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Full Length Article

Docetaxel plus S-1 versus docetaxel plus capecitabine as first-line treatment for advanced breast cancer patients: a prospective randomized phase II study

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ABSTRACT

Background: This study was conducted to evaluate the efficacy and safety of docetaxel/S-1 (TS) compared with docetaxel/capecitabine (TX) as a first-line treatment for advanced breast cancer.

Methods: Patients with advanced metastatic breast cancer were randomly divided into the TS group (n = 54) and the TX group (n = 57) for first-line chemotherapy from August 2015 to April 2019 (ClinicalTrials.org registration no. NCT02947061). Following the completion of combination therapy, patients without progression received S-1 or capecitabine maintenance treatment. The primary end point was progression-free survival (PFS).

Results: Among 111 enrolled patients, the median PFS did not differ significantly between the TS group and the TX group (TS vs. TX, 9.0 vs. 7.4 months, $P = 0.365$, 95% confidence interval [CI]: 0.50–1.11, hazard ratio [HR]: 0.75). There was also no statistically significant difference in median overall survival (OS) between the two groups (TS vs. TX, 40.2 vs. 41.3 months, $P = 0.976$). In addition, visceral metastasis and metastasis sites, such as the liver or lung, did not lead to a significant effect on PFS and OS. The two regimens showed no significant difference in adverse events, except hand-foot syndrome, which predominated in the TX group (38.6% vs. 7.4%, $P = 0.001$), and diarrhea (24.1% vs. 3.6%, $P = 0.003$) and elevation of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels (14.8% vs. 3.5%, $P = 0.049$), which were more frequent in the TS group.

Conclusions: The TS and TX regimens demonstrated similar efficacy and safety for the first-line treatment of advanced breast cancer. The TS regimen had fewer cases of severe hand-foot syndrome than the TX regimen, representing an effective alternative option to the TX regimen. Further studies are warranted to define the efficacy and safety of this strategy in real-world settings.

1. Introduction

Breast cancer is the most common malignancy affecting women worldwide.[1] Approximately 20–50% of women with early-stage breast cancer will relapse with distant metastatic disease after radical treatment. Moreover, advanced breast cancer (ABC) occurs in approximately 6%–10% of newly diagnosed cases.[2,3] Unfortunately, advanced breast cancer is incurable, and only 20% of women will survive 5 years after its diagnosis.[4,5] Therefore, the overall goals of ABC treatment are to control symptoms, maintain or improve quality of life and possibly prolong survival.

The docetaxel/capecitabine (TX) regimen has shown a significantly improved response rate and overall survival in treating ABC.[6,7] According to the National Comprehensive Cancer Network (NCCN) guidelines, the TX regimen is recommended as one of the standard first-line chemotherapies for human epidermal growth factor receptor

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2 (HER2)-negative ABC. However, hand-foot syndrome (HFS) induced by capecitabine is a major obstacle to long-term maintenance in clinical practice. Although not life threatening, it can cause serious discomfort and impairment of function and quality of life. Thus, an alternative oral chemotherapy agent to replace capecitabine for maintenance is urgently needed.

S-1 is an oral fluoropyrimidine that combines tegafur (5-fluorouracil prodrug) with two modulators, gimeracil and oteracil, in a 1:0.4:1 molar concentration ratio,[8] which enables an increase in the fluorouracil concentration while avoiding gastrointestinal toxic effects. S-1 and capecitabine are both oral fluorouracil derivatives. S-1 has shown comparable efficacy but a lower incidence of HFS compared with capecitabine.[9] Recently, it has been proven that various solid tumors, including colorectal cancer[10] and non-small cell lung cancer (NSCLC),[11] can benefit from S-1 monotherapy or combined therapy, leading to the further expansion of S-1 indications.

A preclinical breast cancer xenograft study found that TS combination therapy has a synergistic antitumor effect, which was suggested to be partly caused by a significant downregulation of the activity of dihydrouracil dehydrogenase (DPD), the rate-limiting enzyme in 5-fluorouracil (5-FU) degradation.[12] A phase II clinical study revealed that S-1 monotherapy showed a response rate of 41.7% and a median OS of 30 months for ABC.[13] However, despite promising preclinical and clinical data, there is a paucity of data on the combination of S-1 and docetaxel in ABC. Therefore, we prospectively compared the efficacy and safety of the TS regimen and the TX regimen as first-line treatments for advanced breast cancer. This randomized phase II clinical trial provides preliminary evidence on the potential benefits of TS therapy in ABC management.

2. Materials and methods

2.1. Study design

This was an open-label, randomized phase II trial of TX compared with TS in ABC patients from August 2015 to April 2019. Patients with histologically confirmed ABC in the Cancer Institution and Hospital, Chinese Academy of Medical Sciences (CHCAMS) were randomly assigned (1:1) to either the TX or TS group. Randomization was performed using a computer-generated random sequence system with the dynamic minimization method, stratified by molecular subtype (luminal or triple-negative breast cancer) and visceral metastasis (yes vs. no).

2.2. Patients

The inclusion criteria were as follows: 18–75 years of age; nonpregnant females; Eastern Cooperative Oncology Group performance status (ECOG PS) $\leq$ 2; estimated life expectancy $\geq$ 3 months; histologically or cytologically confirmed HER2-negative unresectable advanced breast cancer; no prior chemotherapy (except endocrine therapy) before recurrence and metastasis; at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; and adequate major organ function (e.g., neutrophil count $\geq$ 1500/μL, hemoglobin $\geq$ 9.0 g/dL, aspartate aminotransferase [AST] or alanine aminotransferase [ALT] $\leq$ 1.5 upper level of normal [ULN], serum bilirubin $\leq$ 1.5 ULN), including adequate hepatic, renal and hematological function. Patients were ineligible if they had HER2-positive tumors, a history of cytotoxic chemotherapy after relapse, or a history of docetaxel and 5-FU used in neoadjuvant or adjuvant therapy and recurrence within 12 months. Patients who had severe upper gastrointestinal ulcer or absorption dysfunction syndrome, organs with rapid progression of invasion (liver and lung lesions more than 1/2 of the organ area or hepatic insufficiency), central nervous system (CNS) disorders or mental disorders, or CNS metastasis (unless asymptomatic) or who had participated in other clinical trials within 4 weeks prior to this study were also excluded.

2.3. Treatment

In the TS group, patients received docetaxel 75 mg/m^2 intravenously (I.V.) on day 1 and oral S-1 on days 1 to 14, every 3 weeks for 6 cycles. The dose of S-1 was determined on the basis of the patient's body surface area (BSA) and was administered at 1 of the following doses twice daily: for BSA < 1.25 m^2, 80 mg/day; 1.25 $\leq$ BSA < 1.50 m^2, 100 mg/day; 1.50 m^2 $\leq$ BSA, 120 mg/day. Patients assigned to the TX group were treated with docetaxel on day 1 (75 mg/m^2, I.V.) and capecitabine (1000 mg/m^2, oral, bid) every 3 weeks for 6 cycles. After 6 cycles, patients discontinued docetaxel administration and continued S-1 or capecitabine at the previous usage and dosage until disease progression or unacceptable toxicity.

Drug dosages and dose adjustment protocols were summarized in Supplementary Table 1. The docetaxel dose was reduced by one level down to a minimum dose of 50 mg/m^2 if an adverse event corresponding to any of the dose reduction criteria occurred during treatment. If an adverse event corresponding to the dose suspension criteria occurred during treatment with S-1 or capecitabine, treatment could be suspended and restarted once the adverse event resolved to grade 1 or better or reduced by one level if the adverse event had resolved to a severity that met the dose reduction criteria. When treatment was resumed after a break, it was at a dose that was reduced by one level. In both treatment groups, once the dose was reduced, it could not be increased, and protocol treatment was discontinued if an adverse event occurred that corresponded to any of the dose reduction criteria during treatment with the minimum dose.

Efficacy assessment was conducted every 2 cycles according to RECIST 1.1 criteria and classified into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Safety evaluations were based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

2.4. Outcomes

The primary end point was progression-free survival (PFS), defined as the length of time from randomization to the first progression or death. Secondary end points were overall survival (OS), duration of response (DOR), objective response rate (ORR), disease control rate (DCR) and safety. OS was defined as the time from randomization to death from any cause. DOR was defined as the time from the first documented response (CR or PR) to the earliest date of PD. ORR was calculated as the sum of CR and PR. DCR was the sum of CR, PR, and SD.

2.5. Statistical analysis

The primary objective of this study was to compare PFS between the two groups. Assuming a 1:1 allocation ratio, a sample size of 111 evaluable patients with 100 events was expected to provide 80% statistical power (at a significance level of 0.05), with an enrollment period of 24 months and a follow-up period of 12 months, to detect a significant improvement in median PFS (mPFS) from 6.1 to 10.7 months based on previous studies.[6,14,15] Accounting for a 5% dropout rate, a total of 117 patients needed to be recruited for the trial.

Kaplan-Meier survival curves were used to analyze the OS and PFS of the enrolled patients. Time to event analysis (PFS, OS and DOR) was conducted using Cox proportional hazards models. Response rates, such as ORR and DCR, were compared using the χ^2 test or Fisher's exact test. Safety analyses were analyzed using descriptive statistics. All statistical analyses were performed with SPSS (version 26.0) and R software 3.6.4. $P < 0.05$ was considered statistically significant.

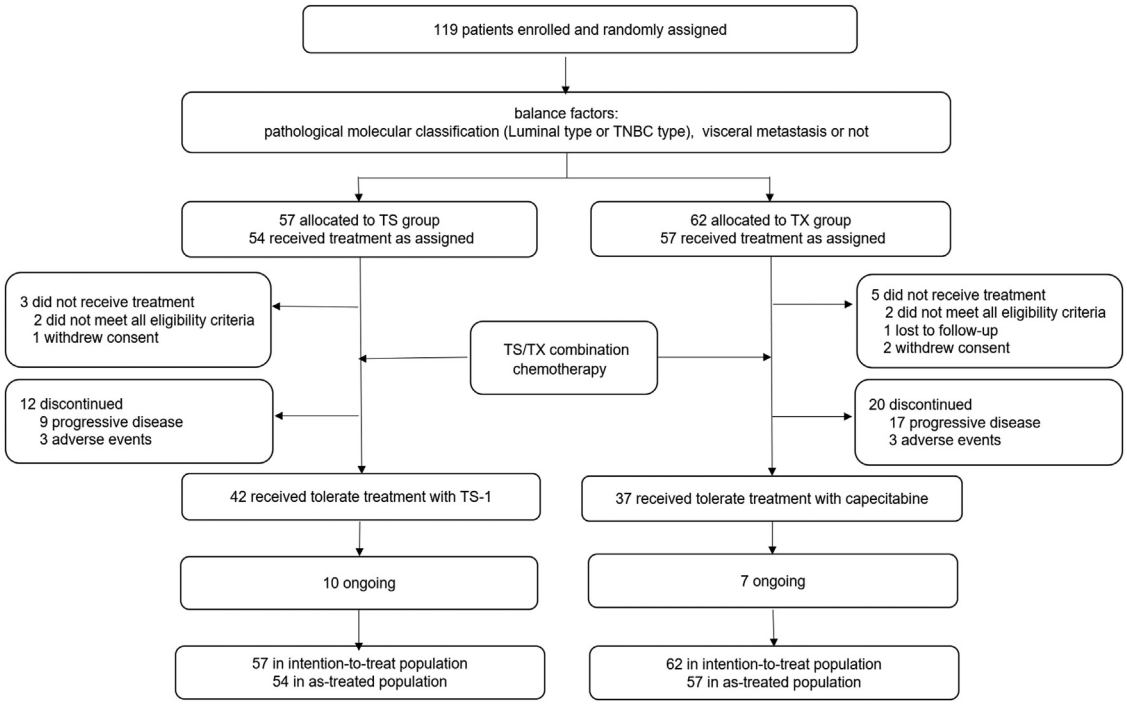

Fig. 1. Flowchart of patient treatment. TNBC, triple-negative breast cancer; TS, docetaxel/S-1; TX, docetaxel/capecitabine.

3. Results

3.1. Patient characteristics

A total of 119 patients with advanced breast cancer were enrolled; 57 patients were assigned to the TS group, and 62 were assigned to the TX group. Four patients were ineligible for the study, 3 patients did not start protocol treatment, and 1 patient was lost to follow-up; 111 patients constituted the full analysis set (Fig. 1). Baseline characteristics were similar in each group (Table 1). In the TS cohort, 50 (92.6%) patients were hormone receptor (HR)-positive, and 4 (7.4%) patients were HR-negative. In the TX group, 51 (89.5%) patients were HR-positive, and 6 (10.5%) patients were HR-negative. No significant differences were found for age, menstrual status, (neo)adjuvant chemotherapy regimens, prior endocrine therapies, HR status or visceral metastatic sites between the two cohorts.

3.2. Treatment details

Patients received a mean of 5.4 cycles of combination chemotherapy in the TS group and 5.1 cycles of chemotherapy in the TX group. The median number of combined chemotherapy cycles was 6 (range, 1–6 cycles) in the two groups. In the TS group, 9 patients discontinued treatment because of PD, and 17 patients discontinued treatment in the TX group. Only 3 patients in each group discontinued therapy due to adverse events. Of these patients, 42 (77.8%, 42/54) received sequential S-1 maintenance therapy, and 37 (65.0%, 37/57) received sequential capecitabine maintenance therapy. The average cycle numbers of maintenance therapy with S-1 and capecitabine were 12.7 and 11.9 cycles, respectively.

Table 1
Baseline characteristics of advanced breast cancer patients recruited (n = 111).

	TS group (n = 54)	TX group (n = 57)	*P* value
Median age, years	46	49	
Menstrual status, No. (%)			0.585
Premenopausal	34 (63.0)	33 (57.9)	
Postmenopausal	20 (37.0)	24 (42.1)	
Adjuvant/neoadjuvant chemotherapy, No. (%)			
Anthracyclines	45 (83.3)	45 (78.9)	0.555
Taxanes	43 (79.6)	40 (70.2)	0.252
HR status, No. (%)			0.743
Positive	50 (92.6)	51 (89.5)	
Negative	4 (7.4)	6 (10.5)	
Endocrine therapy*, No. (%)			
Adjuvant	47 (94.0)	48 (94.1)	0.652
Metastatic	25 (50.0)	25 (49.0)	0.540
ER status, No. (%)			0.609
Positive	48 (88.9)	49 (86.0)	
Negative	5 (9.3)	7 (12.3)	
Unknown	1 (1.8)	1 (1.7)	
PR status, No. (%)			0.218
Positive	34 (63.0)	42 (73.7)	
Negative	19 (35.2)	14 (24.6)	
Unknown	1 (1.8)	1 (1.7)	
Visceral metastasis, No. (%)			0.547
Yes	39 (72.2)	44 (77.2)	
No	15 (27.8)	13 (22.8)	
Metastatic sites, No. (%)			
Liver	18 (33.3)	28 (49.1)	0.091
Lung	23 (42.6)	25 (43.9)	0.893

* Percentage of patients receiving endocrine therapy, as a proportion of hormone receptor-positive patients.
Abbreviations: ER, estrogen receptor; HR, hormone receptor; PR, progesterone receptor; TS, docetaxel/S-1; TX, docetaxel/capecitabine.

3.3. Efficacy and survival

With a median follow-up time of 35.7 months (inter-quartile range [IQR], 17.1–47.3), 45 (83.3%) patients in the TS group and 53 (93.0%) patients in the TX group met the primary endpoint. The mPFS was 9.0 months (95% confidence interval [CI], 7.5–10.5) in the TS group and 7.4 months (95% CI, 6.2–8.6) in the TX group ($P = 0.365$). There was no significant difference in PFS between the two groups (hazard ratio [HR], 0.75 [95% CI, 0.50–1.11], $P = 0.36$; Fig. 2A). Univariate analysis for PFS showed no significant difference regardless of menstrual status, hormone receptor status, visceral metastasis, liver metastasis and

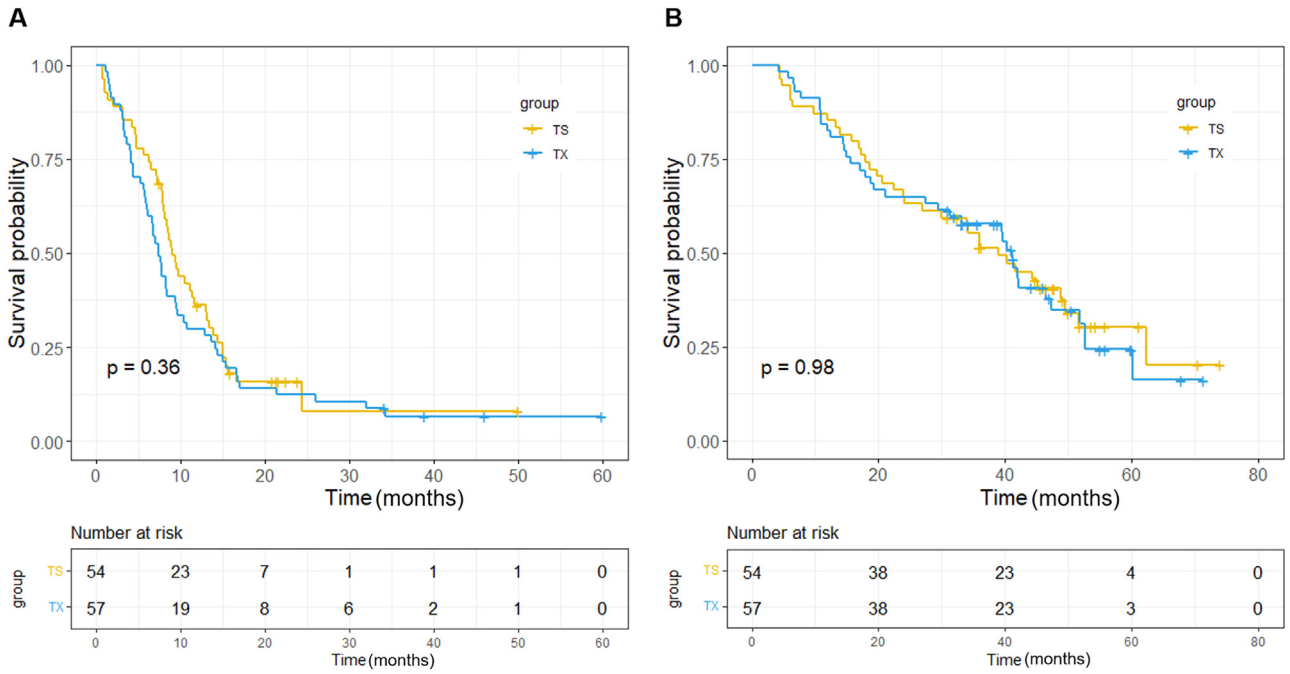

Fig. 2. Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) between the TS group and TX group. TS, docetaxel/S-1; TX, docetaxel/capecitabine.

lung metastasis. There were also no statistically significant differences in DOR between the two groups (TS vs. TX group, 7.6 vs. 8.0 months, $P = 0.899$, HR, 0.96 [95% CI, 0.54–1.71]). By the end of the follow-up period, 34 (63.0%) patients had succumbed in the TS group, and 34 (59.6%) patients had succumbed in the TX group. No differences were observed in median OS (mOS) between the two groups (40.2 vs. 41.3 months, $P = 0.976$, Fig. 2B).

Among the patients with visceral metastasis, the mPFS was 8.7 months in the TS group versus 6.8 months in the TX group ($P = 0.327$, Supplementary Fig. 1A). The mOS was slightly shortened in the TS group compared with the TX group (34.0 vs. 41.1 months, $P = 0.749$, Supplementary Fig.1B) but did not reach statistical significance. For patients with lung metastasis, there was no significant difference in either PFS ($P = 0.172$) or OS ($P = 0.607$) between the two groups, with mPFS of 8.5 months and 4.4 months, respectively, and mOS of 45.1 months and 39.6 months, respectively (Supplementary Fig. 2). Similarly, the mPFS (9.4 vs. 7.8 months, $P = 0.529$) and mOS (24.1 vs. 41.8 months, $P = 0.354$) of patients with liver metastasis were comparable in the two groups (Supplementary Fig. 3). With regard to HR status, subgroup analysis showed that no significant differences in mPFS were found between the TS and TX cohorts in either the HR-positive (9.4 vs. 7.8 months, $P = 0.44$, Supplementary Fig. 4A) or HR-negative (4.2 vs. 5.4 months, $P = 0.640$, Supplementary Fig. 5A) groups. The difference in mOS was also not statistically significant in the HR-positive (39.0 vs. 41.1 months, $P = 0.970$, Supplementary Fig. 4B) and HR-negative (31.5 vs. 14.7 months, $P = 0.280$, Supplementary Fig. 5B) subgroups. Among HR-positive patients with prior or no prior endocrine therapy, there were also no significant differences in median PFS and OS between TS and TX groups (Supplementary Figs. 6 and 7). For the other efficacy end points, no significant differences in ORR (63.0% vs. 54.4%, $P = 0.196$) or DCR (94.4% vs. 94.7%, $P = 0.149$) were identified between the two groups (Table 2).

Table 2
Comparison of efficacy between the TS group and the TX group.

Response rate, No. (%)	TS group (n = 54)	TX group (n = 57)	*P* value
CR	4 (7.4)	0 (0)	–
PR	30 (55.6)	31 (54.4)	–
SD	17 (31.5)	22 (38.6)	–
NE	3 (5.6)	4 (7.0)	–
ORR (CR+PR)	34 (63.0)	31 (54.4)	0.196
DCR (CR+PR+SD)	51 (94.4)	53 (94.7)	0.149

Abbreviations: CR, complete response; DCR, disease control rate; NE, none evaluate; ORR, objective response rate; PR, partial response; SD, stable disease; TS, docetaxel/S-1; TX, docetaxel/capecitabine.

3.4. Safety profiles

We assessed safety in 54 patients in the TS group and 57 patients in the TX group (Table 3). The most common grade 3 or worse adverse events were leucopenia (24.1% of patients in the TS group vs. 26.3% in the TX group, $P = 0.786$) and neutropenia (29.7% vs. 31.5%, $P = 0.824$). All grade 3/4 adverse events were well managed after symptomatic treatment. The TX group showed a significantly higher incidence of HFS than the TS group (38.6% vs. 7.4%, $P = 0.001$); however, the incidence of diarrhea (24.1% vs. 3.6%, $P = 0.003$) and elevation of AST/ALT levels (14.8% vs. 3.5%, $P = 0.049$) was higher in the TS group. The incidence of other adverse events (AEs), such as peripheral neurotoxicity and mucocutaneous toxicity, was low in both groups.

Dose reductions and discontinued treatment because of AEs occurred in 14 (25.9%) patients in the TS group and 17 (29.8%) patients in the TX group ($P = 0.647$). No treatment-related deaths or severe adverse events were reported in either group.

4. Discussion

Our findings showed that the TS regimen and the TX regimen had similar PFS and OS in the first-line treatment of patients with HER2-negative advanced breast cancer. Subgroup analysis demonstrated that there were no significant differences in survival profiles between the treatment groups regardless of the site of metastasis. In addition, HFS was significantly reduced in the TS group. Compared with standard chemotherapy, the TS regimen achieved satisfactory efficacy and good

Table 3
Comparison of adverse events between the TS group and the TX group.

	TS (n = 54)			TX (n = 57)			*P* value[a]
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	
Hematological, No. (%)							
Leukopenia	11 (20.4)	7 (13.0)	6 (11.1)	14 (24.6)	9 (15.8)	6 (10.5)	0.897
Neutropenia	10 (18.5)	9 (16.7)	7 (13.0)	9 (15.8)	10 (17.5)	8 (14.0)	0.984
Anemia	3 (5.6)	–	–	2 (3.5)	–	–	0.673
Thrombocytopenia	5 (9.3)	1 (1.9)	–	1 (1.8)	1 (1.8)	–	0.154
AST/ALT elevation	8 (14.8)	–	–	2 (3.5)	–	–	0.049[b]
Bilirubin	–	–	–	1 (1.8)	–	–	1.000
Non-hematological, No. (%)							
Nausea	33 (61.1)	6 (11.1)	–	28 (49.1)	4 (7.0)	–	0.211
Vomit	23 (42.6)	9 (16.7)	–	23 (40.4)	3 (5.3)	–	0.105
Diarrhea	11 (20.4)	2 (3.7)	–	2 (3.5)	–	–	0.003[b]
Mucocutaneous toxicity	3 (5.6)	1 (1.9)	–	1 (1.8)	2 (3.5)	–	0.513
Peripheral neuropathy	2 (3.7)	–	–	4 (7.0)	–	–	0.679
Hand-foot syndrome	2 (3.7)	2 (3.7)	–	12 (21.1)	10 (17.5)	–	0.001[b]

[a] Pearson chi-square test, comparing adverse events between groups.
[b] *P* values indicate statistically significant results.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TS, docetaxel/S-1; TX, docetaxel/capecitabine.

tolerability for first-line chemotherapy in advanced breast cancer, making it worthy of further investigation.

Combination chemotherapy remains one of the cornerstones of first-line systemic treatment of ABC. The latest NCCN guidelines recommend chemotherapy combinations for patients with high tumor burden, rapidly progressing disease, and visceral crisis. In this study, approximately 75% of patients had visceral metastasis with a high tumor load, and almost all HR-positive patients had received endocrine therapy, which necessitated cytotoxic chemotherapy. Therefore, in clinical practice, a large number of HR-positive patients receive chemotherapy as first-line therapy. According to the NCCN guideline,[16] CDK4/6 inhibitor combined with endocrine therapy are recommended as the first- or second-line treatment for HR-positive ABC patients without visceral crisis. However, HR-positive/HER2-negative ABC patients with visceral crisis or endocrine refractory should be assessed for germline BRCA1/2 mutations to identify candidates for PARP inhibitor therapy at first. If there were no mutations, chemotherapy is recommended, which preferred regimens include anthracyclines, taxanes, anti-metabolites and microtubule inhibitors. Docetaxel and capecitabine combination chemotherapy could be as the first-line treatment for ABC patients with HER2-negative or triple-negative tumors or who have endocrine refractory disease. Other drugs, such as doxorubicin, gemcitabine, vinorelbine, carboplatin and bevacizumab combined with taxanes, are also recommended for those patients. Currently, there are no reliable data on the docetaxel plus S-1 regimen for first-line treatment in ABC patients. The SELECT BC phase III trial included 608 HER2-negative metastatic breast cancer patients treated with taxane (docetaxel or paclitaxel) or S-1 and showed that S-1 is not inferior to taxane with respect to OS as a first-line treatment for metastatic breast cancer, and there were no significant differences in time to treatment failure or PFS between the treatment groups. Furthermore, the AEs of S-1 were tolerable.[17] Another single-arm, nonblind phase II study using S-1 monotherapy as first-line therapy for metastatic breast cancer reported an ORR of 41.7%, a median OS of 29.1 months and no difference in response rate or toxicity between the under 65-year-old group and the older group.[13] These results suggest that S-1 has high efficacy with low toxicity and is expected to be an effective chemotherapy for metastatic breast cancer, especially when considering patient preference as an important factor. In the neoadjuvant setting, Nakagawa *et al.*[18] analyzed 94 operable patients and found that the pathologic CR (pCR) rate of TS was 34.9% and that the regimen was well tolerated, which demonstrates that the combination of docetaxel and S-1 promises to emerge as an effective therapy for breast cancer.

The applications of the TS regimen in the treatment of various cancers have been explored. A phase II study of the TS regimen for advanced gastric cancer reported that the ORR was 57.8%, and the mPFS, median DOR and mOS were 6.9, 8.0 and 15.3 months, respectively. Neutropenia was the most common grade 3/4 toxicity of this regimen, and no treatment-related deaths occurred.[19] Another phase II study involving 80 advanced gastric cancer patients also documented good clinical efficacy along with good tolerance of the TS regimen.[20] Oki *et al.*[21] reported that the ORR obtained with this regimen was 16.3%, with an mPFS of 3 months and an mOS of 9 months in patients with previously treated advanced NSCLC.

To date, relatively few studies have assessed the efficacy of the TS regimen as the first-line treatment for ABC. Li *et al.*[22] conducted a retrospective study focusing on the comparison of TS and TX regimens for ABC. They found that there were no significant differences in median TTP (9.04 vs. 10.94 months, $P = 0.473$), ORR (63.6% vs. 61.5%), DCR (100% vs. 96.2%), or clinical benefit rate (CBR) (66.7% vs. 84.6%) between the TS group and TX group. In terms of safety, both regimens showed good tolerability, but grade 3 HFS was more frequent in the TX group (23.1% vs. 0%, $P = 0.025$). The above studies are consistent with the conclusion of our study. Hence, TS demonstrates non-inferior efficacy in treating locally advanced and metastatic breast cancer, and our prospective randomized trial provides convincing evidence for the use of the TS regimen in ABC.

Regarding safety, toxicities, such as leucopenia, neutropenia, nausea and vomiting, were identified to be similarly common between the two groups. However, HFS (38.6% vs. 7.4%, $P = 0.001$) was more common in the TX group, whereas diarrhea (24.1% vs. 3.6%, $P = 0.003$) and AST/ALT elevation (14.8% vs. 3.5%, $P = 0.049$) were more prominent in the TS group. The reported incidence of capecitabine-induced all-grade HFS varies from 29% to 77%,[23,24] but the incidence of S-1-induced HFS ranges from 5% to 13%,[25-27] which is in accordance with our findings. Generally, patients who experienced diarrhea and HFS were well managed after symptomatic treatment. No AE-associated deaths or severe AEs occurred in our patients. Compared with the TX regimen, TS was also well tolerated. For patients with intolerable HFS, S-1 is therefore a useful alternative.

This prospective, randomized clinical trial compared for the first time the efficacy and safety of the TS regimen with those of the TX regimen as a first-line treatment in ABC. TS might be a surrogate option for first-line therapy of patients with ABC. Inevitably, our study has some limitations. First, this study has a relatively small sample size due to the phase II exploratory trial design. Additionally, due to the protracted

impact of the COVID-19 pandemic, patient enrollment was slower than anticipated, leading to a longer overall timeline than originally planned. Of note, during the enrollment period of the trial, some effective new drugs, such as CDK4/6 inhibitors, PARP inhibitors and PD-L1 inhibitors, were not readily accessible in China, which may potentially impact the generalizability of the study results, and further data from real-world settings are needed to validate the findings.

5. Conclusions

In conclusion, the TS regimen showed good tolerability and considerable clinical efficacy compared with the TX regimen for first-line chemotherapy in ABC. The efficacy of this regimen in visceral metastasis disease warrants further study. It is expected that the TS regimen may become an alternative option as a first-line treatment for ABC. Further real-world studies with larger sample sizes are required to understand the efficacy and safety of TS as a first-line treatment in ABC.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Ethics statement

The trial was conducted in accordance with the principles of Good Clinical Practice as specified in the Declaration of Helsinki. The trial was approved by the Ethics Investigation Committees of the CHCAMS (approval number. 15-016/943). Written informed consent was obtained from each participant before study entry. This study was registered on ClinicalTrials.org (NCT02947061).

Author contributions

B.X. and J.W. conducted the study design. All authors were responsible for the data collection and case confirmation. N.A. and Y.W. performed the statistical analyses and drafted the manuscript. B.X. and J.W. modified and revised the manuscript. All authors have read and approved the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2023.05.003.

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