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Effect of Capecitabine Maintenance Therapy Using Lower Dosage and Higher Frequency vs Observation on Disease-Free Survival Among Patients With Early-Stage Triple-Negative Breast Cancer Who Had Received Standard Treatment

The SYSUCC-001 Randomized Clinical Trial

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IMPORTANCE Among all subtypes of breast cancer, triple-negative breast cancer has a relatively high relapse rate and poor outcome after standard treatment. Effective strategies to reduce the risk of relapse and death are needed.

OBJECTIVE To evaluate the efficacy and adverse effects of low-dose capecitabine maintenance after standard adjuvant chemotherapy in early-stage triple-negative breast cancer.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted at 13 academic centers and clinical sites in China from April 2010 to December 2016 and final date of follow-up was April 30, 2020. Patients (n = 443) had early-stage triple-negative breast cancer and had completed standard adjuvant chemotherapy.

INTERVENTIONS Eligible patients were randomized 1:1 to receive capecitabine (n = 222) at a dose of 650 mg/m^2 twice a day by mouth for 1 year without interruption or to observation (n = 221) after completion of standard adjuvant chemotherapy.

MAIN OUTCOMES AND MEASURES The primary end point was disease-free survival. Secondary end points included distant disease-free survival, overall survival, locoregional recurrence-free survival, and adverse events.

RESULTS Among 443 women who were randomized, 434 were included in the full analysis set (mean [SD] age, 46 [9.9] years; T1/T2 stage, 93.1%; node-negative, 61.8%) (98.0% completed the trial). After a median follow-up of 61 months (interquartile range, 44-82), 94 events were observed, including 38 events (37 recurrences and 32 deaths) in the capecitabine group and 56 events (56 recurrences and 40 deaths) in the observation group. The estimated 5-year disease-free survival was 82.8% in the capecitabine group and 73.0% in the observation group (hazard ratio [HR] for risk of recurrence or death, 0.64 [95% CI, 0.42-0.95]; *P* = .03). In the capecitabine group vs the observation group, the estimated 5-year distant disease-free survival was 85.8% vs 75.8% (HR for risk of distant metastasis or death, 0.60 [95% CI, 0.38-0.92]; *P* = .02), the estimated 5-year overall survival was 85.5% vs 81.3% (HR for risk of death, 0.75 [95% CI, 0.47-1.19]; *P* = .22), and the estimated 5-year locoregional recurrence-free survival was 85.0% vs 80.8% (HR for risk of locoregional recurrence or death, 0.72 [95% CI, 0.46-1.13]; *P* = .15). The most common capecitabine-related adverse event was hand-foot syndrome (45.2%), with 7.7% of patients experiencing a grade 3 event.

CONCLUSIONS AND RELEVANCE Among women with early-stage triple-negative breast cancer who received standard adjuvant treatment, low-dose capecitabine maintenance therapy for 1 year, compared with observation, resulted in significantly improved 5-year disease-free survival.

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Visual Abstract
Editorial
Supplemental content

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The poor prognosis of triple-negative breast cancer (TNBC) results from a lack of available targeted treatment options coupled with the aggressive biological behavior of this subtype, which is associated with a high risk of early recurrence, particularly visceral metastasis.[1,2] Maintenance endocrine or *ERBB2* (formerly *HER2*)-targeted therapy has been used to reduce the risk of recurrence and death significantly in patients with hormone receptor-positive or *ERBB2*-overexpressing early-stage breast cancer. However, chemotherapy is the only adjuvant treatment option for patients with early-stage TNBC. Effective maintenance therapies to reduce the risk of relapse and death are needed.

Chemotherapy using lower dosage and higher frequency is thought to exert its anticancer activity by targeting 2 mechanisms of metastasis: angiogenesis and immune escape.[3] Therefore, low-dose chemotherapy might prevent TNBC from metastasizing.

Capecitabine, an orally administered chemotherapeutic drug used widely in the treatment of metastatic breast cancer, is a potential candidate therapy for low-dose administration as maintenance to prevent recurrence.[4-6] Several previous clinical trials added high-dose capecitabine to standard breast cancer adjuvant chemotherapy regimens and have reported conflicting results,[7-11] although those trials were not restricted to women with TNBC. The present trial, Sun Yat-sen University Cancer Center 001 (SYSUCC-001), was designed to evaluate the effect of low-dose capecitabine maintenance therapy after completion of standard adjuvant treatment on disease-free and overall survival in women with early-stage TNBC.

Key Points

Question Does therapy with low-dose capecitabine maintenance after standard adjuvant chemotherapy reduce the risk of relapse and death in early-stage triple-negative breast cancer?

Findings In this randomized clinical trial of 434 women with early-stage triple-negative breast cancer who received standard adjuvant treatment, low-dose capecitabine maintenance therapy for 1 year, compared with observation, resulted in significantly higher 5-year disease-free survival (82.8% vs 73.0%; hazard ratio for risk of recurrence or death, 0.64).

Meaning Among women with early-stage triple-negative breast cancer, maintenance therapy with low-dose capecitabine significantly improved disease-free survival at 5 years.

Methods

Study Design and Patient Eligibility

The SYSUCC-001 trial (ClinicalTrials.gov: NCT01112826) is an open-label, multicenter, randomized, phase 3 study that compared the efficacy and adverse events of low-dose capecitabine maintenance with observation following standard adjuvant treatment in patients with early-stage TNBC. The trial was sponsored by Sun Yat-sen University and was approved by the SYSUCC ethics committee, together with the ethics committees at each participating institution. All patients provided written informed consent. The study protocol and statistical analysis plan are available in Supplement 1.

Eligible trial participants were women who had pathologically confirmed invasive breast ductal carcinoma that was hormone receptor negative (<1% positive cells by immunohistochemistry staining) and *ERBB2* negative. Participants had early-stage tumors that were stage T1b-3N0-3cM0, without positive supraclavicular or internal mammary lymph node involvement based on the American Joint Committee on Cancer (AJCC 2010, seventh edition) staging criteria, and they received standard treatments, including modified radical mastectomy or breast-conserving surgery, neo-/adjuvant chemotherapy, and radiotherapy according to institutional guidelines. Key exclusion criteria included inflammatory or bilateral breast cancer; a history of invasive breast cancer or other malignancies; receipt of other biologic agents or immunotherapy; lactation or pregnancy; or severe coexisting illness.

Intervention

Eligible patients were randomly assigned in a 1:1 ratio to receive either low-dose capecitabine maintenance (intervention group) or observation (control group) within 4 weeks after completion of standard adjuvant chemotherapy, with a block size of 6 (known to the statistician [Y.G.]) and participants were stratified by lymph node status (negative vs positive). Random assignment was performed using a computer-generated code generated using SAS software version 8.01 (SAS Institute) with a random seed of 37 277 generated centrally at the Clinical Trials Centre of Sun Yat-sen University Cancer Center. Details of the random allocations were contained in sequentially numbered, opaque, sealed envelopes, which were prepared by the study statistician (Y.G.).

Study treatment was initiated at randomization. The capecitabine maintenance group received oral capecitabine at 650 mg/m^2, twice daily continuously for 1 year. Collection of capecitabine dose received and adverse events were assessed monthly during capecitabine maintenance in the capecitabine group. In both groups, physical examination, assessment of menopausal status, breast ultrasound, and abdominal ultrasound were performed every 3 months during years 1 to 2, every 6 months during years 3 to 5, and yearly thereafter; mammography and chest x-ray were performed yearly. Patients who had not experienced recurrence or death at the time of data analysis were censored as alive and event-free at the date of last follow-up.

Outcome Measures

The primary end point of the study was 5-year disease-free survival, defined as the time from randomization to the first occurrence of the following events: local relapse, distant metastasis, contralateral breast cancer, or death from any cause. Secondary end points included distant disease-free survival

(the time from randomization to distant recurrence, contralateral invasive breast cancer, or death from any cause), overall survival (the time from randomization to death from any cause), locoregional recurrence-free survival (the time from randomization to locoregional invasive recurrence or death), and adverse events. Adverse events were assessed and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0. Hand-foot syndrome (a common adverse effect of the fluoropyrimidine chemotherapy agent capecitabine) events were graded from 1 to 3 (Supplement 1).[12]

Statistical Analysis

The estimated 5-year disease-free survival for patients with TNBC was 68%.[13,14] To detect an absolute improvement of 12%[15] in 5-year disease-free survival from 68.0% in the control group to 80.0% in the capecitabine maintenance group, approximately 109 disease-free survival events would be required to achieve 80% power at a 2-sided significance level of 5%. The period of enrollment and follow-up required were estimated at 60 and 36 months, respectively. After considering a 9% dropout rate, approximately 424 patients (212 patients in each group) were required to detect an absolute 12% improvement in 5-year disease-free survival to be enrolled in the study. Originally, the study planned to enroll 684 participants under the assumption of 20% dropout with power of 90%; however, dropout was less than anticipated and 80% power was deemed acceptable such that the independent data monitoring committee recommended revising the sample size calculations as above.

The number of disease-free survival events was lower than expected at the prespecified 3-year follow-up performed in December 2019. Although the required number of events had not been reached, the independent data monitoring committee recommended completion of the final analysis. The study investigators followed the independent data monitoring committee's advice and performed the final analysis with 3 years of follow-up and 94 events, rather than the projected 109 events. This final analysis was performed with a cutoff date of April 30, 2020.

Cumulative survival probabilities were estimated using the Kaplan-Meier analysis method and compared using log-rank tests in the full analysis set, defined as all randomized patients except for those who withdrew informed consent before starting protocol treatment or who had no follow-up after randomization. Hazard ratios (HRs) with 95% CIs were estimated using the Cox proportional hazards model. The proportional hazards assumption was confirmed based on the Schoenfeld residuals.[16] The last observation carried forward method was used for handling missing outcome data.

The prespecified exploratory subgroup analyses were conducted according to prognostic factors including age at random assignment, tumor size at diagnosis, histological grade, nodal status, lymphovascular invasion, Ki-67 index, and neo-/adjuvant chemotherapy regimens. The consistency of the treatment effect was measured for each prespecified subgroup and evaluated using an unadjusted Cox proportional hazard model. Treatment effects were evaluated among subgroups by adding interaction terms to Cox proportional hazards models. This study was designed as center randomization and heterogeneity between centers was evaluated using the Breslow-Day test.

The differences between treatment groups were compared using a χ^2 test or Fisher exact test for categorical variables, and *t* test or the Mann-Whitney test for continuous variables, when appropriate.

The frequency and severity of each adverse event was recorded according to the National Cancer Institute's Common Toxicity Criteria for Adverse Events version 4.0. The most severe adverse event grade per category for each patient was reported. A preplanned interim analysis was canceled by the independent data monitoring committee in January 2017 and was reviewed by the SYSUCC Ethics Committee based on the low number of events. A significance level of a 2-tailed *P* value at .047 (according to the O'Brien-Fleming method) for the final disease-free survival analysis was used; all other statistical tests were 2-tailed at a significance level of .05. The findings for the analyses of secondary end points should be interpreted as exploratory because of the potential for type I error resulting from multiple comparisons. All statistical analyses were performed using SAS version 9.4 (SAS Institute).

Results

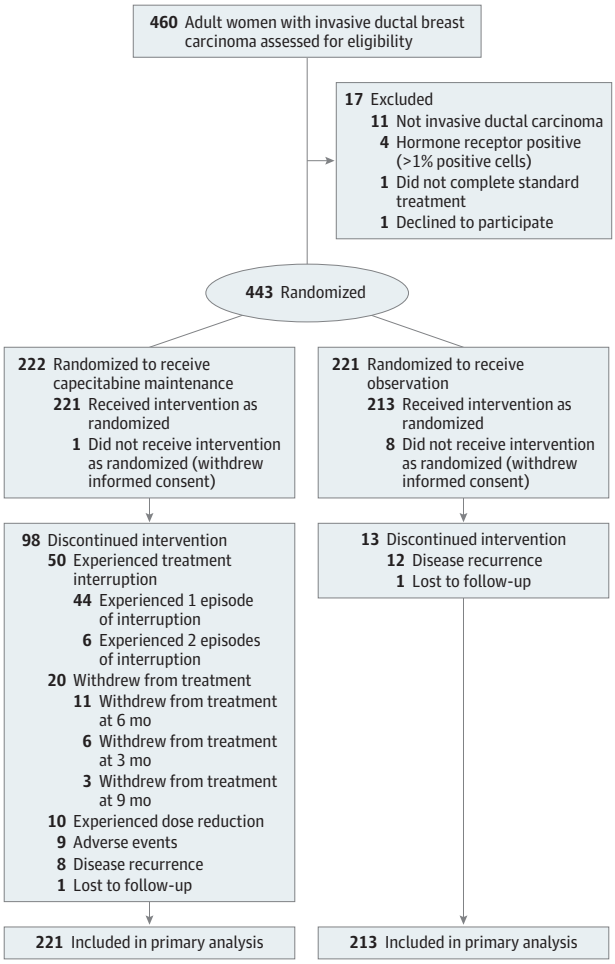
From April 2010 to December 2016, 443 patients from 13 Chinese study sites were enrolled and randomly assigned to the capecitabine group (222 patients) or the observational group (221 patients). Nine patients were excluded because of withdrawal of informed consent before starting the intervention. A total of 434 patients were included in the primary analyses (221 patients in the capecitabine group and 213 in the observation group) (**Figure 1**).

Two patients were lost to follow-up, and both had been followed up for more than the preplanned 3 years (1 in the capecitabine group for 49 months, 1 in the observation group for 51 months). Patient, disease, and treatment characteristics at baseline were well balanced between the 2 groups (**Table 1**). The median (SD) age at randomization was 46 (9.9) years (range, 24-70), and 66.8% were premenopausal. Most patients had undergone a mastectomy (86.4%) and had received anthracycline- and taxane-based regimens as neoadjuvant chemotherapy (5.8%) or adjuvant chemotherapy (78.8%). Most tumors were of T1/T2 (93.1%), node-negative (61.8%), and grade 3 (72.8%).

Primary Outcome

After a median follow-up of 61 months (interquartile range, 44-82), 94 events were observed, of which 38 events (37 recurrences and 32 deaths) were in the capecitabine group and 56 events (56 recurrences and 40 deaths) were in the observation group. The primary outcome of estimated 5-year disease-free survival in the capecitabine group vs the observation group was 82.8% vs 73.0% (HR for risk of

Figure 1. Flow of Patients Through the SYSUCC-001 Trial of Capecitabine for Triple-Negative Breast Cancer



recurrence or death, 0.64 [95% CI, 0.42-0.95]; *P* = .03) (**Figure 2**A).

Secondary Outcomes

For the secondary end points, the estimated 5-year distant disease-free survival in the capecitabine group vs the observation group was 85.8% vs 75.8% (HR for risk of distant metastasis or death, 0.60 [95% CI, 0.38-0.92]; *P* = .02) (Figure 2C). The estimated 5-year overall survival in the capecitabine group vs the observation group was 85.5% vs 81.3% (HR for risk of death, 0.75 [95% CI, 0.47-1.19]; *P* = .22) (Figure 2B). The estimated 5-year locoregional recurrence-free survival in the capecitabine group vs the observation group was 85.0% vs 80.8% (HR for risk of locoregional recurrence or death, 0.72 [95% CI, 0.46-1.13]; *P* = .15) (Figure 2D).

Prespecified Exploratory Analysis

A prespecified exploratory subgroup analysis was conducted, and no significant interactions were observed between the treatment groups and the subgroups. The effect of capecitabine on disease-free survival was consistent across all patient subgroups (**Figure 3**). For patients with

Table 1. Patient and Tumor Characteristics at Baseline

Variable	No. (%) Capecitabine group (n = 221)	Observation group (n = 213)
Age, y		
≤40	62 (28.1)	49 (23.0)
41-50	85 (38.5)	72 (33.8)
≥51	74 (33.5)	92 (43.2)
Median, IQR	45 (39-53)	48 (40-57)
Premenopausal	157 (71.0)	133 (62.4)
Tumor size, cm[a]		
≤2	79 (35.7)	79 (37.1)
>2 to ≤5	122 (55.2)	124 (58.2)
>5	20 (9.1)	10 (4.7)
Node status		
Negative	135 (61.1)	133 (62.4)
1-3 positive nodes	46 (20.8)	41 (19.2)
4-9 positive nodes	14 (6.3)	25 (11.7)
≥10 positive nodes	26 (11.8)	14 (6.6)
Stage at diagnosis (AJCC 2010)[b]		
I	56 (25.3)	59 (27.7)
II	120 (54.3)	116 (54.5)
III	45 (20.4)	38 (17.8)
Histological grade[c]		
1	5 (2.3)	3 (1.4)
2	52 (23.5)	58 (27.2)
3	164 (74.2)	152 (71.4)
Ki-67 index at diagnosis <30%[d]	44 (19.9)	57 (26.8)
Lymphovascular invasion	42 (19.0)	23 (10.8)
Type of surgery		
Mastectomy	186 (84.2)	189 (88.7)
Lumpectomy	35 (15.8)	24 (11.3)
Lymph node dissection		
Axillary-node dissection	176 (79.6)	169 (79.3)
Sentinel-node biopsy only	45 (20.4)	44 (20.7)
Chemotherapy received		
Adjuvant only	209 (94.5)	195 (91.5)
Neoadjuvant only	7 (3.2)	11 (5.2)
Adjuvant and neoadjuvant	5 (2.3)	7 (3.3)
Chemotherapy regimen		
Anthracyclines and taxane	198 (89.6)	189 (88.7)
Taxane only	20 (9.0)	21 (9.9)
Anthracyclines only	3 (1.4)	3 (1.4)
Received radiotherapy	111 (50.2)	86 (40.6)

Abbreviations: AJCC, American Joint Committee on Cancer; IQR, interquartile range.

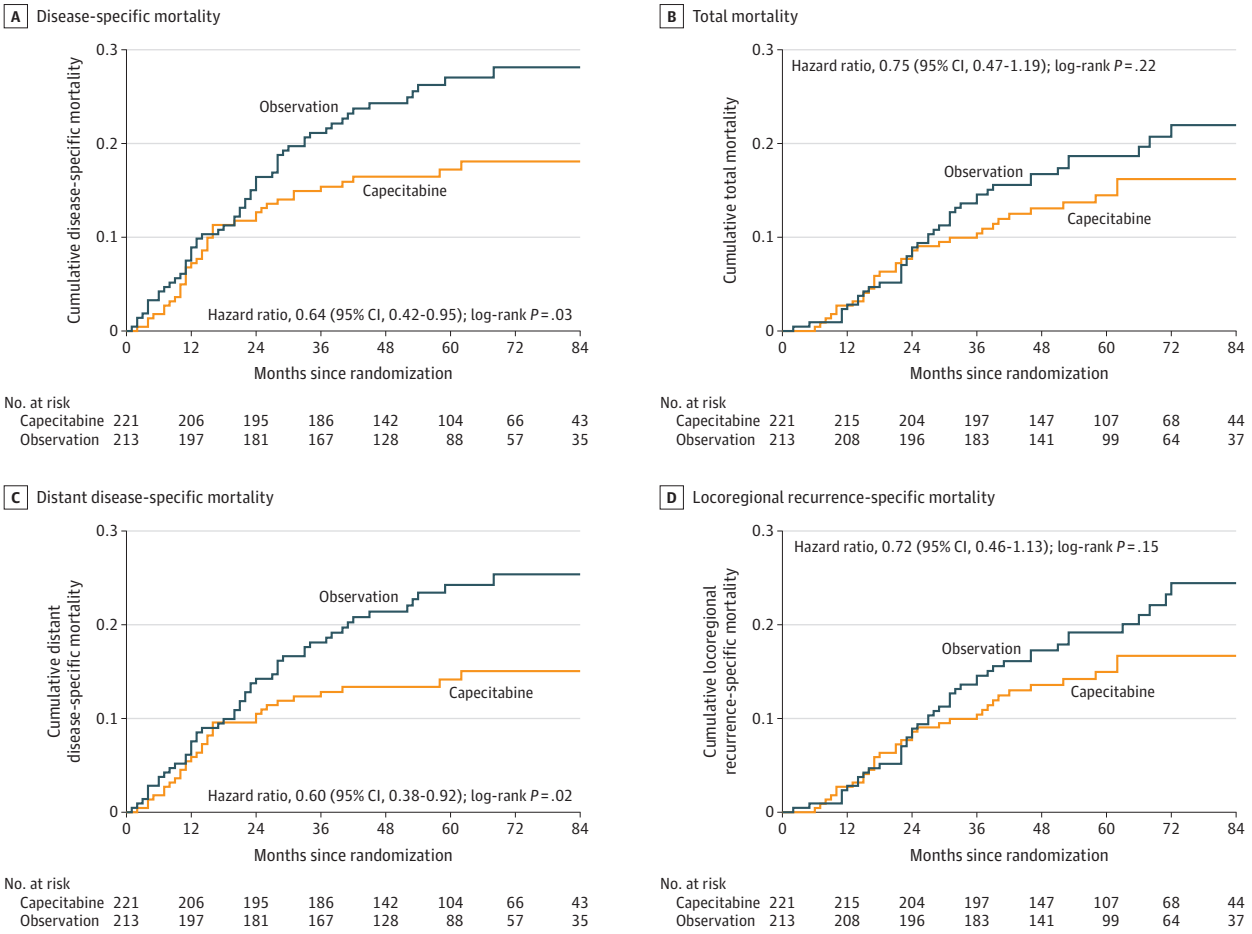
[a] Tumor size at diagnosis was based on pathological assessment.

[b] Stage at diagnosis was based on AJCC 2010, seventh edition.

[c] Histological grade at diagnosis was based on the degree of the tumor's histologic differentiation.

[d] Ki-67 index at diagnosis indicates DNA synthetic activity as measured by immunocytochemistry.

Figure 2. Kaplan-Meier Estimates of Disease-Specific Mortality, Total Mortality, Distant Disease-Specific Mortality, and Locoregional Recurrence-Specific Mortality in 434 Patients With Triple-Negative Breast Cancer



Median observation for all curves was 61 months (interquartile range, 44-82). Cumulative survival probabilities were estimated using the Kaplan-Meier analysis method and compared using log-rank tests. Hazard ratios with 95% CIs were estimated using the Cox proportional hazards model.

node-negative disease, the HR for risk of recurrence or death was 0.37 (95% CI, 0.17-0.79; P = .008). For patients with node-positive disease, the HR for risk of recurrence or death was 0.82 (95% CI, 0.50-1.34; P = .42) (eFigure in Supplement 2). However, the interaction analysis suggested no interaction between capecitabine and nodal status on disease-free survival (P for interaction = .07).

Of the 221 patients who were assigned to the capecitabine group, 183 patients (82.8%) completed 1 year of treatment according to the treatment protocol. Of these, 44 patients experienced 1 episode of treatment interruption, 6 had 2 episodes of treatment interruption, and 10 required dose reduction. Thirty-seven patients (16.7%) discontinued capecitabine before completing 1 year of treatment: 20 (9.0%) because of the patient's desire to withdraw from the study, 9 (4.1%) because of unacceptable toxicity of hand-foot syndrome, and 8 (3.6%) because of disease recurrence. The median relative dose intensity for capecitabine was 84.7%, and the median cumulative dose of capecitabine was 480 000 mg/m^2 (minimum-maximum, 33 000-480 000 mg/m^2).

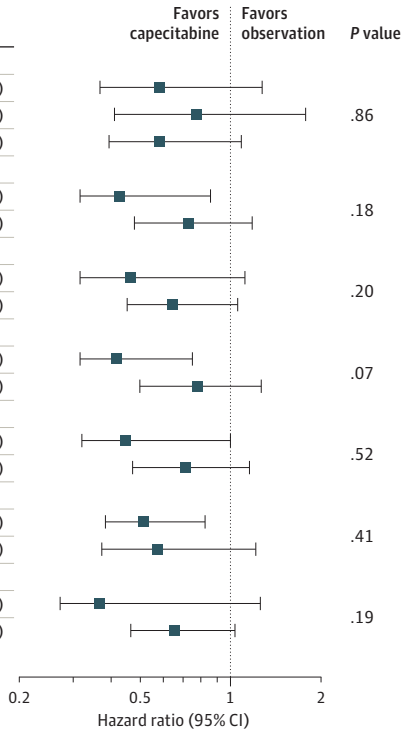
In addition, the number and type of disease-free events were analyzed (eTable in Supplement 2). The median time from randomization to the first recurrence was 18.5 months (range, 4-68). Distant recurrence, particularly lung and bone metastasis, was more frequent in the observation group than in the capecitabine group (lung: 12 in the capecitabine group and 25 in the observation group, P = .02; bone: 7 in the capecitabine group and 19 in the observation group; P = .01). Testing for heterogeneity between treatment sites revealed consistent effects across centers (P = .49).

Adverse Events

In the capecitabine group, hand-foot syndrome was the most frequent adverse event, occurring in 100 patients (45.2%), including 17 patients (7.7%) with a grade 3 event. Other common adverse events in the capecitabine group were leucopenia (23.5%), elevated bilirubin (12.7%), abdominal pain/diarrhea (6.8%), and elevated alanine aminotransferase/aspartate transaminase levels (5.0%). All these adverse events were grade 1 or 2 in severity (**Table 2**).

Figure 3. Subgroup Analysis of Disease-Specific Mortality in 434 Patients With Triple-Negative Breast Cancer

Subgroup	Disease-specific mortality, No./total No.		Hazard ratio (95% CI)	P value
	Capecitabine	Observation		
Age, y				
≤40	11/62	14/49	0.61 (0.28-1.35)	
41-50	11/85	12/72	0.81 (0.36-1.83)	.86
≥51	16/74	30/92	0.61 (0.33-1.12)	
Tumor size at diagnosis, cm[a]				
≤2	8/79	19/79	0.39 (0.17-0.89)	.18
>2	30/142	37/134	0.77 (0.47-1.24)	
Histological grade[b]				
1/2	6/57	14/61	0.45 (0.17-1.16)	.20
3	32/164	42/152	0.68 (0.43-1.08)	
Lymph node				
Negative	9/135	23/133	0.37 (0.17-0.79)	.07
Positive	29/86	33/80	0.82 (0.50-1.34)	
Ki-67, %[c]				
<30	7/44	20/57	0.42 (0.18-1.00)	.52
≥30	31/177	36/156	0.75 (0.46-1.21)	
Lymphovascular invasion				
Negative	22/179	44/190	0.52 (0.31-0.86)	.41
Positive	16/42	12/23	0.60 (0.29-1.28)	
Chemotherapy regimen				
Anthracyclines or taxanes based	2/23	7/24	0.28 (0.06-1.33)	.19
Anthracyclines and taxanes based	36/198	49/189	0.69 (0.45-1.05)	



Using the unadjusted Cox model, exploratory subgroup analyses were conducted to estimate hazard ratios with 95% CIs and to test for interactions among subgroups using 2-sided *P* values. The median observation was 61 months.

[a] Tumor size at diagnosis was based on pathological assessment.

[b] Histological grade at diagnosis was based on the degree of tumor's histologic differentiation.

[c] Ki-67 index at diagnosis indicates DNA synthetic activity as measured by immunocytochemistry.

Table 2. Adverse Events

Event[a]	No. (%)				
	Capecitabine group (n = 221)			Observation group (n = 213)[b]	
	Mild (grade 1)	Moderate (grade 2)	Severe (grade 3)	Mild (grade 1)	Moderate (grade 2)
Hand-foot syndrome[c]	41 (18.6)	42 (19.0)	17 (7.7)	0	0
Leukocytes <4000/μL	40 (18.1)	12 (5.4)	0	12 (5.6)	5 (2.3)
Bilirubin ≥1.5 times high normal value	17 (7.7)	11 (5.0)	0	3 (1.4)	0
Abdominal pain/diarrhea	7 (3.2)	8 (3.6)	0	2 (0.9)	0
ALT/AST >2.5 times high normal value	8 (3.6)	3 (1.4)	0	11 (5.2)	2 (0.9)
Fatigue	4 (1.9)	0	0	3 (1.4)	0
Nausea	3 (1.4)	0	0	3 (1.4)	0
Vomiting	1 (0.5)	0	0	0	0
Stomatitis	1 (0.5)	0	0	2 (0.9)	0
Patients with ≥1 adverse events	145 (65.6)			41 (19.2)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase.

[a] Severity of adverse events was graded by investigators according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. For events not listed in NCI CTCAE version 4.0, mild, moderate, or severe were determined based on any, mild, or significant effect on the daily activities of patients.

[b] No patients in the observation group experienced severe adverse events.

[c] Hand-foot syndrome events were graded using the following criteria: mild (grade 1) was defined as numbness, tingling sensation, or erythema of hands and/or feet that cause painless swelling or discomfort without affecting daily activities; moderate (grade 2) as painful erythema or swelling of hands and/or feet that affect daily activities; and severe (grade 3) as wet desquamation, ulceration, blistering, severe pain of hands and/or feet, and/or unable to work or perform daily activities[12] (as detailed in the study protocol, see Supplement 1).

Discussion

In this randomized clinical trial conducted among Chinese women with early-stage TNBC, the addition of low-dose capecitabine as maintenance therapy for 1 year following standard adjuvant treatment, compared with placebo, significantly improved disease-free survival. The treatment effects on disease-free survival were consistent across all patient subgroups. Capecitabine was associated with significant improvement in distant disease-free survival but not significant improvement in overall survival or locoregional recurrence-free survival.

Chemotherapy with low-dose capecitabine may reduce recurrence for women with TNBC by targeting 2 mechanisms of metastasis: angiogenesis and immune escape.[3] However, there has been uncertainty regarding both the efficacy and acceptability of prolonged treatment necessary to reduce recurrence. The current trial demonstrated that a year of capecitabine was tolerable for most women without significant treatment discontinuation due to toxicity. More than 80% of participants completed a year of treatment and less than a quarter required any treatment interruption.

Four previous randomized trials in women with early-stage breast cancer, the FinXX trial,[9] the USO01062 trial,[10] the GEICAM-CIBOMA trial,[11] and the GEICAM/2003-10 trial,[17] each failed to demonstrate that the addition of capecitabine to standard adjuvant chemotherapy improved either disease-free or overall survival. There are 2 potential explanations for the conflicting results between these previous trials and the current study. First, the benefit of maintenance capecitabine may be limited to TNBC.[9,10] The FinXX, USO01062, GEICAM-COBOMA, and GEICAM/2003-10 studies included patients with breast cancer subtypes other than TNBC. Subgroup analyses of these studies suggested benefit for participants with TNBC. The CBCSG010 trial was restricted to early-stage TNBC and showed that the addition of capecitabine to standard adjuvant regimens improved 5-year disease-free survival rates by 6% compared with standard adjuvant therapy without capecitabine.

The present study result is also consistent with findings from the CREATE-X trial,[8] which compared adjuvant capecitabine vs no adjuvant treatment in patients with *ERBB2*-negative breast cancer who had completed neoadjuvant chemotherapy but had residual invasive tumor identified on surgical pathology. The CREATE-X trial included women with hormone receptor-positive tumors as well as women with TNBC, but showed that the TNBC subgroup derived greater benefit from the addition of capecitabine. A meta-analysis of neoadjuvant and adjuvant capecitabine trials also suggested that the benefit of adding capecitabine to standard chemotherapy was observed only in the subgroup of patients with TNBC.[18]

Second, the extended duration of capecitabine may influence the efficacy of maintenance treatment. The GEICAM-CIBOMA trial randomized participants with TNBC to 8 cycles of capecitabine (24 weeks) or to no further treatment and the results showed no statistically significant increase in disease-free survival. Because the study designs and patient characteristics were otherwise similar, the longer duration of capecitabine maintenance of 52 weeks in the present study vs 24 weeks in the GEICAM-CIBOMA trial may explain the discrepant findings.

Low-dose capecitabine maintenance was generally well tolerated and most participants completed a year of treatment without requiring treatment interruptions. The most common adverse event of capecitabine monotherapy was hand-foot syndrome, which occurred in 45.2% of patients. For 7.7%, hand-foot syndrome was grade 3, which involves blistering and interference with the ability to function in routine daily activities. Other adverse events included diarrhea, hyperbilirubinemia, and leucopenia but events were not severe. All toxicity and adverse events other than hand-foot syndrome were grade 1 or 2.

Limitations

This study has several limitations. First, the optimal dose and duration of low-dose capecitabine maintenance merits further exploration. The dose selected for this trial was 650 mg/m^2 twice daily based on the dose used in a randomized trial of frail women with metastatic breast cancer that demonstrated fewer adverse effects and better quality of life when compared with higher doses given on a 2 week on, 1 week off schedule.[19] Various dosages of low-dose capecitabine ranging from a fixed dose of 500 mg 3 times daily to 800 mg/m^2 twice daily[20-22] have been evaluated. However, there is residual uncertainty about the optimal dose that minimizes toxicity without compromising efficacy. The treatment duration of 1 year was selected because that is the duration of trastuzumab used in the HERA study[23] for maintenance treatment of women with *ERBB2*-positive breast cancer. The long duration was also justified based on the high rates of recurrence for patients with TNBC. Whether 1 year of capecitabine therapy is sufficient for patients with early-stage TNBC remains uncertain because the peak risk of recurrence is within the first 2 years of diagnosis.[24]

Second, the trial was limited to recruitment at 13 Chinese hospitals and, therefore, results may not be generalizable to patients with breast cancer from other geographic regions and from other racial/ethnic backgrounds. For example, the tolerability of capecitabine may vary based on different genetic backgrounds and/or dietary folate intake.[25,26]

Third, in the current study, only 5.8% of patients received neoadjuvant chemotherapy, which is the current standard of care for patients with node-positive TNBC in Europe and North America.[27] Fourth, there was some imbalance in the randomization, with a higher proportion of older women assigned to receive placebo, which could have favored the capecitabine group.

Conclusions

Among women with early-stage TNBC who received standard adjuvant treatment, low-dose capecitabine maintenance therapy for 1 year, compared with observation, resulted in significantly improved 5-year disease-free survival.

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