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ORIGINAL REPORT

Chemoendocrine Therapy for Premenopausal Women With Axillary Lymph Node–Positive, Steroid Hormone Receptor–Positive Breast Cancer: Results From INT 0101 (E5188)

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
Chemotherapy, tamoxifen, and ovarian ablation/suppression (OA/OS) are effective adjuvant approaches for premenopausal, steroid hormone receptor–positive breast cancer. The value of combined therapy has not been clearly established.

Patients and Methods
Premenopausal women with axillary lymph node–positive, steroid hormone receptor–positive breast cancer (1,503 eligible patients) were randomly assigned to six cycles of cyclophosphamide, doxorubicin, and fluorouracil (CAF), CAF followed by 5 years of monthly goserelin (CAF-Z), or CAF followed by 5 years of monthly goserelin and daily tamoxifen (CAF-ZT). The primary end points were time to recurrence (TTR), disease-free survival (DFS), and overall survival (OS) for CAF-Z versus CAF, and CAF-ZT versus CAF-Z.

Results
With a median follow-up of 9.6 years, the addition of tamoxifen to CAF-Z improved TTR and DFS but not OS. There was no overall advantage for addition of goserelin to CAF.

Conclusion
Addition of tamoxifen to CAF-Z improves outcome for premenopausal node-positive, receptor-positive breast cancer. The role of OA/OS alone or with other endocrine agents should be studied more intensely.

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INTRODUCTION

Despite local treatment, up to 50% of women with early-stage breast cancer die of metastatic disease in the absence of adjuvant systemic therapy. Older trials conducted several decades ago suggested that ovarian ablation by surgery or radiation could reduce the risk of recurrence in premenopausal women younger than 50 years.[1] Further, individual trials of adjuvant chemotherapy demonstrated improved recurrence-free and overall survival for premenopausal women with node-positive breast cancer.[2,3] In 1985, the results from these initial trials were first combined in a meta-analysis of all randomized trials of adjuvant ovarian ablation or chemotherapy.[4] This analysis unequivocally demonstrated the benefit of adjuvant chemotherapy in premenopausal women with node-positive breast cancer, leading the National Institutes of Health Consensus Conference to recommend adjuvant chemotherapy as a standard approach for these women.[5] This combined analysis also demonstrated improved outcome for younger women treated with ovarian ablation. In addition, possible benefit from the administration of tamoxifen to postmenopausal women with

node-positive breast cancer was also documented. Finally, in other studies, the equivalence of oophorectomy and chemical ovarian suppression by chronic administration of luteinizing hormone-releasing hormone agonists for treatment of premenopausal women with steroid receptor–positive metastatic breast cancer was demonstrated.[6]

Because of these findings, in 1988 the US Intergroup led by the Eastern Cooperative Oncology Group (ECOG) undertook a randomized clinical trial, E5188 or INT 0101, to evaluate the value of chemohormonal therapy for premenopausal women with node-positive breast cancer that expresses estrogen and/or progesterone receptors. We report here the results of a phase III trial in which these women were randomly assigned to receive chemotherapy alone; chemotherapy followed by ovarian suppression with the luteinizing hormone-releasing hormone agonist, goserelin; or chemotherapy followed by goserelin and tamoxifen. The primary end point of the trial was to compare the time to recurrence (TTR), disease-free survival (DFS), and survival (OS) for women receiving the three treatments. Secondary end points were toxicity and evaluation of effects on hormone levels (luteinizing hormone, follicle-stimulating hormone [FSH], and 17β estradiol). Analysis of amenorrhea and hormone levels will be reported elsewhere.

PATIENTS AND METHODS

Study Design

Premenopausal women with operable invasive estrogen and/or progesterone receptor (ER and/or PR) –positive breast cancer involving one or more axillary lymph nodes by conventional histology were eligible for the study. Premenopausal status was defined by any one of the following: less than 4 months since last menstrual period, 4 to 12 months since last menstrual period with premenopausal FSH level, or less than 61 years of age with a previous ovary-sparing hysterectomy and premenopausal FSH level. Patients on hormone replacement therapy were considered premenopausal if they were younger than 56 years and had a premenopausal FSH level after stopping therapy. Positive ER and PR were defined as $\geq$ 10 fm/mg protein by biochemical assay or positive immunohistochemistry according to individual institutional standards. All patients received appropriate local therapy with modified radical mastectomy or lumpectomy (with clear margins pathologically) and underwent axillary dissection within 12 weeks of random assignment. Local radiotherapy was required for individuals who chose breast conservation and optional for mastectomy patients. Women were excluded if they had bilateral breast malignancies, locally advanced breast cancer or metastases, history of other invasive malignancies diagnosed less than 5 years before study entry, concomitant serious medical illness, were pregnant or lactating, or had received tamoxifen for more than 2 weeks or prior chemotherapy for breast cancer. The trial was conducted in accordance with the Declaration of Helsinki with the approval of the institutional review board at each center. All patients provided written informed consent.

Staging before random assignment included normal chest x-ray, mammogram, and blood studies for hematologic, hepatic, and renal function. After stratification by number of positive axillary lymph nodes (1 to 3, 4 to 9, $>$ 9), hormone receptor status (ER+/PR+, ER−PR+, ER+PR−), and time since primary surgery ($\leq$ 6 weeks, $>$ 6 weeks), patients were randomly assigned to receive chemotherapy, chemotherapy followed by goserelin, or chemotherapy followed by goserelin and tamoxifen. Chemotherapy (CAF) was administered for six cycles of 28 days each. Cyclophosphamide was administered at 100 mg/m^2/d po on day 1 through 14. Doxorubicin (30 mg/m^2 intravenously) and fluorouracil (500 mg/m^2 intravenously) were given on days 1 and 8. Dose modification algorithms have been previously reported.[7] Colony-stimulating factors were permitted only for treatment of febrile neutropenia. Patients assigned to receive goserelin (Z) received a 3.6-mg depot (Zoladex; AstraZeneca, Wilmington, DE) subcutaneously every 4 weeks for 5 years beginning on cycle 6, day 29 of CAF. Patients randomly assigned to receive goserelin plus tamoxifen (ZT) also took tamoxifen 10 mg po bid for 5 years beginning on cycle 6, day 29 of CAF. Goserelin dose was doubled if a patient was not amenorrheic and if serum estradiol level was not in the postmenopausal range after 8 weeks. Patients were seen every 3 months for the first 6 months, every 4 months after CAF for the first 5 years, every 6 months for the next 3 years, and yearly thereafter.

Statistical Considerations

TTR was defined as time from random assignment to disease recurrence or new breast cancer primary, where death without recurrence was censored. DFS was defined as time from random assignment to disease recurrence, new breast cancer primary, or death, whichever occurred first. OS was defined as time from random assignment to death.

This study was designed to test two separate hypotheses: whether goserelin improves TTR, DFS, or OS when added to CAF and whether tamoxifen improves TTR, DFS, or OS when added to CAF-Z. Its initial accrual goal was 960 patients; this was expanded to 1,500 patients in 1992 to improve statistical power. There was 80% power using a one-sided type I error rate of 2.5% to detect a 33.3% reduction in the failure and death hazard rates by adding goserelin to CAF and a 40% reduction in the failure and death hazard rates by adding tamoxifen to CAF-Z. One-sided tests were used since the only alternative of interest was that adding goserelin or ZT following CAF leads to an improved outcome. Full information for the TTR and OS comparisons was defined as 120 recurrences and 124 deaths, respectively, among women on the CAF arm who were eligible and event-free for the first 6 months.

The ECOG Data Monitoring Committee reviewed accrual and safety data twice a year. Two interim analyses for TTR and survival were performed, and study continuation was recommended on both occasions. At the scheduled final analysis of TTR in September 1996, the boundary for the CAFZ-T to CAF-Z comparison was crossed, but the boundary for CAF-Z versus CAF was not. Because many patients were still receiving treatment, and a late difference in treatment effect was felt to be plausible, the ECOG Data Monitoring Committee and Group and Breast Committee Chairs agreed to keep the study blinded until November 1998, when all patients would be more than 4 years from start of hormonal therapy. At that time, the CAF-ZT to CAF-Z comparison for TTR remained significant, and the CAF-Z to CAF comparison was not; the boundaries for survival were not crossed at any time.

The primary analysis of outcome is an intent-to-treat analysis on eligible patients from time of random assignment. Fisher's

exact test was used to test for differences across treatment arms with respect to baseline characteristics.[8] The Kruskal-Wallis test for ordered data was used to compare maximum toxicity grade between treatment groups.[9] The Kaplan-Meier method was used to estimate distributions for TTR, DFS, and survival.[10] The log-rank test was used to assess differences between these distributions with respect to treatment.[11] Cox proportional hazards models were used to estimate the effect of treatment after adjustment for baseline covariates.[12] The Wald test was used to test for significant covariates in the proportional hazards models.[13] The following covariates were considered: age (<40 years, ≥ 40 years); nodal status (1 to 3, 4 to 9, >9); and steroid receptor status (ER+/PR+, ER−/PR+, ER+/PR−). P values $\leq .05$ for the Fisher's exact tests and those $\leq .025$ for the Wald and log-rank tests were considered significant. The Subpopulation Treatment Effect Pattern Plot (STEPP) analysis was performed as previously described.[14]

RESULTS

Patient Eligibility and Characteristics

Between July 1989 and February 1994, 1,537 patients were enrolled, of whom 1,503 were eligible. The most common reasons for ineligibility included positive surgical margins (10 patients), missing or abnormal laboratory data (11 patients), postmenopausal status (three patients), and metastatic disease (two patients). There were no significant differences in baseline characteristics across treatment groups (Table 1).

Outcomes

All analyses are reported at a median follow-up for survival of 9.6 years among those patients still alive on April 30, 2002. Within this observation period, there have been 551 recurrences, 585 events, and 427 deaths (n = 201, n = 212, and n = 154, respectively for CAF alone). Sites of recurrence and types of events are presented in Table 2. The use of goserelin after CAF did not significantly improve TTR, DFS, or OS compared with CAF alone, whether or not the hazard ratio (HR) was adjusted for age, nodal status, and steroid hormone receptor status (Table 3). The addition of tamoxifen to CAF-Z significantly improved TTR and DFS, but did not significantly improve survival, whether or not the HR was adjusted for the aforementioned baseline covariates. Similar results were obtained on analysis of all 1,537 randomly assigned patients (data not shown).

Table 1. Characteristics of Eligible Patients

	CAF		CAF-Z		CAF-ZT		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
No. of nodes								
1-3	291	59	299	59	296	58	886	59
4-9	158	32	154	31	163	32	475	32
≥ 10	45	9	49	10	48	10	142	9
Age, years								
< 40	138	28	151	30	149	29	438	29
≥ 40	356	72	351	70	358	71	1,065	71
ER/PR status								
ER+/PR+	378	77	375	75	395	78	1,148	76
ER−/PR+	61	12	72	14	58	12	191	13
ER+/PR−	55	11	55	11	54	10	164	11
Tumor size								
≤ 2	183	39	184	38	202	42	569	40
> 2	289	61	297	62	278	58	864	60
Unknown	22		21		27		70	
Prior surgery								
Mastectomy	411	83	410	82	393	78	1,214	81
Breast conservation	83	17	92	18	114	22	289	19
Postmastectomy radiation								
Yes	44	11	46	11	37	9	127	10
No	367	89	364	89	356	91	1,087	90
Race								
White	404	82	418	83	413	82	1,235	82
Black	45	9	47	9	48	9	140	9
Other	45	9	37	7	45	9	127	8
Unknown					1		1	
Total	494		502		507		1,503	

Abbreviations: CAF, cyclophosphamide, doxorubicin, and fluorouracil; CAF-Z, CAF followed by 5 years of monthly goserelin; CAF-ZT, CAF followed by 5 years of monthly goserelin and daily tamoxifen; ER, estrogen receptor; PR, progesterone receptor.

Table 2. Sites of Recurrence

	CAF (n = 494)		CAF-Z (n = 502)		CAF-ZT (n = 507)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Sites of failure						
Local	24	5	25	5	16	3
Regional ± local	30	6	22	4	14	3
Distant						
Soft tissue/nodes ± any of above	5	1	4	1	7	1
Bone ± any of above	48	10	48	10	42	8
Visceral ± any of above	68	14	72	14	61	12
Unknown	6	1	7	1	4	1
Contralateral breast cancer*						
Isolated	14	3	13	3	8	2
Other site	6	1	6	1	1	0
Total recurrences	201	41	197	39	153	30
Deaths	154	30	143	28	130	26
Death without recurrence	11	2	11	2	12	2
Nonbreast, second primary cancers	21	4	18	4	14	3

Abbreviations: CAF, cyclophosphamide, doxorubicin, and fluorouracil; CAF-Z, CAF followed by 5 years of monthly goserelin; CAF-ZT, CAF followed by 5 years of monthly goserelin and daily tamoxifen.
*Invasive only. In situ contralateral breast cancers were diagnosed in one, two, and four women on arms CAF, CAF-Z, and CAF-ZT, respectively.

Figure 1 shows the Kaplan-Meier estimates for TTR, DFS, and OS for the eligible study population by treatment assignment. The 9-year DFS was 57% for CAF, 60% for CAF-Z, and 68% for CAF-ZT. Survival differences began to emerge after 6 years of follow-up. However, the differences in 9-year OS—70% for CAF, 73% for CAF-Z, and 76% for CAF-ZT—are not statistically significant at present. Table 4 presents the hazard ratios for treatment effect within age, node, ER/PR, and racial subgroups.

Table 3. Univariate and Adjusted Hazard Ratios for Eligible Patients

	CAF-Z Versus CAF			CAF-ZT Versus CAF-Z		
	HR*	95% CI	P†	HR‡	95% CI	P†
TTR	0.93	0.76 to 1.14	.25	0.73	0.59 to 0.90	< .01
Adjusted§	0.91	0.74 to 1.11	.17	0.73	0.59 to 0.90	< .01
DFS	0.93	0.76 to 1.12	.22	0.74	0.60 to 0.91	< .01
Adjusted§	0.90	0.74 to 1.09	.15	0.74	0.60 to 0.91	< .01
OS	0.88	0.70 to 1.11	.14	0.91	0.71 to 1.15	.21
Adjusted§	0.86	0.69 to 1.08	.10	0.91	0.72 to 1.16	.23

Abbreviations: CAF, cyclophosphamide, doxorubicin, and fluorouracil; CAF-Z, CAF followed by 5 years of monthly goserelin; CAF-ZT, CAF followed by 5 years of monthly goserelin and daily tamoxifen; HR, hazard ratio; TTR, time to recurrence; DFS, disease-free survival; OS, overall survival.
*HR < 1 indicates improved outcome for CAF-Z.
†1-sided (compared with $\alpha = .025$).
‡HR < 1 indicates improved outcome for CAF-ZT.
§Adjusted for age, nodal and ER/PR status.

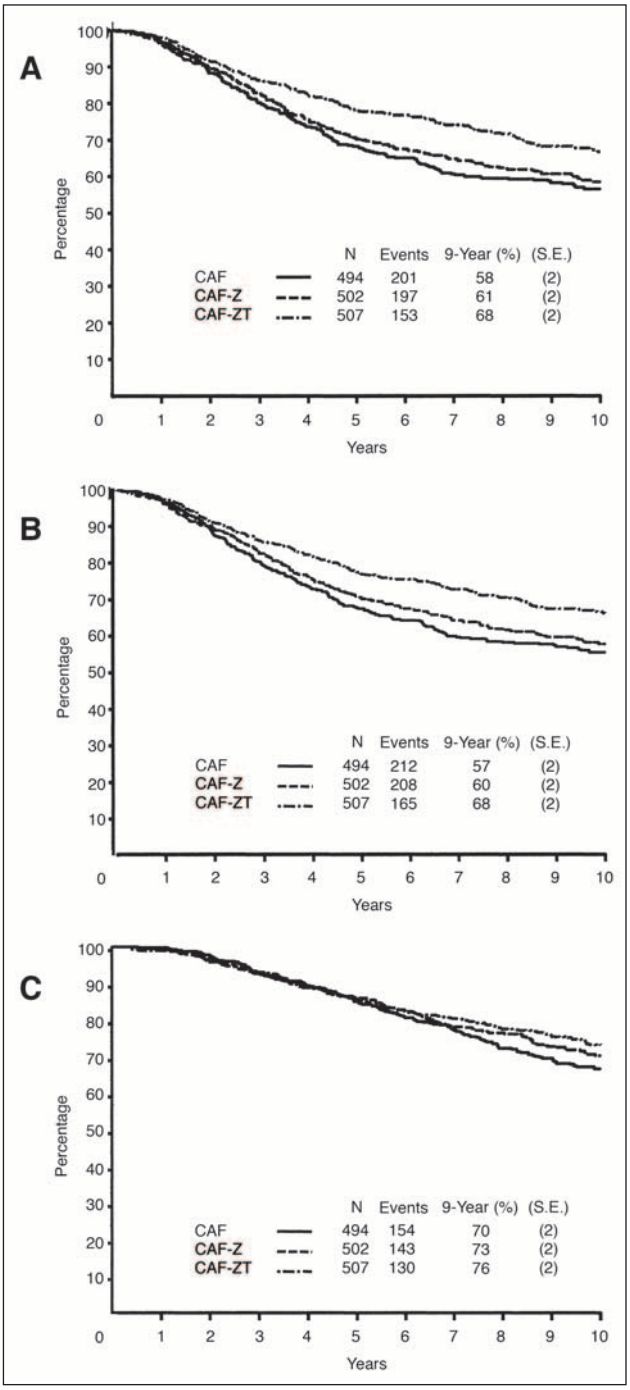

Fig 1. Outcomes for all patients. (A) Time to recurrence; (B) disease-free survival; (C) overall survival. CAF, cyclophosphamide, doxorubicin, and fluorouracil; CAF-Z, CAF followed by 5 years of monthly goserelin; CAF-ZT, CAF followed by 5 years of monthly goserelin and daily tamoxifen.

One effect of CAF chemotherapy may be induction of chemotherapy-induced ovarian ablation; women with chemotherapy-induced ovarian failure could be less likely to derive benefit from goserelin. Since several studies suggest that chemotherapy-induced ovarian ablation is seen in a majority of women ≥ 40 years of age who receive

Table 4. Treatment Effect and Patient Characteristics

	CAF-Z Versus CAF		CAF-ZT Versus CAF-Z	
	HR*	95% CI	HR†	95% CI
Age < 40 (n = 438)				
TTR	0.80	0.57 to 1.12	0.75	0.52 to 1.08
DFS	0.78	0.56 to 1.08	0.76	0.53 to 1.09
OS	0.79	0.54 to 1.14	0.79	0.52 to 1.19
Age ≥ 40 (n = 1,065)				
TTR	1.00	0.78 to 1.27	0.72	0.56 to 0.94
DFS	1.00	0.79 to 1.26	0.73	0.57 to 0.94
OS	0.92	0.69 to 1.23	0.98	0.73 to 1.32
1 to 3 nodes (n = 886)				
TTR	0.92	0.68 to 1.23	0.63	0.45 to 0.88
DFS	0.95	0.71 to 1.27	0.64	0.47 to 0.88
OS	1.02	0.71 to 1.46	0.74	0.50 to 1.08
4 to 9 nodes (n = 475)				
TTR	1.05	0.76 to 1.43	0.70	0.50 to 0.97
DFS	1.02	0.75 to 1.38	0.72	0.52 to 0.99
OS	0.98	0.68 to 1.39	0.98	0.68 to 1.40
> 9 nodes (n = 142)				
TTR	0.59	0.35 to 0.99	1.14	0.68 to 1.90
DFS	0.55	0.33 to 0.90	1.17	0.71 to 1.93
OS	0.43	0.24 to 0.75	1.21	0.66 to 2.22
ER+/PR+ (n = 1,148)				
TTR	0.95	0.76 to 1.20	0.73	0.57 to 0.93
DFS	0.93	0.74 to 1.16	0.74	0.58 to 0.93
OS	0.91	0.70 to 1.19	0.90	0.68 to 1.18
ER−/PR+ (n = 191)				
TTR	0.97	0.55 to 1.70	0.92	0.51 to 1.65
DFS	0.91	0.52 to 1.59	1.03	0.58 to 1.81
OS	0.71	0.37 to 1.36	1.51	0.79 to 2.89
ER+/PR− (n = 164)				
TTR	0.79	0.45 to 1.38	0.62	0.32 to 1.19
DFS	0.91	0.53 to 1.56	0.53	0.28 to 1.00
OS	0.90	0.49 to 1.63	0.58	0.28 to 1.19
White (n = 1,235)				
TTR	0.97	0.78 to 1.21	0.76	0.60 to 0.97
DFS	0.97	0.78 to 1.20	0.76	0.61 to 0.96
OS	0.93	0.72 to 1.21	0.94	0.72 to 1.23
Black (n = 140)				
TTR	0.61	0.34 to 1.09	0.73	0.37 to 1.42
DFS	0.62	0.36 to 1.08	0.72	0.38 to 1.35
OS	0.57	0.31 to 1.05	0.84	0.41 to 1.72
Other race (n = 127)				
TTR	1.04	0.55 to 2.00	0.49	0.23 to 1.04
DFS	1.00	0.53 to 1.90	0.55	0.27 to 1.13
OS	1.07	0.51 to 2.23	0.70	0.31 to 1.55

Abbreviations: CAF, cyclophosphamide, doxorubicin, and fluorouracil; CAF-Z, CAF followed by 5 years of monthly goserelin; CAF-ZT, CAF followed by 5 years of monthly goserelin and daily tamoxifen; HR, hazard ratio; TTR, time to recurrence; DFS, disease-free survival; OS, overall survival.
*HR < 1 indicates improved outcome with CAF-Z.
†HR < 1 indicates improved outcome with CAF-ZT.

combination chemotherapy, Kaplan-Meier plots for DFS and OS by age were derived in an unplanned retrospective analysis (Fig 2). These suggest a possible trend for benefit for the use of goserelin after CAF for women younger than 40 years of age, as well as a benefit of adding tamoxifen to CAF-Z (9-year DFS rates of 48%, 55%, and 64% for CAF, CAF-Z, and CAF-ZT, respectively). For the older women, DFS curves for CAF and CAF-Z are superimposable, while CAF-ZT seems to provide superior outcomes (9-year DFS rates of 61%, 62%, and 69% for CAF, CAF-Z, and CAF-ZT, respectively). A further evaluation of treatment differences according to age using the STEPP analysis is shown in Figure 3. This suggests that the addition of goserelin to CAF may enhance 9-year DFS for younger women, while the addition of tamoxifen to CAF-Z is associated with improved outcomes overall.

Compliance and Toxicity

Seventy-eight percent of patients completed CAF chemotherapy as prescribed by protocol; there was no difference between the three arms. There were four lethal adverse events during CAF chemotherapy (sepsis in two, myocardial infarction in one, and cardiomyopathy and pneumonitis in one), and 62% of patients sustained ≥ grade 4 adverse events, largely related to granulocytopenia and leukopenia.

Of the 494 eligible patients randomized to receive CAF, 428 (87%) received no endocrine therapy; one patient took nonprotocol goserelin (0.2%), 61 patients took nonprotocol tamoxifen (12%), and four patients received both goserelin and tamoxifen (0.8%). Of 502 eligible patients assigned to CAF-Z, 413 (82%) received goserelin, with a median treatment duration of 4.7 years, while 28 (6%) received no endocrine therapy, 37 (7%) opted for tamoxifen without goserelin (median duration, 4.5 years), and 24 (5%) received goserelin (median duration, 1.3 years) and nonprotocol tamoxifen (median duration, 2.8 years). For the 507 eligible patients assigned to CAF-ZT, 438 (86%) received goserelin (median duration, 4.7 years) and tamoxifen (median duration, 4.9 years). Thirty patients (6%) in the CAF-ZT group received no hormone therapy, while one (0.2%) received goserelin alone, and 38 (8%) received only tamoxifen. Goserelin was stopped in 65 patients assigned to CAF-Z and in 95 patients assigned to CAF-ZT because of toxicity or patient withdrawal/refusal. Of patients assigned to CAF-ZT, 78 stopped tamoxifen because of toxicity or patient withdrawal/refusal.

There were five lethal adverse events during the maintenance phase—two in the CAF group, one in the CAF-Z arm, and two in the CAF-ZT group (suicide, unspecified pulmonary disease, cardiomyopathy, cardiac ischemia, and stroke). Statistically significant differences in a number of nonlethal adverse events were seen with the addition of goserelin to CAF during the maintenance period, as indicated in Table 5. These were generally of low grade and uncertain clinical significance. Clinically and statistically noteworthy increases in weight gain, hypertension, diabetes, and hot flashes were noted. An increase in grade 1 anemia was also noted. The further addition of tamoxifen to CAF-Z increased the incidence of diabetes, hot flashes, and anemia, but did not affect the incidence of hypertension or weight gain.

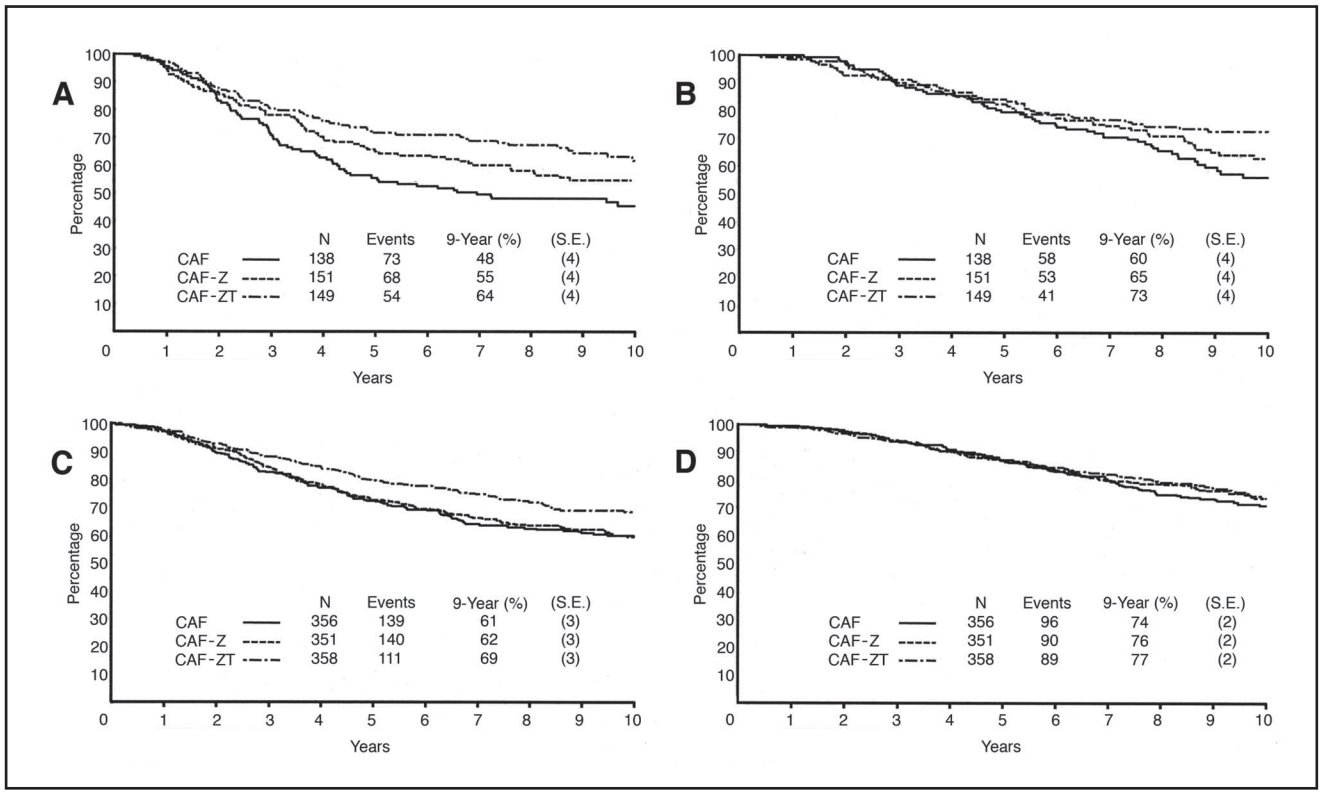

Fig 2. Outcomes for patients by age at trial entry. (A) Disease-free survival for women younger than 40 years; (B) overall survival for women younger than 40 years; (C) disease-free survival for women ≥ 40 years of age; (D) overall survival for women ≥ 40 years of age. CAF, cyclophosphamide, doxorubicin, and fluorouracil; CAF-Z, CAF followed by 5 years of monthly goserelin; CAF-ZT, CAF followed by 5 years of monthly goserelin and daily tamoxifen.

DISCUSSION

E5188 tested the value of chemohormonal therapy through a randomized trial of CAF alone, CAF-Z, and CAF-ZT in premenopausal women with node-positive, receptor-positive breast cancer. Results reported here show that CAF-ZT significantly improves TTR and DFS compared with CAF-Z, but the addition of goserelin did not significantly improve outcome compared with CAF alone. Retrospective subset analysis suggests that women younger than 40 years (who are most likely to remain premenopausal after adjuvant chemotherapy according to several data sets) seemed to benefit from the addition of goserelin to CAF, and those older than 40 years showed little benefit from the addition of goserelin. These subgroup analyses lack the power to make definitive conclusions.

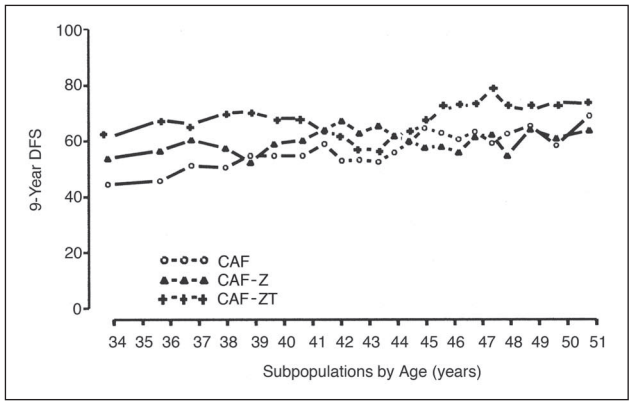

Fig 3. STEPP plot of 9-year disease-free survival (DFS) by age. CAF, cyclophosphamide, doxorubicin, and fluorouracil; CAF-Z, CAF followed by 5 years of monthly goserelin; CAF-ZT, CAF followed by 5 years of monthly goserelin and daily tamoxifen.

E5188 is the largest and most mature trial of combination chemotherapy and ovarian suppression for node-positive breast cancer reported to date. A major strength is that trial eligibility was defined by a physiological definition for the premenopausal state, rather than age, as truly premenopausal women are most likely to benefit from such an approach. Further, participation was restricted to patients with an ER- and/or PR-positive tumor—the subset of women most likely to benefit from endocrine therapy. A single anthracycline-containing regimen was administered to all women, ensuring homogeneity of chemotherapy effects across all patients. Tamoxifen was used for 5 years and was administered after completion of chemotherapy, a strategy that seems to be optimal based on randomized clinical trials and the meta-analysis.[15,16] All patients had axillary lymph node–positive disease, allowing focus on a

Table 5. Toxicity of CAF Versus CAF-Z and CAF-Z Versus CAF-ZT During Maintenance Therapy

Toxicity	% of Patients												*P*	
	CAF Toxicity Grade				CAF-Z Toxicity Grade				CAF-ZT Toxicity Grade				CAF-Z Versus CAF	CAF-ZT Versus CAF-Z
	1	2	3	4	1	2	3	4	1	2	3	4		
Granulocytopenia	14.3	4.7	0.6	0.2	12.8	5.9	1.4	0.0	17.2	6.3	2.0	0.2	NS	.05
Anemia	29.4	1.8	0.0	0.0	35.7	2.6	0.4	0.0	44.2	3.3	0.0	0.0	.01	< .01
Infection	13.0	17.0	1.0	0.0	16.0	25.4	1.4	0.0	15.7	32.5	1.5	0.0	< .01	.01
Fever	25.4	0.2	0.0	0.0	32.0	1.0	0.0	0.0	39.3	1.4	0.0	0.0	< .01	< .01
Nausea	4.7	0.6	0.6	0.0	8.7	2.0	0.6	0.0	10.8	2.7	0.0	0.0	.01	NS
Diarrhea	3.6	1.0	0.0	0.0	5.9	2.4	0.2	0.0	6.7	0.8	0.0	0.0	< .01	NS
Stomatitis	0.4	0.0	0.0	0.0	3.0	0.8	0.0	0.0	3.1	0.6	0.0	0.0	< .01	NS
Liver	59.0	4.1	1.6	0.0	58.0	6.1	2.2	0.0	52.1	8.4	1.0	0.0	.02	NS
Hypertension	5.9	0.8	2.4	0.0	6.7	2.2	8.3	0.0	5.7	3.3	9.8	0.0	< .01	NS
Skin	12.2	4.5	0.0	0.0	17.2	7.1	0.0	0.0	20.9	8.4	0.6	0.2	< .01	.03
Local	0.8	0.2	0.0	0.0	6.5	0.8	0.0	0.0	4.1	0.6	0.0	0.0	.01	NS
Alopecia	11.4	5.9	0.0	0.0	13.0	9.7	0.0	0.0	18.0	9.8	0.0	0.0	.05	.04
Weight gain	23.5	17.9	10.5	0.0	23.1	24.5	11.4	0.0	22.3	29.5	11.0	0.0	.01	NS
Neurosensory	9.7	1.2	0.0	0.0	13.6	2.2	0.2	0.0	12.5	2.2	0.2	0.0	.01	NS
Neuromotor	3.9	0.2	0.0	0.0	5.7	2.6	0.8	0.0	6.5	1.6	0.2	0.0	< .01	NS
Neuropsychiatric	7.5	7.7	0.8	0.4	15.6	13.8	2.4	0.4	13.7	15.5	2.0	1.0	< .01	NS
Neuroclinical	21.9	3.7	0.6	0.0	24.5	10.7	1.6	0.2	27.6	8.4	0.6	0.0	< .01	NS
Metabolic	7.1	2.0	0.2	0.0	12.4	1.0	0.2	0.0	11.2	1.4	0.0	0.2	.04	NS
Diabetes	29.0	4.7	3.2	0.0	35.3	6.1	2.8	0.0	42.1	9.4	3.5	1.0	.03	< .01
Hot flashes	41.0	18	0.4	0.0	55.0	23.0	1.6	0.0	49.5	29.7	3.1	0.0	< .01	< .01

NOTE. Five patients died from adverse events during maintenance therapy (two in CAF, one in CAF-Z, and two in CAF-ZT).
Abbreviations: CAF, cyclophosphamide, doxorubicin, and fluorouracil; CAF-Z, CAF followed by 5 years of monthly goserelin; CAF-ZT, CAF followed by 5 years of monthly goserelin and daily tamoxifen; NS, not significant.

group of women with higher recurrence rate with any type of adjuvant systemic therapy who might be most likely to benefit from combined therapy.

A major caveat about this trial is that it lacks an arm of CAF followed by tamoxifen. At the time that the trial was designed, tamoxifen was not felt to be beneficial for premenopausal women, and allocation to a CAF-T arm was not felt to be justified based on the meta-analysis. A second concern is that newer regimens such as anthracycline-taxane regimens or dose dense regimens may give different results than CAF, limiting our ability to extrapolate findings from this trial to current adjuvant chemotherapy regimens. Also, this study of 1,500 patients is relatively underpowered; it is possible that a higher accrual goal could have shown a small but significant benefit for CAF-Z compared with CAF. Also, because 13% of patients assigned to CAF alone also received nonprotocol endocrine therapy and 18% of patients assigned to CAF-Z received no endocrine therapy (6%) or nonprotocol tamoxifen (12%), it is possible that the contribution of goserelin to CAF has been underestimated in this intent-to-treat analysis. Finally, no prospective quality-of-life assessment was undertaken.

Toxicity of chemoendocrine therapy was acceptable. Administration of goserelin was associated with a higher incidence of toxicities of diverse types than CAF alone. As patients receiving goserelin were seen monthly for injection, whereas patients on CAF alone were seen every 4 months, it is not known whether the increased frequency of some of these toxicities was a function of more frequent ascertainment or a true increase in the incidence and/or severity of the side effects themselves. However, it does seem that administration of goserelin may be associated with more weight gain, diabetes, and hot flashes. Addition of tamoxifen to CAF-Z was associated with increased diabetes and hot flashes without further weight gain, an observation consistent with the findings of the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 breast cancer prevention trial of tamoxifen versus placebo.[17,18] Unexpectedly, an increase in low-grade anemia was seen with the addition of goserelin to CAF and with the addition of tamoxifen to CAF-Z. There was no difference in the frequency of non–breast cancer second malignancies (Table 2). Addition of tamoxifen to CAF-Z reduced the incidence of contralateral invasive breast cancers, a finding consistent with the meta-analysis and the NSABP P1 Breast Cancer Prevention Trial.[17]

Indirect comparison of outcomes from the meta-analysis has suggested that combination chemotherapy and ovarian ablation/suppression (OA/OS) gave similar results for women younger than 50 years old with receptor-positive breast cancer.[19,20] A number of trials have directly evaluated the efficacy of OA/OS strategies versus CMF (cyclophosphamide, methotrexate, and fluorouracil) chemotherapy for premenopausal women. The Scottish-Guys,[21] ZEBRA

(Zoladex Early Breast Cancer Research Association),[22] Scandanavian,[23] IBCSG (International Breast Cancer Study Group) VIII,[24] and TABLE (Takeda Adjuvant Breast Cancer Study With Leuprorelin Acetate)[25] trials showed that OA/OS gave similar results to CMF for women with ER-positive breast cancer, but CMF was superior for women with ER-negative breast cancer. The GROCTA (Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group), ABCSG (Austrian Breast and Colorectal Cancer Study) 5, and French Adjuvant Study Group (FASG) 06 trials[26-28] showed that total endocrine blockade with ovarian suppression and tamoxifen is as good as or better than CMF chemotherapy for premenopausal women with early-stage hormone-responsive disease. In aggregate, these studies demonstrate that OS/OA and CMF chemotherapy have similar effects in premenopausal women with receptor-positive disease.

Information about the effects of OA/OS after chemotherapy is more limited. The 1995 meta-analysis showed a trend for an advantage for OA plus chemotherapy over OA alone in women with ER-positive but not ER-poor tumors.[20] In IBCSG VIII, a trial of chemohormonal therapy in node-negative premenopausal women, a strategy of CMF-Z gave nonsignificantly improved results over CMF alone.[18] Retrospective subset analysis showed that CMF-Z significantly improved 5-year DFS compared with CMF for women younger than 40 years of age with ER-positive tumors; there was no difference for women $\geq$ 40 years old with ER-positive tumors.[24] The Zoladex in Premenopausal Patients (ZIPP) trial used a 2 $\times$ 2 factorial design to compare tamoxifen for 2 years, goserelin for 2 years, tamoxifen and goserelin for 2 years, and no hormonal therapy in 2,648 premenopausal women with early-stage breast cancer with variable characteristics.[29] With a median follow-up of approximately 4 years, there was a significant reduction in first events in women treated with goserelin ($P = .001$), but the benefit was less pronounced in those who received chemotherapy or tamoxifen. Finally, a report from Arriagada et al[30] showed no advantage for adjuvant chemotherapy plus OA compared with chemotherapy. This trial had relaxed entry criteria, permitting any type of adjuvant chemotherapy or ovarian intervention; 90% of patients were node-positive, and 63% had receptor-positive tumors. Thus, these trials are diverse with regard to patient characteristics such as nodal and hormone-receptor status and type of chemotherapy permitted. They are relatively underpowered and did not use tamoxifen in an optimal fashion.

E5188 provides additional support for the value of tamoxifen in premenopausal, receptor-positive breast cancer. An earlier ECOG trial was among the first to show that 5 years of tamoxifen significantly improved TTR for premenopausal women with ER-positive node-positive breast cancer who had also received combination chemotherapy.[31] The 1995 meta-analysis showed that the benefit of 5 years of tamoxifen for women with ER-positive breast cancer was seen regardless of age, menopausal status, or use of chemotherapy.[16] In this study, all endocrine therapy was administered after completion of chemotherapy. Results from INT 0100 (S8814) have shown that sequential administration of chemotherapy followed by tamoxifen, rather than concurrent use, is associated with better outcome, supporting the treatment strategy used in E5188.[32] One cannot assume, however, that the negative impact of simultaneous treatment with CAF and tamoxifen necessarily applies to other endocrine therapies, such as estrogen deprivation, that may work by different mechanisms of action.

E5188 provides the most extensive information to date about the utility of chemoendocrine therapy in premenopausal women with node-positive, receptor-positive breast cancer. It demonstrates that addition of tamoxifen to CAF-Z significantly improves TTR and DFS. The addition of goserelin after CAF chemotherapy did not improve overall outcome. The findings from this study clearly support the use of tamoxifen after chemotherapy for premenopausal, node-positive, receptor-positive breast cancer. Together with results from other studies of OA/OS, this study suggests that the role of OA/OS deserves more careful scrutiny, but the results from this study do not support the routine use of OA/OS after chemotherapy. Patients and investigators are encouraged to participate in three ongoing international trials: Suppression of Ovarian Function Trial (SOFT), Tamoxifen and Exemestane Trial (TEXT), and Premenopausal Endocrine Responsive Chemotherapy Trial (PERCHE), which will definitively establish the roles of chemotherapy, OA/OS, tamoxifen, and aromatase inhibitor in premenopausal women with early-stage receptor-positive breast cancer.

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