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ORIGINAL REPORT

Low-Dose Oral Cyclophosphamide and Methotrexate Maintenance for Hormone Receptor–Negative Early Breast Cancer: International Breast Cancer Study Group Trial 22-00

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ABSTRACT

Purpose

To evaluate the benefit of low-dose cyclophosphamide and methotrexate (CM) maintenance, which previously demonstrated antitumor activity and few adverse effects in advanced breast cancer, in early breast cancer.

Patients and Methods

International Breast Cancer Study Group (IBCSG) Trial 22-00, a randomized phase III clinical trial, enrolled 1,086 women (1,081 intent-to-treat) from November 2000 to December 2012. Women with estrogen receptor– and progesterone receptor–negative (< 10% positive cells by immunohistochemistry) early breast cancer any nodal and human epidermal growth factor receptor 2 status, were randomly assigned anytime between primary surgery and 56 days after the first day of last course of adjuvant chemotherapy to CM maintenance (cyclophosphamide 50 mg/day orally continuously and methotrexate 2.5 mg twice/day orally on days 1 and 2 of every week for 1 year) or to no CM. The primary end point was disease-free survival (DFS), which included invasive recurrences, second (breast and nonbreast) malignancies, and deaths.

Results

After a median of 6.9 years of follow-up, DFS was not significantly better for patients assigned to CM maintenance compared with patients assigned to no CM, both overall (hazard ratio [HR], 0.84; 95% CI, 0.66 to 1.06; $P = .14$) and in triple-negative (TN) disease (n = 814; HR, 0.80; 95% CI, 0.60 to 1.06). Patients with TN, node-positive disease had a nonstatistically significant reduced HR (n = 340; HR, 0.72; 95% CI, 0.49 to 1.05). Seventy-one (13%) of 542 patients assigned to CM maintenance did not start CM. Of 473 patients who received at least one CM maintenance dose (including two patients assigned to no CM), 64 (14%) experienced a grade 3 or 4 treatment-related adverse event; elevated serum transaminases was the most frequently reported (7%), followed by leukopenia (2%).

Conclusion

CM maintenance did not produce a significant reduction in DFS events in hormone receptor–negative early breast cancer. The trend toward benefit observed in the TN, node-positive subgroup supports additional exploration of this strategy in the TN, higher-risk population.

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INTRODUCTION

Affordable, effective tailored adjuvant chemotherapy regimens for hormone receptor–negative breast cancer continue to be missing from our ever-expanding arsenal of treatments. Endocrine nonresponsive breast cancer has a worse 5-year disease-free survival (DFS) than luminal disease,[1,2] and adjuvant chemotherapy may be particularly effective at inhibition of the growth of these tumors that are not susceptible to the effects of endocrine therapies because of the lack of estrogen receptor (ER).[3] No targeted therapy has been approved for hormone receptor–negative, human epidermal growth factor receptor 2 (HER2) –negative disease (triple-negative [TN] disease). Cyclophosphamide, methotrexate, and fluorouracil (CMF) regimens were widely used in the late 1990s and were followed by the introduction of anthracycline-containing regimens

and anthracycline- and taxane-containing regimens as suitable options for these patients.[4,5]

There are conflicting results on antitumor activity for chemotherapy administered for a prolonged time. Results from meta-analyses failed to show a significant benefit for chemotherapy administered for more than 6 months versus shorter regimens.[6,7] Conversely, a trial to compare 24 months of low-dose CMF administered on day 1 and 8 versus no adjuvant treatment showed a significantly prolonged overall survival in the low-dose chemotherapy arm at a median follow-up time of 10 years. Patients with one to three positive axillary nodes and patients with ER-negative tumors especially benefited from chemotherapy.[8]

Preclinical and clinical studies support the notion that less-toxic, low-dose continuous chemotherapy, also called metronomic chemotherapy, is of clinical value. Chronically administered cyclophosphamide at a low dose produces apoptosis of endothelial cells in the tumor microvasculature with a compromised repairing process, which thereby induces a prolonged antiangiogenic effect.[9] Low-dose methotrexate inhibits endothelial cell proliferation in vitro and blocks endothelial cell growth factor-induced neovascularization in the rabbit cornea assay.[10] Mouse tumors resistant to a conventionally administered drug (maximum tolerated dose schedule) may respond for a long period of time to the same drug when a lower, more frequent dose scheduling is used.[11]

Phase II trials in patients with advanced disease demonstrated activity and limited incidence of adverse effects associated with low-dose cyclophosphamide and methotrexate (CM) treatment; an overall clinical benefit rate (defined as complete response plus partial response plus stable disease for $>$ 24 weeks) of up to 40% was observed in heavily pretreated cohorts of patients.[12,13] In 2000, the International Breast Cancer Study Group (IBCSG) initiated a randomized, phase III trial for women with hormone receptor–negative early breast cancer to test the efficacy of the CM maintenance regimen administered after a standard adjuvant chemotherapy program.

PATIENTS AND METHODS

Patients

Patients with histologically proven ER-negative and progesterone–negative ($<$ 10% positive cells by immunohistochemistry) early breast cancer with any HER2 status were eligible. Primary treatment included total mastectomy with axillary clearance and optional radiotherapy, or a lesser procedure (quadrantectomy or lumpectomy) with required radiotherapy and either axillary lymph node dissection or sentinel lymph node biopsy. Biopsy positivity required axillary dissection or, if micrometastatic, allowed random assignment to IBCSG Trial 23-01.[14] Patients with any nodal status, T1-3 disease, or pT4 with minimal dermal invasion and no detectable metastatic disease were eligible.

Study Design

IBCSG Trial 22-00 was an open-label, two-arm, phase III, randomized study to evaluate efficacy and safety of the 12-month CM maintenance regimen (cyclophosphamide 50 mg/day orally continuously and methotrexate 2.5 mg twice/day orally on days 1 and 2 of every week for 1 year) versus no CM after standard adjuvant chemotherapy. Random assignment in a 1:1 ratio was performed by the IBCSG internet-based system with permuted blocks stratified by institution, menopausal status, and adjuvant chemotherapy regimen. Patients were to have received one of the approved adjuvant chemotherapy regimens specified in the protocol. After November 2005, adjuvant trastuzumab was administered according to national guidelines to patients with HER2-positive primary breast cancer. Originally, patients were randomly assigned and began adjuvant chemotherapy within 6 weeks of definitive breast cancer surgery. In 2002, random assignment any time before day 28 of the last cycle of adjuvant chemotherapy was permitted, and, in 2005, enrollment within 56 days after the first day of the last cycle was permitted.

The primary end point was DFS, defined as the time from random assignment to the first appearance of one of the following: invasive recurrence of breast cancer (local, regional, or distant), invasive contralateral breast cancer, second (nonbreast) invasive cancer, or death without recurrence or second invasive cancer. For patients who did not have a DFS event, the times were censored at the date of the last follow-up visit. Secondary end points, defined in the Data Supplement, included breast cancer-free interval, distant recurrence-free interval, and overall survival.

IBCSG coordinated the trial and is responsible for the study design, random assignment, collection and management of data, medical review, data analysis, and reporting. No pharmaceutical company supported or was involved in any aspect of IBCSG Trial 22-00. The IBCSG Ethics Committee and ethics committees at each center approved the study, and all patients provided written informed consent. The IBCSG data and safety monitoring committee reviewed safety data semiannually and efficacy data at predefined interim analyses and provided advice about trial continuation.

Study Procedures

Patient assessments and adverse event (AE) evaluations followed a protocol-defined schedule (Data Supplement). Study visits were monthly during CM maintenance, then every 6 months for the first 5 years; follow-up was yearly thereafter, and the date adjuvant chemotherapy began was day 0. Study visits required physical exam and collection of AEs and concomitant medications; laboratory tests were collected as medically indicated. Dose received, hematology, and grade 3 or greater AEs were collected monthly during CM maintenance. AEs were graded according to the National Cancer Institute Common Toxicity Criteria (version 2).

Statistical Analysis

A total of 900 patients was planned to provide 256 events to detect a hazard ratio (HR) of 0.70 (ie, an improvement in 5-year DFS from 70% to 77.9%) in the final analysis, with 80% power by using a log-rank test and a two-sided type I error of 5%. In June 2010, we observed that 57 (14.3%) of the 398 patients assigned to CM maintenance who had treatment information did not receive any protocol therapy. To recover half of the statistical power reduction that resulted from nonadherence, Amendment 5 (August 2010) increased the sample size to 1,080 and the target number of events to 307.

The Data and Safety Monitoring Committee reviewed two planned interim efficacy analyses and released the trial results to the study team at the second interim, because additional follow-up was not likely to yield a statistically significant difference for the primary end point. The current analysis is based on the January 14, 2015, database with 1,081 patients in the intent-to-treat population (Fig 1) and 271 DFS events, which provided a 70% power to detect a 0.70 HR, taking into consideration that 13% of patients randomly assigned to CM maintenance did not start study treatment.

Kaplan-Meier estimates of time-to-event end points were calculated according to treatment assignment.[15] Hypothesis tests to compare the two groups used the log-rank test with a two-sided α of .05, stratified by menopausal status (premenopausal *v* postmenopausal) and adjuvant regimen (4 cycles of AC or EC *v* other regimens). The stratified Cox proportional hazards model was used to estimate the HR and 95% CI.[16] Secondary and exploratory analyses included the following: multivariable Cox proportional hazards models adjusted for known prognostic factors; Cox models to evaluate the use of anti-HER2 therapy (trastuzumab) as

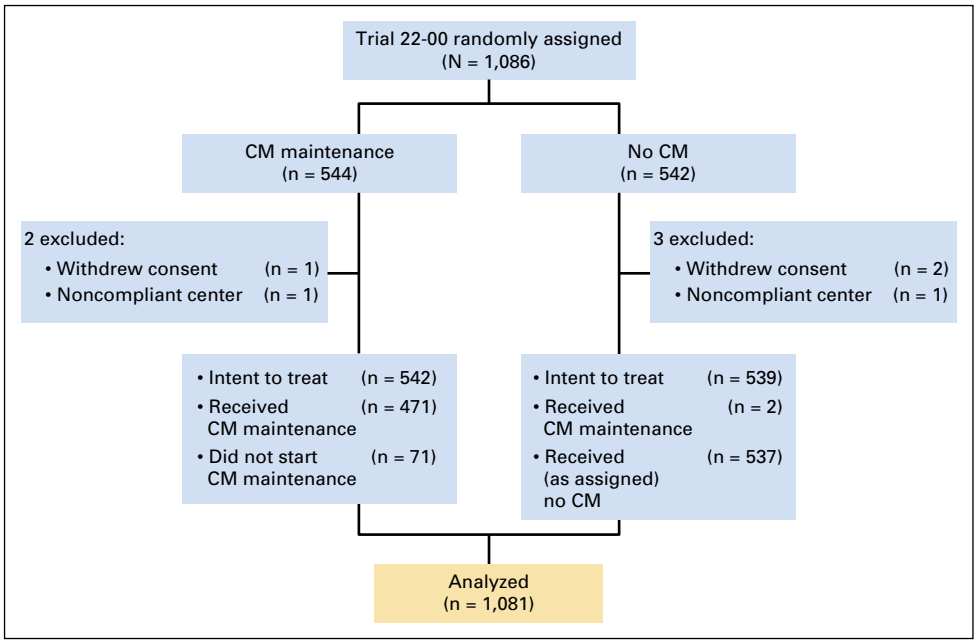

Fig 1. CONSORT diagram. The flow diagram shows the intent-to-treat population of 1,081 patients included in the primary efficacy analysis of cyclophosphamide + methotrexate (CM) maintenance compared with no CM and the 473 patients included in the treatment/safety population for CM maintenance in International Breast Cancer Study Group (IBCSG) Trial 22-00.

a time-varying covariate; and exploratory landmark analyses[17] to compare outcomes on the basis of CM maintenance adherence (CM ≥ 75% scheduled dose; CM < 75% scheduled dose; no CM). The 75% threshold was prospectively selected to have approximately one third of the evaluable patients who received CM maintenance in the high-dose group, and the landmark time was 365 days (ie, scheduled duration of CM maintenance) plus 56 days (random assignment window allowance) since the first day of last cycle adjuvant chemotherapy. The heterogeneity of the treatment effect according to subgroup was investigated by means of tests of the treatment-by-covariate interaction.

RESULTS

Study Population

Between January 23, 2001, and December 27, 2012, 1,086 patients from 32 participating centers were enrolled, and 1,081 patients (n = 542 in CM maintenance; n = 539 in no CM) were included in the intent-to-treat population (Table 1; Fig 1). The median age at random assignment was 52 years (range, 23 to 80 years), and 45% were premenopausal. Overall, 458 patients(42%) had lymph node–positive disease; 204 (19%) had HER2-positive disease (106 [52%] of whom received trastuzumab); and 814 (75%) had TN disease. Tumor size was greater than 2 cm among 54% of patients, and 84% had grade 3 tumors. Prior locoregional treatment was mastectomy for 27% (11% with and 16% without radiotherapy). Patients received a median of six cycles (range, 1 to 19 cycles) of adjuvant chemotherapy; 60% received anthracycline ± CMF chemotherapy, 14% received CMF alone, and 26% received anthracycline + taxane ± CMF chemotherapy.

CM Maintenance Treatment Received

Seventy-one (13%) of the 542 patients randomly assigned to receive CM maintenance did not start study treatment. Of the 473 patients who started CM (n = 471 assigned to CM maintenance and n = 2 assigned to no CM), 456 had fully reported dose information. The median cyclophosphamide dose received was 16,175 mg (89% of scheduled doses), and the median methotrexate dose received was 312 mg (60% of scheduled doses). CM maintenance was stopped early in 141 patients because of AEs (n = 56), patient decision (n = 52), DFS events (n = 22), late histology report of an ER-positive tumor (n = 1), and other unspecified reasons (n = 10).

Efficacy

At a median of 6.9 years of follow-up, the estimated 5-year DFS was 78.1% among patients assigned CM maintenance versus 74.7% among patients assigned no CM. The reduction in DFS events, however, was not statistically significant; the HR for CM maintenance versus no CM was 0.84 (95% CI, 0.66 to 1.06; $P = .14$; Fig 2A). The results of the multivariable analysis were consistent after adjustment for significant covariates (tumor size, nodal status, and use of trastuzumab as a time-varying covariate; Data Supplement).

For the prespecified secondary analysis of the TN cohort, the estimated 5-year DFS was 78.7% among patients assigned CM maintenance versus 74.6% among patients assigned no CM, and the reduction in hazard with CM maintenance versus no CM was consistently observed for the primary end point of DFS (HR, 0.80; 95% CI, 0.60 to 1.06; Fig 2B).

In addition, we evaluated the efficacy of CM maintenance in the cohort of patients with TN and node-positive disease (n = 340). The estimated 5-year DFS was 72.5% for the CM maintenance group and was 64.6% for the no-CM group (HR, 0.72; 95% CI, 0.49 to 1.05; Fig 2C).

The nonstatistically significant reduction in hazard with CM maintenance versus no CM was consistently observed for secondary end points of breast cancer-free interval, distant recurrence-free interval, and overall survival for the overall population and for the cohorts of patients analyzed (Data Supplement).

Table 1. Patient, Disease, and Treatment Characteristics for the IBCSG Trial 22-00 Intent-To-Treat Population of 1,081 Patients

Characteristic	Treatment Assignment: CM Maintenance No. (n = 542)	%	Treatment Assignment: No CM No. (n = 539)	%	Overall No. (N = 1,081)	%
Median (range) age, years	52 (28-79)		52 (23-80)		52(23-80)	
Menopausal status						
Premenopausal	238	43.9	245	45.5	483	44.7
Postmenopausal	304	56.1	294	54.5	598	55.3
Tumor size, cm						
≤ 1	39	7.2	47	8.7	86	8.0
>1 to ≤ 2	196	36.2	211	39.1	407	37.7
>2 to ≤ 5	285	52.6	250	46.4	535	49.5
> 5	22	4.1	31	5.8	53	4.9
Tumor grade						
1	7	1.3	4	0.7	11	1.0
2	76	14.0	78	14.5	154	14.2
3	456	84.1	456	84.6	912	84.4
Unknown/not assessed	3	0.6	1	0.2	4	0.4
HER2 status						
Positive	102	18.8	102	18.9	204	18.9
Negative	409	75.5	406	75.3	815*	75.4
Not assessed†	31	5.7	31	5.8	62	5.7
Triple negative						
Yes	408	75.3	406	75.3	814*	75.3
No	103	19.0	102	18.9	205	19.0
Unknown/incomplete info	31	5.7	31	5.8	62	5.7
Lymph node status						
N0	307	56.6	305	56.6	612	56.6
N1-3	156	28.8	122	22.6	278	25.7
N4+	74	13.7	106	19.7	180	16.7
Unknown	5	0.9	6	1.1	11	1.0
Local therapy						
Mastectomy with no RT	88	16.2	81	15.0	169	15.6
Mastectomy with RT	61	11.3	58	10.8	119	11.0
Breast-conserving surgery, no RT	13	2.4	15	2.8	28	2.6
Breast-conserving surgery with RT	380	70.1	383	71.1	763	70.6
Other	—	—	2	0.4	2	0.2
Standard adjuvant chemotherapy						
CMF alone	76	14.0	73	13.5	149	13.8
Anthracycline ± CMF	311	57.4	339	62.9	650	60.1
Anthracycline + taxane ± CMF	155	28.6	127	23.6	282	26.1
Timing of random assignment						
Before adjuvant therapy	119	22.0	111	20.6	230	21.3
During or after adjuvant therapy	423	78.0	428	79.4	851	78.7

Abbreviations: CM, cyclophosphamide + methotrexate; CMF, cyclophosphamide + methotrexate + fluorouracil; HER2, human epidermal growth factor receptor 2; IBCSG, International Breast Cancer Study Group; RT, radiotherapy.
*One patient with HER2-negative breast cancer was not in the triple-negative cohort because receptor status was estrogen receptor positive and progesterone receptor negative.
†Before 2005, HER2 status determination was not required for eligibility. (Among the 62 patients without HER2 assessment, 38 were randomly assigned before 2005.)

Interactions between the CM maintenance effect on DFS and relevant baseline characteristics were not statistically significant (Fig 3). For patients with HER2-positive disease, the use of trastuzumab (time-varying covariate) was associated with a significant reduction in the hazard of a DFS event (HR, 0.46; 95% CI, 0.25 to 0.84; $P = .01$).

The results of the exploratory landmark analysis, performed to assess how CM maintenance nonadherence may have influenced the DFS outcomes, are shown in Fig 4. Patients who received 75% or more of the scheduled CM maintenance dose had a reduced hazard of a DFS event compared with patients assigned to no CM (HR, 0.62; 95% CI, 0.39 to 1.0; multivariable analysis results; Fig 4A). No hazard reduction was observed for patients who received less than 75% of the CM maintenance dosing compared with patients assigned to no CM. Similar analyses were performed for the subgroup of patients with known TN disease (n = 708), and the results were consistent with the overall landmark population (Fig 4B).

Adverse Events

In the CM safety population of 473 patients (Fig 1), 64 patients (14%) experienced a grade 3 or 4 treatment-related AE, of which elevated ALT (which was reversible) was the most frequently reported (7%), followed by leukopenia (2%) (Table 2). There were no occurrences of myelodysplasia. Two patients, both with ages in the early 60 years and both assigned to CM maintenance, developed acute myeloid leukemia (AML). One patient received one

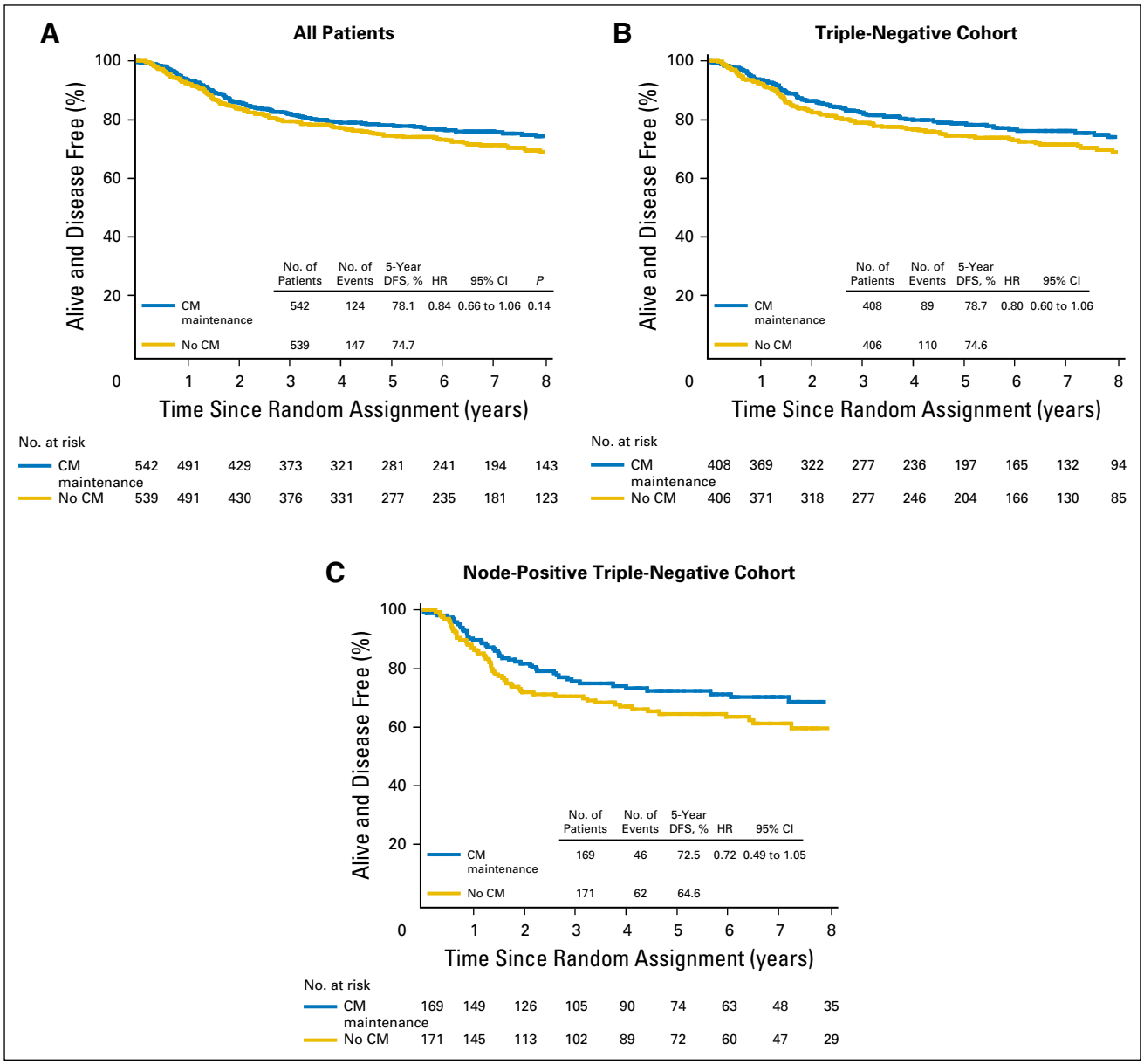

Fig 2. Kaplan-Meier estimates of disease-free survival (DFS) according to treatment assignment (A) for the intent-to-treat population of International Breast Cancer Study Group Trial 22-00, for the cohort with triple-negative breast cancer (B), and for the cohort with triple-negative, node-positive breast cancer (C). CM, cyclosphosphamide + methotrexate; HR, hazard ratio. *P* represents the stratified log-rank test *P* value.

month of CM maintenance, developed AML 15 months later, and died 10 months after AML diagnosis. The second patient received the full year of CM maintenance, developed AML 71 months later, and died 18 months after AML diagnosis.

DISCUSSION

The IBCSG Trial 22-00 analysis shows that the addition of low-dose maintenance cytotoxic drugs after completion of standard adjuvant chemotherapy does not significantly improve DFS. The current analysis is based on 271 DFS events at a median of almost 7 years of follow-up, which provided 70% power to detect a 30% reduction in the hazard of a DFS event between randomly assigned arms. Despite the low event rate and high nonadherence, patients with TN, node-positive disease assigned to CM maintenance had relative and absolute reductions in DFS events of 24% and 7.9%, respectively.

For this high-risk subgroup, the effect observed, although not statistically significant, merits additional investigation because of the current lack of tailored therapies for TN disease. Several treatment strategies, including the use of biologic agents,[18] high-dose chemotherapy,[19] and dose-dense[20] chemotherapy, were attempted previously. Despite some positive results observed in the TN subgroup,[20] the current standard adjuvant treatment of TN disease is still based on the use of anthracycline- and taxane-containing chemotherapy, and there

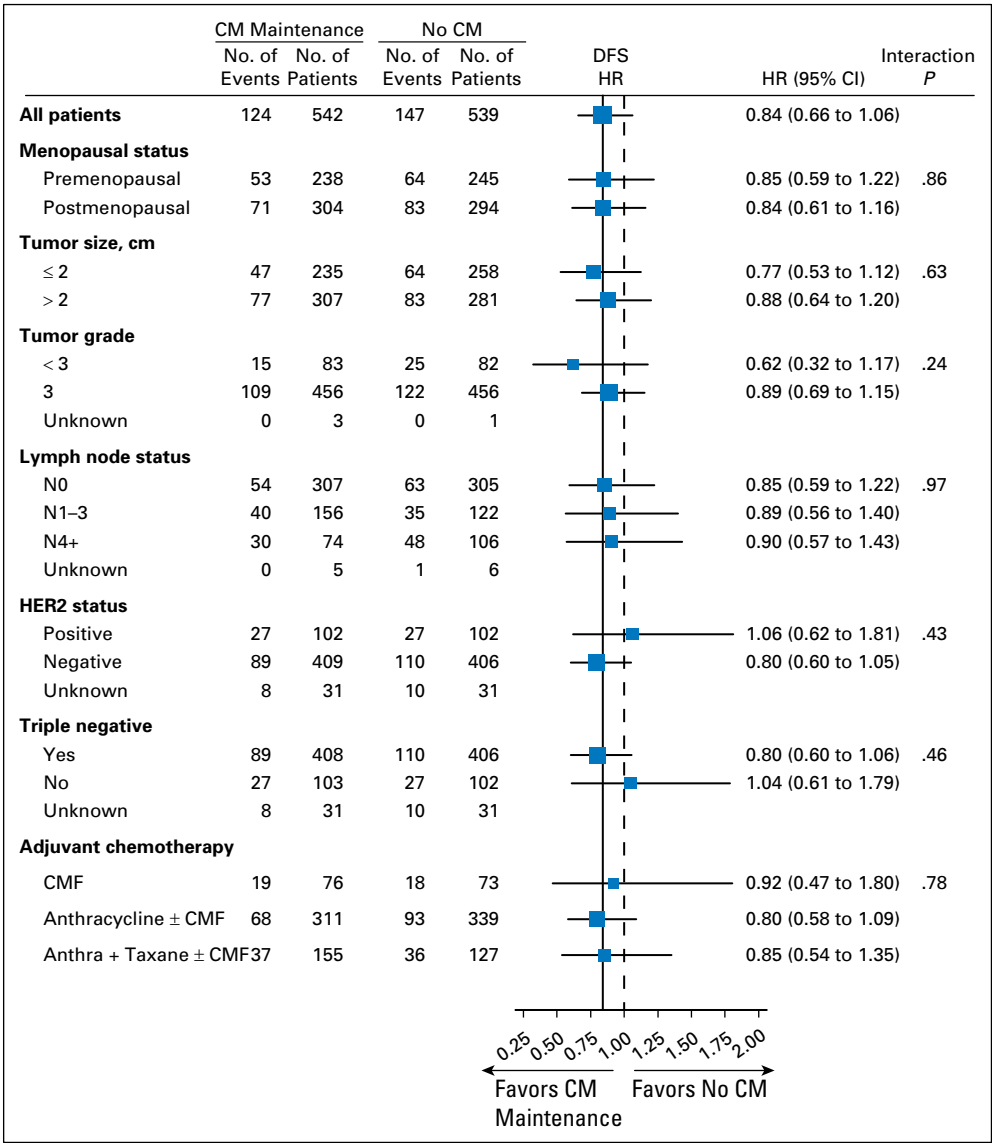

Fig 3. Results of Cox proportional-hazards models for the comparisons of disease-free survival (DFS) according to treatment assignment among all the patients and according to baseline characteristics. The solid vertical line at 0.84 indicates the overall hazard ratio (HR) estimate for DFS. The *P* value is a test of heterogeneity of the treatment effect across subgroups, by using a test of treatment-by-variable interaction from a stratified Cox model with unknown omitted from the test. The size of the squares is inversely proportional to the standard error of the HR. CM, cyclosphosphamide + methotrexate; CMF, cyclophosphamide + methotrexate + fluorouracil; HER2, human epidermal growth factor receptor 2.

is no preferred regimen for these patients, unlike for patients who have other subtypes of breast cancer (eg, luminal disease).[21]

Low-dose maintenance also is an attractive approach for additional studies in TN disease, because of its low economical cost. Issues related to the costs of therapies in the adjuvant setting are crucial and are relevant not only in developing countries but elsewhere as well.[22] The drugs used as maintenance in Trial 22-00 have low-cost generic equivalents available for approximately $100 total cost per month in the United States. CM maintenance is also an oral regimen, which avoids the need for costly hospital stays and intravenous injections.

A potential limitation of our trial is the prolonged accrual period, which is partially related to the absence of pharmaceutical company support to recruit the greater than 1,080 patients enrolled. Selection bias and the type of adjuvant treatments used during more than a decade of accrual might have influenced the results observed. Since the start of the IBCSG Trial 22-00, several new regimens demonstrated significant activity in well-conducted randomized clinical trials and were then approved as adjuvant regimens for this trial. In particular, a shift toward anthracycline- and taxane-containing regimens was noted, and fewer patients received CMF-like adjuvant chemotherapy.[4,5] The use of improved adjuvant chemotherapy may be responsible for the better-than-anticipated overall DFS outcomes, which reduced the statistical power of our analyses. In our study, however, there was no clear evidence that the CM maintenance effect differed according to adjuvant regimen (Fig 3).

The use of trastuzumab for patients with HER2-positive disease after 2005 might also have influenced the results. As expected,[23,24] patients who received trastuzumab had a reduced risk of a DFS event, which thus reduced the event rate for the HER2-positive cohort. We also observed no improvement in DFS with CM-maintenance for this cohort, although CIs were wide.

The low-dose maintenance tolerability profile was good; the incidence of grades 3 and 4 AEs was only 14%, and no grade 5 AEs occurred. When the protocol was developed, potential

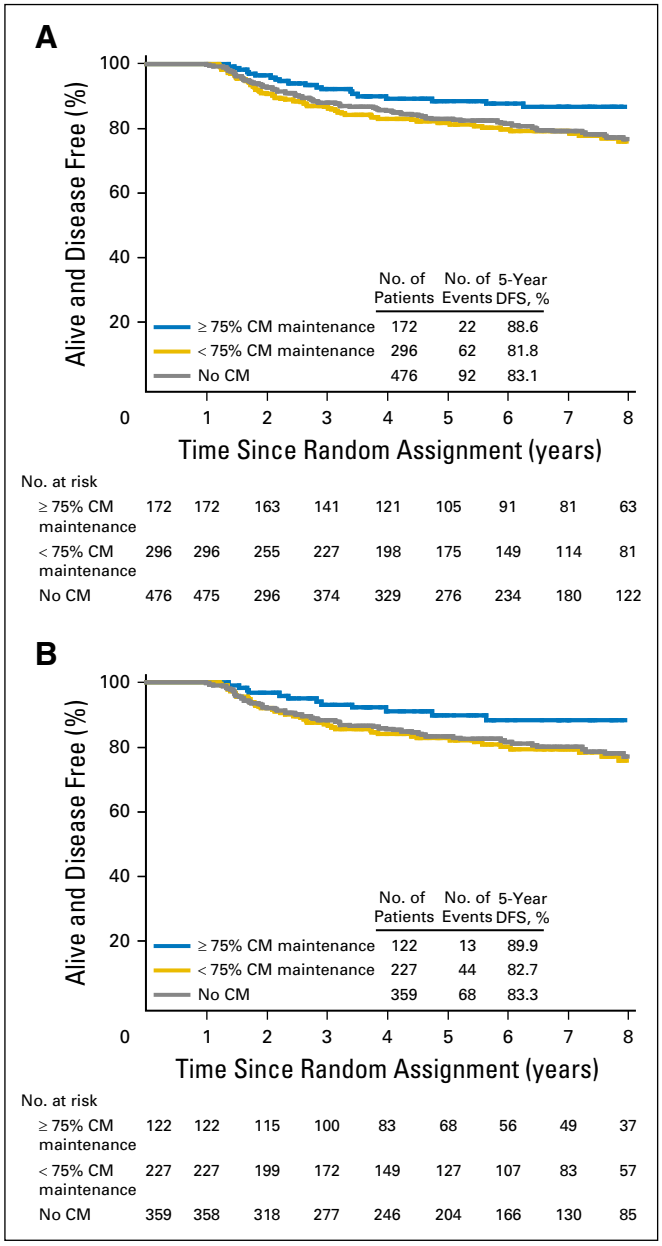

Fig 4. Landmark analysis to illustrate relationship between adherence to cyclophosphamide + methotrexate (CM) maintenance and disease-free survival (DFS) for the trial population (A) and for the triple-negative cohort (B), with groupings for CM maintenance at 75% or greater of the scheduled dose; CM maintenance less than 75% of the scheduled dose; and no CM. The 75% dose threshold was prospectively selected to have approximately one third of evaluable CM maintenance patients in the higher-dose group. The landmark population included patients who were alive, in follow-up, and free of a DFS event at the landmark time of 365 days (scheduled duration of CM maintenance) plus 56 days (random assignment window allowance) since the first day of last cycle adjuvant chemotherapy.

Table 2. Selected Adverse Events for the Safety Population of 473 Patients Who Received at Least One Dose According to CM Maintenance

Adverse event	No. of Patients* by Worst-Grade Adverse Event	
	Grade 3 (n = 58; 12.3%)	Grade 4 (n = 6; 1.3%)
Leukopenia	8	1
Neutropenia	2	4
Elevated AST	9	—
Elevated ALT	32	1
Nausea	4	—
Vomiting	3	—
Dysuria	2	—
Infection	4	—
Pain	3	—
Cardiovascular	3	—
Neurologic	3	—
Ocular/visual	—	1

NOTE. Of the 473 patients, 471 patients were assigned to CM maintenance and two were assigned to no CM.
Abbreviation: CM, cyclophosphamide + methotrexate.
*Individual patients may have had multiple types of specific adverse events. Those adverse events attributed by the investigators to CM maintenance are shown.

myelodysplasia and leukemia associated with alkylating agents were major concerns. A low risk was anticipated, on the basis of the cumulative dose levels of cyclophosphamide proposed, which ranged approximately from 23,000 to 35,000 mg. For 972 patients evaluated on IBCSG Trials I to III, only one occurrence of leukemia was observed. These patients, who received 12 cycles of CMF (cumulative total cyclophosphamide dose, 25,000 to 33,600 mg), had a median follow-up time of 18 years.[25] In Trial 22-00, the incidence of leukemia was similarly low.

Treatment nonadherence was an issue for Trial 22-00, in part because of the study design. To facilitate accrual, two trial amendments changed the timing of random assignment from strictly before the standard adjuvant regimen began to any time during, which provided a random assignment window up to 56 days from the first day of the last cycle of standard adjuvant chemotherapy. These changes improved accrual, but random assignment of patients before or anytime during standard adjuvant chemotherapy may have contributed to the high incidence (13%) of not-started assigned CM maintenance. Although a study design to enroll patients during or soon after their final course of adjuvant chemotherapy might have reduced overall enrollment, the number of patients not starting CM maintenance might have been substantially lower, perhaps resulting in a clearer conclusion about CM maintenance efficacy. Although the exploratory landmark analysis suggests that patients who received at least 75% of scheduled CM maintenance benefited from the treatment, it is well known that patients who adhere to medication do better than those who do not.[26] Hence, we can only conclude that the patients who took their oral medication appeared to do better; we cannot conclude that adherence to CM maintenance was the cause of the better outcome.

Trial 22-00 was developed on the basis of the concept that angiogenesis, the process that leads to the formation of new blood vessels, plays a central role in tumor progression of solid neoplasia.[27] Despite this premise, no improvement in DFS was observed in previous studies that explored the value of known antiangiogenic agents in the adjuvant treatment of breast cancer,[18,28,29] supporting the use of different treatment strategies such as CM maintenance.

The recently reported Create-X trial showed that treatment with capecitabine increased DFS and overall survival in patients who had HER2-negative breast cancer with residual disease after

neoadjuvant chemotherapy.[30] The hormone receptor–negative subgroup experienced a 42% reduction in risk of relapse. On the basis of these data and given the trend toward benefit observed in the Trial 22-00 node-positive, TN population, future plans include a study to evaluate low-dose oral maintenance for high-risk postadjuvant (node-positive, TN disease) therapy and for high-risk postneoadjuvant (no pathological complete response, TN disease) therapy. We conclude that the addition of CM maintenance treatment should not be recommended for women with hormone receptor–negative early breast cancer. The trend suggests a positive effect on selected subpopulations, however, and is hypothesis generating, so it supports additional studies on maintenance approaches in high-risk patients with TN disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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