized, with a rare incidence of serious adverse events and a drug-related treatment withdrawal rate of less than

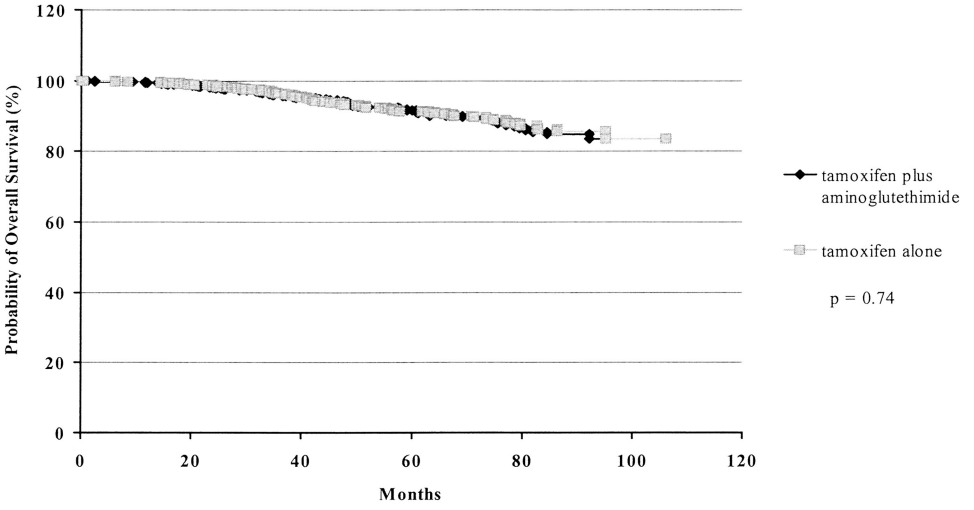

Fig. 2 Kaplan and Meier[19] estimate of overall survival (%).

Table 3. Major Side Effects of Treatment

Side Effect	First 2 Years				Following 3 Years			
	T (n = 972)		T+AG (n = 973)		T (n = 972)		T+AG (n = 973)	
	1,2*	3,4*	1,2*	3,4*	1,2*	3,4*	1,2*	3,4*
Stomatitis	14	0	20	3	10	0	9	0
Nausea	63	1	105	9†	22	1	18	2
Obstipation	54	4	52	4	27	1	22	2
Alopecia	35	2	58	2†	22	3	21	2
Cutaneous	28	4	69	16†	18	1	9	1
Allergy	9	1	31	3†	8	1	4	0
Disorders of consciousness	12	0	27	3†	3	0	4	0
Neurologic	17	0	44	0	11	2	11	2
Incidence								
Headache	113		111		87†		56	
Dizziness	173		183		129†		90	
Hot flashes	513		493		355†		279	
Depressive discharge	133		138		79		57	
Changes of blood pressure	95†		62		74		57	

Abbreviations: T, tamoxifen; T+AG, tamoxifen plus aminoglutethimide.

*World Health Organization grade.

†Significant differences between the treatment groups ($P < .05$).

5%.[29] Conversely, the National Surgical Adjuvant Breast and Bowel Project (NSABP) demonstrated that 10 years of tamoxifen does not improve survival compared with 5 years, whereas it significantly increases the risk of endometrial hyperplasia and cancer.[27,30]

The use of tamoxifen with other drugs therefore promises to be a rewarding approach. The addition of cytotoxic chemotherapy to adjuvant tamoxifen has been suggested, and data have been presented to argue that this combination may be superior to tamoxifen alone, at least in the intermediate-risk group of postmenopausal patients.[7,31] Recently presented data from Intergroup Trial 0100 investigating the proper timing of these two systemic modalities in 1,477 patients indicate a significant benefit in DFS from sequentially administered chemohormonal therapy when compared with the concurrent use of these agents.[32] The data are consistent with the hypothesis that tamoxifen may antagonize cyclophosphamide, adriamycin, and fluorouracil, or drugs used in similar regimens, and support a practice standard of starting adjuvant tamoxifen when chemotherapy is completed.

Our approach to improve the efficacy of adjuvant tamoxifen was a combination with another highly tolerable endocrine agent showing an acceptable side effect profile. The hypothesis underlying ABCSG Trial 6 was that tamoxifen and the aromatase inhibitor—by means of the agents' different mechanisms—would develop complementary, additive, or potentially synergistic activity. Because aminoglutethimide alone leads to a 91% reduction of in vivo aromatage metabolism and an 87% reduction in peripheral plasma estrogen levels, the overall reduction of circulating estradiol would allow tamoxifen to act more effectively as a competitive inhibitor.[33] Aminoglutethimide has been shown to be a highly active drug with proven efficacy in the second-line treatment of advanced breast cancer.[34,35] However, no clear-cut benefit has been established in that setting for the combination of aminoglutethimide with tamoxifen. Conversely, the preliminary analysis of a small trial conducted by Coombes et al[15] reported a significant benefit for aminoglutethimide in an adjuvant treatment setting. Although the overall benefit for the whole patient cohort could not be shown after completion of that study, a benefit arising from adjuvant aminoglutethimide in the receptor-positive subgroup of patients was still observed after a follow-up of 8 years. That trial also reported increased toxicity in the aminoglutethimide treatment group, which was another aspect we aimed to explore in our large-scale phase III trial.

To avoid the high incidence of side effects that reportedly occur with a daily dose of 1,000 mg aminoglutethimide,[36,37] the patients in this study were administered 500 mg/d. This dose was selected because lower doses of aminoglutethimide (250 to 500 mg/d) potentially suppress circulating estrogens to the same levels as full doses without compromising treatment efficacy[38-40] and do not require hydrocortisone substitution. Conceptualized approximately the same time as Trial 6, two investigations comparing 500 and 1,000 mg daily in the metastatic setting showed no significant difference in response rates or survival.[41,42] A prospective trial, carried out by the Italian Oncology Group for Clinical Research, that applied a lower dose of aminoglutethimide than our own revealed no difference in outcome or side effects between monotherapy and a combination with hydrocortisone as first-line endocrine treatment for advanced breast cancer.[43]

In the mid-1980s, 2-year courses of adjuvant aminoglutethimide administration, alone or in combination, were regarded as feasible and effective duration of adjuvant antiaromatase therapy. Ten years ago, Jones et al[36] reported on a double-blind, placebo-controlled investigation, with 8 years of follow-up and application of adjuvant aminoglutethimide in 354 patients with lymph node-positive disease. Their data were consistent with previously published interim analyses showing significant, yet merely transient, improvements in event-free survival and OS for patients receiving longer-term drug. Results of the Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group 04B study have recently become available; the trial explored sequential endocrine therapy and accrued 380 women from 1992 to 1998.[44] Switching patients from tamoxifen to aminoglutethimide

resulted in comparable event-free survival but longer OS time in those switched to the aromatase inhibitor.

In our trial, toxicity was observed to be much higher in the combination endocrine treatment group than in that given tamoxifen monotherapy. Side effects obviously induced by aminoglutethimide were seen less frequently than previously reported in the literature.[15,45,46] Along with a lack of survival superiority, this fact led to the conclusion that the addition of aminoglutethimide to tamoxifen fails to bring about the treatment improvement we had hoped for.

Although the overall results of Trial 6 did not show a benefit for combination endocrine therapy, an interesting significant treatment interaction was observed with grading. Patients with grade 3 tumors have been observed to experience a superior outcome after addition of aminoglutethimide compared with tamoxifen alone. Given the limitations of retrospective subgroup analyses, it will be necessary to test this finding in prospective randomized studies and to investigate newer aromatase inhibitors in combination with tamoxifen.

It remains to be determined whether this negative result holds true for other aromatase inhibitors, such as letrozole or anastrozole. Preclinical and early clinical trials have shown these third-generation aromatase inhibitors to be superior to aminoglutethimide.[47-49] Nonsteroidal inhibitors show well-defined mechanisms of action, a greater specificity and potency[50] than earlier agents, and a superior tolerability profile.[47,51,52] Several ongoing clinical investigations apply tamoxifen for 5 years followed by aromatase inhibitors for a total duration of adjuvant hormones exceeding 7 years. With a target of 4,800 participants, the United States–Canadian MA.17 intergroup trial is currently randomizing postmenopausal patients who are disease-free after standard tamoxifen administration to an additional 5 years of letrozole or placebo. Similarly designed, National Surgical Adjuvant Breast and Bowel Project B-33 is assigning this patient population to 2 years of the steroidal aromatase inactivator exemestane or placebo after the standard 5 years of tamoxifen treatment.[53]

Preliminary results of the Anastrozole, Tamoxifen Alone or in Combination (ATAC) Trial have more recently been presented.[54] A benefit was identified for anastrozole (1 mg/d) alone over tamoxifen (20 mg/d) alone, yet the combination of the two agents did not yield results superior to tamoxifen monotherapy. Although this is consistent with our findings for the combination of tamoxifen with aminoglutethimide, the precise reasons remain to be elucidated. It has been suggested that aromatase inhibitors reduce estrogen levels and lead to a subsequent hypersensitivity by receptor upregulation in tumor cells, which counteracts the tamoxifen effect. An alternative interpretation of the presented results of Trial 6 may also be formulated with respect to the deficiencies shown by the tamoxifen-aminoglutethimide combination: First, the concept of peripheral inhibition of aromatase action may simply not apply in the presence of tamoxifen. This is suggested by reports of in vitro differences between different-generation aromatase inhibitors with regard to in vivo aromatase inhibition. Then, decrease of serum estradiol levels might be irrelevant for a clinically notable effect. If new-generation aromatase inhibitors show similar or superior efficacy in early breast cancer, sequential use following tamoxifen may prove more effective. The Italian Cooperative Group, for example, recently published preliminary results of a study investigating possible survival benefits to arise from tamoxifen sequenced with aminoglutethimide treatment.[55] The Arimidex-Nolvadex Trial examined anastrozole treatment after initial tamoxifen administration. Finally, the ABCSG is currently comparing 5 years of tamoxifen with 2 years of tamoxifen followed by 3 years of the third-generation, nonsteroidal inhibitor. With the establishment of large-scale multicenter collaborative groups, the clinical efficacy, tolerability, and patients' acceptance of newer-generation aromatase inhibitors will eventually be conclusively evaluated, thus serving to clarify the role of these agents in the adjuvant treatment of early breast cancer in postmenopausal patients.

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APPENDIX

The appendix is available online at www.jco.org.

REFERENCES

1. Nolvadex Adjuvant Trial Organisation: Controlled trial of tamoxifen as adjuvant agent in management of early breast cancer: Interim analysis at four years by the Nolvadex Adjuvant Trial Organisation. Lancet 1:257-261, 1983

2. Scottish Cancer Trials Office: Adjuvant tamoxifen in the management of operable breast cancer: The Scottish trial. Lancet 2:171-175, 1987

3. Rose C, Thorpe SM, Andersen KW, et al: Beneficial effect of adjuvant tamoxifen therapy in primary breast cancer patients with high oestrogen receptor values. Lancet 1:16-19, 1985

4. Rutqvist LE, Cedermark B, Glas U, et al: The Stockholm trial on adjuvant tamoxifen in early breast cancer: Correlation between estrogen receptor level and treatment effect. Breast Cancer Res Treat 10:255-266, 1987

5. Fisher B, Brown A, Wolmark N, et al: Prolonging tamoxifen in therapy for primary breast cancer: Findings from the National Surgical Adjuvant Breast and Bowel Project clinical trial. Ann Intern Med 106:649-654, 1987

6. Nolvadex Adjuvant Trial Organisation: Controlled trial of tamoxifen as a single adjuvant agent in the management of early breast cancer: Br J Cancer 57:608-611, 1988

7. Early Breast Cancer Trialists' Collaborative Group: Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: An overview of 61 randomized trials among 28,896 women. N Engl J Med 319:1681-1692, 1988

8. Early Breast Cancer Trialists' Collaborative Group: Tamoxifen for early breast cancer: An overview of the randomised trials. Lancet 351:1451-1467, 1998

9. Fornander T, Rutqvist LE, Cedermark B, et al: Adjuvant tamoxifen in early breast cancer: Occurrence of new primary cancers. Lancet 1:117-120, 1989

10. Fornander T, Rutqvist LE, Cedermark B, et al: Adjuvant tamoxifen in early-stage breast cancer: Effects on intercurrent morbidity and mortality. J Clin Oncol 9:1740-1748, 1991

11. Lipton A, Santen RJ: Medical adrenalectomy using aminoglutethimide and dexamethasone in advanced breast cancer. Cancer 33:503-512, 1974

12. Smith IE, Fitzharris BM, McKinna JA, et al: Aminoglutethimide in the treatment of metastatic breast carcinoma. Lancet 2:646-649, 1978

13. Santen RJ, Worgul TJ, Samojlik E, et al: A randomized trial comparing surgical adrenalectomy with aminoglutethimide plus hydrocortisone in women with advanced breast cancer. N Engl J Med 305:545-551, 1981

14. Lawrence BV, Lipton A, Harvey HA, et al: Influence of estrogen receptor status on response of metastatic breast cancer to aminoglutethimide therapy. Cancer 45:786-791, 1980

15. Coombes RC, Powles TJ, Easton D, et al: Adjuvant aminoglutethimide therapy for post-menopausal patients with primary breast cancer. Cancer Res 47:2494-2497, 1987

16. Bloom HJG, Richardson WW: Histological grading and prognosis in breast cancer: A study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer 11:359-377, 1957

17. Pocock SJ, Simon R: Sequential treatment assignment with balancing for prognostic factors in controlled clinical trials. Biometrics 31:103-115, 1975

18. Lien EA, Anker G, Lonning PE, et al: Decreased serum concentrations of tamoxifen and its metabolites induced by aminoglutethimide. Cancer Res 50:5851-5857, 1990

19. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

20. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966

21. Cox DR: Regression model and life-tables. J R Stat Soc B 34:187-220, 1972

22. Stewart HJ, Prescott RJ, Forrest AP: Scottish adjuvant tamoxifen trial: A randomized study updated to 15 years. J Natl Cancer Inst 93:456-462, 2001

23. DeFriend DJ, Howell A: Tamoxifen withdrawal responses: Chance observations or clinical clues to antioestrogen resistance? Breast 3:199-201, 1994

24. Katzenellenbogen BS, Montano MM, Ekena K, et al: Antiestrogens: Mechanism of action and resistance in breast cancer. Breast Cancer Res Treat 44:23-38, 1997

25. Fornander T, Hellstrom AC, Moberger B: Descriptive clinicopathologic study of 17 patients with endometrial cancer during or after adjuvant tamoxifen in early breast cancer. J Natl Cancer Inst 85:1850-1855, 1993

26. Current Trials Working Party of the Cancer Research Campaign Breast Cancer Trials Group: Preliminary results from the Cancer Research Campaign trial evaluating tamoxifen duration in women aged fifty years or older with breast cancer. J Natl Cancer Inst 88:1834-1839, 1996

27. Fisher B, Dignam J, Bryant J, et al: Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. J Natl Cancer Inst 88:1529-1542, 1996

28. Swedish Breast Cancer Cooperative Group: Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. J Natl Cancer Inst 88:1543-1549, 1996

29. Jaiyesimi IA, Buzdar AU, Decker DA, et al: Use of tamoxifen for breast cancer: Twenty-eight years later. J Clin Oncol 13:513-529, 1995

30. Fisher B, Dignam I, Bryant J, et al: Five versus more than five years of tamoxifen for lymph node-negative breast cancer: Updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. J Natl Cancer Inst 93:684-690, 2001

31. Albain K, Green S, Ravdin P, et al: Overall survival after cyclophosphamide, adriamycin, 5-FU, and tamoxifen (CAFT) is superior to T alone in postmenopausal, receptor (+), node (+) breast cancer: New findings from Phase III Southwest Oncology Group Intergroup Trial S8814 (INT-0100). Proc Am Soc Clin Oncol 20: 24a, 2001 (abstr 92)

32. Albain KS, Green SJ, Ravdin PM, et al: Adjuvant chemohormonal therapy for primary breast cancer should be sequential instead of concurrent: Initial results from Intergroup Trial 0100 (SWOG-8814). Proc Am Soc Clin Oncol 21: 37a, 2002 (abstr 143)

33. Lonning PE, Geisler J, Johannessen DC, et al: Plasma estrogen suppression with aromatase inhibitors evaluated by a novel, sensitive assay for estrone sulphate. J Steroid Biochem Mol Biol 61:255-260, 1997

34. Rose C: Proper sequence of endocrine therapies in advanced breast cancer. Acta Oncol 35:44-49, 1996 (suppl 5)

35. Kaufmann M: A review of endocrine options for the treatment of advanced breast cancer. Oncology 54:2-5, 1997 (suppl 2)

36. Jones AL, Powles TJ, Law M, et al: Adjuvant aminoglutethimide for postmenopausal patients with primary breast cancer: Analysis at 8 years. J Clin Oncol 10:1547-1552, 1992

37. Stuart-Harris RC, Smith IE: Aminoglutethimide in the treatment of advanced breast cancer. Cancer Treat Rev 11:189-204, 1984

38. Murray R, Pitt P: Low-dose aminoglutethimide without steroid replacement in the treatment of postmenopausal women with advanced breast cancer. Eur J Cancer Clin Oncol 21:19-22, 1985

39. Harris AL, Cantwell BM, Sainsbury JR: Low dose aminoglutethimide (125 mg twice daily) with hydrocortisone for the treatment of advanced postmenopausal breast cancer. Breast Cancer Res Treat 7:41-44, 1986 (suppl)

40. Bruning PF, Bonfrer JMG, Hart AAM: Low dose aminoglutethimide without hydrocortisone for the treatment of advanced postmenopausal breast cancer. Eur J Cancer Clin Oncol 25:369-376, 1989

41. Bonneterre J, Coppens H, Mauriac L, et al: Aminoglutethimide in advanced breast cancer: Clinical results of a French multicenter randomized trial comparing 500 mg and 1 g/day. Eur J Cancer Clin Oncol 21:1153-1158, 1985

42. Robustelli della Cuna G, Pannuti F, Martoni A, et al: Aminoglutethimide in advanced breast cancer: Prospective, randomized comparison of two dose levels. Anticancer Res 13:2367-2372, 1993

43. Cocconi G, Bisagni G, Ceci G, et al: Low-dose aminoglutethimide with and without hydrocortisone replacement as first-line endocrine treatment in advanced breast cancer: A prospective randomized trial of the Italian Oncology Group for Clinical Research. J Clin Oncol 10:984-989, 1992

44. Boccardo F, Rubagotti A, Amoroso D, et al: Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: Results of an Italian cooperative study. J Clin Oncol 19:4209-4215, 2001

45. Ingle JN, Green SJ, Ahmann DL, et al: Randomized trial of tamoxifen alone or combined with aminoglutethimide and hydrocortisone in women with metastatic breast cancer. J Clin Oncol 4:958-964, 1986

46. Corkery J, Leonhard RCF, Henderson IC, et al: Tamoxifen and aminoglutethimide in advanced breast cancer. Cancer Res 42:3409-3414, 1982 (suppl 8)

47. Gershanovich H, Chaudri HA, Campos D, et al: Letrozole, a new oral aromatase inhibitor: Randomised trial comparing 2.5 mg daily, 0.5 mg daily and aminoglutethimide in postmenopausal women with advanced breast cancer. Ann Oncol 9:639-645, 1998

48. Dowsett M, Jones A, Johnston SRD, et al: In vivo measurement of aromatase inhibition by letrozole (CGS 20267) in postmenopausal patients with breast cancer. Clin Cancer Res 1:1511-1515, 1995

49. Geisler J, King N, Dowsett M, et al: Influence of anastrozole (Arimidex), a selective, non-steroidal aromatase inhibitor, on in vivo aromatisation and plasma oestrogen levels in postmenopausal women with breast cancer. Br J Cancer 74:1286-1291, 1996

50. Roseman BJ, Buzdar AU, Singletary E: Use of aromatase inhibitors in postmenopausal women with advanced breast cancer. J Surg Oncol 66:215-220, 1997

51. Masamura S, Adlercreutz H, Harvey H, et al: Aromatase inhibitor development for treatment of breast cancer. Breast Cancer Res Treat 33:19-26, 1995

52. Goss PE, Gwyn KMEH: Current perspectives on aromatase inhibitors in breast cancer. J Clin Oncol 12:2460-2470, 1994

53. Goss PE: Preliminary data from ongoing adjuvant aromatase inhibitor trials. Clin Cancer Res 7:4397-4401, 2001 (suppl 12)

54. Anastrozole, Tamoxifen Alone or in Combination Trialists' Group: Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial. Lancet 359:2131-2139, 2002

55. Boccardo F, Rubagotti A, Amoroso D, et al: Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: Results of an Italian cooperative study. J Clin Oncol 19:4209-4215, 2001