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Capecitabine maintenance therapy in patients with recurrent or metastatic breast cancer

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Abstract

Our objective was to investigate the efficacy and safety of capecitabine maintenance therapy (CMT) after capecitabine-based combination chemotherapy in patients with metastatic breast cancer. The clinical data of 139 metastatic breast cancer patients treated from March 2008 to May 2012 with capecitabine-based combination chemotherapy were retrospectively analyzed. When initial disease control was achieved by the combination chemotherapy, we used CMT for 50 patients, while 37 patients were treated with a different (non-CMT) maintenance therapy. We compared time to progression (TTP), objective response rate, disease control rate, clinical benefit rate, and safety of the two groups, and a sub-group analysis was performed according to pathological characteristics. Sixty-four percent of the patients received a median of six cycles of a docetaxel + capecitabine combination chemotherapy regimen (range 1-45); the median TTP (MTTP) for the complete treatment was 9.43 months (95%CI = 8.38-10.48 months) for the CMT group and 4.5 months (95%CI = 4.22-4.78 months; P = 0.004) for the non-CMT group. The MTTPs for the maintenance therapies administered after the initial capecitabine combined chemotherapy were 4.11 months (95%CI = 3.34-4.87 months) for the CMT group and 2.0 months (95%CI = 1.63-2.38 months) for the non-CMT group. Gastrointestinal side effects, decreased white blood cells and palmar-plantar erythrodysesthesia were the main adverse reactions experienced with the combination chemotherapies, CMT and non-CMT treatments. No significant differences in the incidence of adverse reactions were detected in the CMT and non-CMT patients. After initial disease control was achieved with the capecitabine-based combination chemotherapy, CMT can significantly prolong TTP rates with a favorable safety profile.

Key words: Capecitabine; Maintenance therapy; Metastatic breast cancer

Introduction

Breast cancer is the most common malignant tumor in women; its morbidity is increasing year by year, but the mortality rate has been decreasing due to early diagnosis and improvements in therapy. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) large sample meta-analysis reported that adjuvant chemotherapy could significantly improve the prognosis of breast cancer patients (1), but that the recurrence or metastasis rates were still 20-35% (2). The major goal of recurrent or metastatic breast cancer treatment is to prolong survival time, relieve symptoms and improve quality of life (3). After initial disease control is achieved by various treatments and medications in metastatic breast cancer patients, maintaining progression-free survival and ensuring a relatively high quality of life present a major challenge for clinicians. The present study demonstrates that extending the duration of first-line chemotherapy of advanced breast cancer can improve overall survival and progression-free survival to a certain extent. However, further clinical studies are required to elucidate the role of maintenance therapies, improve suitable medication regimens, and evaluate the duration for medical maintenance therapies (2).

Anthracyclines are effective drugs for treating breast cancer, but they are not suitable as a long-term maintenance treatment because of cardiac toxicity caused by drug accumulation. In addition, in the maintenance

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paclitaxel 1 (MANTA 1) study, 255 metastatic breast cancer patients who received a first-line anthracycline/paclitaxel combination chemotherapy followed by a paclitaxel maintenance regimen had a median time to progression (MTTP) that was not significantly better than that of the control group [8 months in the sequential paclitaxel maintenance therapy group *vs* 9 months in the control group ($P = 0.817$)], and the median overall survival rates were 28 and 29 months ($P = 0.547$). The study was terminated because no survival advantage of a paclitaxel maintenance medication was demonstrated (4).

The effect of oral vinorelbine as maintenance therapy was investigated in a phase II multicenter clinical trial. After achieving an overall response rate (ORR) of 70% and a clinical benefit rate (CBR) of 83% in 30 patients in response to intravenous first-line chemotherapy with 3-6 cycles of vinorelbine + anthracycline combined chemotherapy regimens, maintenance therapy with sequential oral vinorelbine therapy resulted in an ORR of 38% and CBR of 44%. The MTTP was 8 months (33% of patients were stage IV; 67% had local metastasis). Although this small trial achieved good results, the main side effect of bone marrow suppression resulted in an incidence of grade III-IV leukopenia of 44% during the combined chemotherapy and 18% in maintenance therapy (5), thereby not really making it the best choice for a long-term maintenance therapy when safety is considered.

Capecitabine is a novel oral fluoropyrimidine carbamate that is inactive and absorbed quickly by the mucous membrane of the small intestine. After conversion into 5′-deoxy-5-fluorouridine, it is transformed into cytotoxic 5-fluorouracil (5-FU) by thymidine phosphorylase (TP). 5-FU reduces DNA synthesis via inhibiting thymidylate synthase, and by blocking nucleoside analogues, hinders the synthesis of RNA particularly in tumor cells. In breast cancer cells with high proliferative activity, the concentration of the key enzyme TP is essentially higher than in other tissues, and even in tumors that are in chemotherapy-resistant areas with an inadequate blood supply, the concentration of 5-FU in tumor tissues has been reported to be 127 times higher than in the blood, accounting for the high selectivity of capecitabine. Due to its specific antitumor activity, capecitabine can stop tumor cell proliferation with better tolerability, higher efficiency and lower toxicity compared with other chemotherapies. Paclitaxel, docetaxel, gemcitabine, vinorelbine, and other cytotoxic drugs can upregulate the activity of the TP enzyme (6-10), thus inducing a synergistic anti-tumor effect enhancement with capecitabine without increasing adverse side effects. Therefore, capecitabine or capecitabine-based combination therapies show unique advantages in the treatment of metastatic breast cancer. According to reports in the literature, when using capecitabine as first-line treatment for advanced breast cancer, the ORR was as high as 30-36%, and was 15-28% when used as the second-line treatment for anthracycline and/or taxane-resistant metastatic breast cancer patients (11-14). The ORR of docetaxel + capecitabine (TX), gemcitabine + capecitabine (GX), and vinorelbine + capecitabine (NX) combination therapies was 40-60% (15,16). The existing data thus support the suitability for long-term application. In China, a retrospective analysis by Huang et al. (3) evaluated capecitabine maintenance therapy (CMT) in recurrent or metastatic breast cancer patients after an initial response to a capecitabine combination chemotherapy with a median treatment duration of 3 months. The results showed that 32.2% of the patients had clinical benefits and 81% maintained the original therapeutic efficacy, with an MTTP of 4 months. However, as it was a single-arm study, no control data were available, and at present there are limited reports on CMT. Based on the single-arm research by Huang et al. (3), the present study was designed to further examine the efficacy and safety of CMT for metastatic breast cancer, with a non-capecitabine maintenance control group, after initial relief or stability was achieved with capecitabine-based combination therapy.

Patients and Methods

Study population

A total of 139 female advanced breast cancer patients who were treated at our hospital between March 2008 and May 2012 were included in this study. The inclusion criteria were 1) pathologically confirmed recurrent or metastatic breast cancer; 2) Karnofsky performance status (KPS) score of 80-100 and expected survival time >6 months; 3) detectable response evaluation criteria in solid tumors (RECIST) (17); 4) treated with a capecitabine combination chemotherapy; 5) good compliance with the prescribed medication and regular follow-up; 6) signed informed consent. The research was approved by the Ethics Committee of the General Hospital of the Chinese People's Liberation Army and informed consent was obtained from all participants.

Therapy methods

All patients included in this study received 900-1000 mg/m^2 capecitabine (orally, twice a day on D1-14, combined with 70-75 mg/m^2 docetaxel (intravenous drip, D1; TX regimen), 900-1000 mg/m^2 gemcitabine (intravenous drip, D1 and 8; GX regimen) or 20-25 mg/m^2 vinorelbine (intravenous drip, D1 and 8; NX regimen) based on their previous therapy and recurrence/metastasis status. The therapeutic efficacy was evaluated after every 2 of the 21-day capecitabine chemotherapy cycles. Patients who completed 4-8 cycles and achieved disease control [complete relief (CR), partial relief (PR), or stable disease (SD)] were given CMT (50 patients), other maintenance treatments or no treatment (37 patients) based on the chemotherapy efficacies, adverse reactions and the willingness of the patients. Maintenance continued until disease progression or appearance of intolerable side effects.

Assessment of therapy efficacy

According to the RECIST, assessment of therapy efficacy can be divided into CR, PR, SD, and progression of disease (PD). Based on the common toxicity grading criteria of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3 (NCI-CTC V3.0) (18), subacute, acute, and long-term adverse reactions were evaluated and classified as: 0 (none), I (minor reaction), II (moderate reaction), III (severe reaction), IV (serious life-threatening adverse reaction). The primary endpoint was time to progression (TTP) of disease beginning at the start of treatment, including death, or no disease progression at the last investigation. Secondary endpoints included the ORR (ORR = CR + PR), disease control rate (DCR = CR + PR + SD), and CBR (CBR = CR + PR + SD $\geqslant$6 months) as well as safety.

Statistical methods

Intention-to-treat (ITT) and PP (per-protocol) analyses were used in this study; ITT analysis was used for the treatment of all subjects, while subjects for PP analysis were those who meet the inclusion criteria and strictly complied with the protocol.

The SPSS19.0 software (IBM, USA) was utilized for all statistical analyses, and measurement data are reported as median, while count data are reported as the rate of distribution and percentage. A chi-square test was used for the comparison between groups (Pearson χ^2 test, two-tailed test, and a value of $P<0.05$ was considered to be statistically significant). Kaplan-Meier curves were calculated for the survival analyses and a log-rank test was used to compare survival data. Multivariate Cox survival regression analysis was conducted using a backward stepwise method (the statistical level of significance determined with the Wald test was $P<0.05$).

Results

ITT and PP analyses

In the ITT population, 91 patients received a first-line and 48 patients received a second-line chemotherapy or higher; 89 patients were treated with a TX, 45 patients with a GX, and 5 patients with an NX combination chemotherapy. The median number of chemotherapy cycles was 6 (1-45). In the PP population, 80 patients received a first-line and 43 patients a second-line chemotherapy or higher; 80 patients were given a TX, 39 patients a GX, and 4 patients an NX combination chemotherapy, including 8 who received a combined Herceptin therapy. The median number of chemotherapy cycles for the PP patients was 6 (2-8). In the PP population, PD did not develop in the 87 patients who completed 4-8 chemotherapy cycles, 50 of whom entered sequentially into the CMT group. The median number of maintenance treatment cycles was 5 (1-37); 6 patients had 16 or more cycles, and 12 patients had 10 or more. The remaining 37 patients given the combined chemotherapies, who did not reach PD, and did not accept capecitabine maintenance treatment, were combined and included in the non-CMT group. According to the estrogen receptor/progesterone receptor (ER/PR) and Her-2 receptor status, previous treatments and patient agreement, 16 were given endocrine maintenance therapies, 6 received single agent chemotherapies such as gemcitabine or paclitaxel, 1 was medicated with a Herceptin treatment and 1 was treated with local radiotherapy. The other 13 patients did not continue any treatment.

Baseline characteristics of the CMT *vs* non-CMT groups

One hundred and thirty-nine patients met the initial inclusion criteria, including 50 cases in the CMT and 37 cases in non-CMT groups. No significant differences in baseline characteristics, such as the median age at registration, the median KPS score, menstrual status, the median age of definite diagnosis, the median disease-free survival (DFS), postoperative pathologic staging, histological classification and grading, hormone receptor status, HER2, Ki-67, Luminal type (19), metastatic sites, number of metastatic lesions, and previous treatments were detected between the two groups (Table 1). Therefore, TTP, as well as ORR, DCR, CBR and safety were unbiased and comparable between the two groups.

Therapeutic efficacy

TTP. All of the 139 patients were assessable for the safety evaluation in this study, but 16 were lost to follow-up, leaving 123 patients for the efficacy evaluation. The overall TTP of these 123 patients from the beginning of the chemotherapy to disease progression was 6.05 months (95%CI = 4.92-7.17 months) The median duration of combination chemotherapy was 4.17 months (1.05-9.0 months), while the second line treatment MTTP of the 50 patients in the CMT group was 4.11 months (95%CI = 3.34-4.87 months), and for the non-CMT patients it was 2.0 months (95%CI = 1.63-2.38 months). There was a significant difference in therapeutic efficacy between CMT and non-CMT patients. The MTTP for the complete treatment was 9.43 months (95%CI = 8.38-10.48 months), for the CMT group 4.5 months (95%CI = 4.22-4.78 months) P = 0.004, and for the non-CMT group (Figure 1, Table 2), being about two times higher in the CMT patients.

Correlations between the MTTPs of the included patients with clinical features (ER/PR status, Her-2 status, menstrual status, DFS, with or without gut metastasis, number of metastatic lesions) were further analyzed and no correlation could be detected through multiple regression analyses (Table 2). As shown in Table 3, a multivariate Cox regression analysis demonstrated that the metastasis recurrence rate risks in the non-CMT group, second or more line chemotherapy and premenopausal patients were

Table 1. Baseline characteristics of the capecitabine maintenance therapy (CMT) and the non-CMT groups.

Baseline characteristics in patients without PD	CMT	Non-CMT
Number	50	37
Median age at registration/ years (range)	44 (24-69)	46 (34-64)
Median KPS score	90 (80, 90)	90 (80, 100)
90-100	45 (90%)	33 (89.2%)
80	5 (10%)	4 (10.8%)
Menstrual status		
Premenopausal	35 (70%)	26 (70.3%)
Postmenopausal	15 (30%)	11 (29.7%)
Median definite diagnosis/ years (range)	40.5 (22-60)	42 (30-63)
<35	14 (28%)	6 (16.2%)
⩾35	36 (72%)	31 (83.8%)
Median DFS/months (range)	45.2 (1.5-189.4)	36.6 (10.7-95.8)
Postoperative pathological staging		
I	2 (4%)	5 (13.5%)
II	16 (32%)	12 (32.4%)
III	17 (34%)	9 (24.3%)
IV	10 (20%)	6 (16.2%)
Not clear	5 (10%)	5 (13.5%)
Histological classification		
Invasive ductal carcinoma	45 (90%)	33 (89.2%)
Invasive lobular carcinoma	1 (2%)	1 (2.7%)
Other	4 (8%)	3 (8.1%)
Histological grading		
I	1 (2%)	0 (0%)
I-II	0 (0%)	1 (2.7%)
II	10 (20%)	10 (27%)
II-III	3 (6%)	0 (0%)
III	14 (28%)	9 (24.3%)
No grading	22 (44%)	17 (45.9%)
Hormone receptor status		
Positive	35 (70%)	29 (78.4%)
Negative	15 (30%)	8 (21.6%)
Her-2 status		
Positive	18 (36%)	12 (32.4%)
Negative	29 (58%)	23 (62.2%)
Unknown	3 (6%)	2 (5.4%)
Ki-67		
<25	14 (28%)	7 (18.9%)
25-50	5 (10%)	4 (10.8%)
50-75	3 (6%)	2 (5.4%)
>75	4 (8%)	4 (10.8%)
Unknown	24 (48%)	20 (54.1%)
Luminal type*		
A	8 (16%)	5 (13.5%)
B1	19 (38%)	18 (48.6%)
B2	9 (18%)	7 (18.9%)
Her-2	9 (18%)	5 (13.5%)
Basal	5 (10%)	2 (5.4%)
Metastatic sites		
Gut metastasis	31 (62%)	27 (73%)
No gut metastasis	19 (38%)	10 (27%)
Lung	22 (44%)	16 (43.2%)
Liver	16 (32%)	12 (32.4%)
Brain	5 (10%)	4 (10.8%)
Bone	34 (68%)	23 (62.2%)
Lymph node	17 (34%)	15 (40.5%)
Walls of the chest	8 (16%)	6 (16.2%)
Number of metastatic lesions		
1	23 (46%)	12 (32.4%)
2	11 (22%)	10 (27%)
3	11 (22%)	9 (24.3%)
⩾4	5 (10%)	6 (16.3%)
Previous treatment		
Antharcycline	42 (84%)	33 (89.2%)
Taxanes	37 (74%)	25 (67.6%)
Antharcycline and taxanes	33 (66%)	23 (62.2%)

Data are reported as number (%) or median (range). PD: progression of disease; KPS: Karnofsky performance status; DFS: disease-free survival. Luminal A: ER/PR+, HER2–, Ki-67≤14%. Luminal B: ER/PR+, HER2–, Ki-67>14% or ER/PR+, HER2+. Her-2: ER–, PR–, HER2+. Basal-like: ER–, PR–, HER2–. There were no significant differences between the groups (P>0.05, Pearson chi-square test).

2.676, 2.260, 1.905 times the CMT group.

ORR, CBR, and DCR outcomes of CMT and non-CMT medications. Comparisons of ORR and CBR in the CMT and non-CMT groups demonstrated that ORR was not significantly different (58 *vs* 51.4%), but that CBR was significantly better in the CMT patients (86 *vs* 54.1%; P = 0.001). Comparing first- and second-line treatments, the first-line therapy ORR outcome was 55% (twice that of the second-line treatment) and the first-line therapy CBR outcome was 63.8% (1.7 times that of the second-line treatment). Correlation analyses between ORR, DCR, and CBR with clinical pathological features demonstrated no correlations of ORR, DCR, CBR with ER/PR, Her-2 and menstrual status, DFS, with or without metastasis, and number of metastatic lesions (Table 4).

Safety analysis

All 139 patients who received at least one cycle of chemotherapy were assessable for a safety evaluation. The main adverse reactions in this study were gastrointestinal side effects (67.6%), decreased white blood cells (76.3%) and palmar-plantar erythrodysesthesia (PPE, 58.3%), and the incidence of grade III-IV severity of these adverse reactions in the combination chemotherapy were

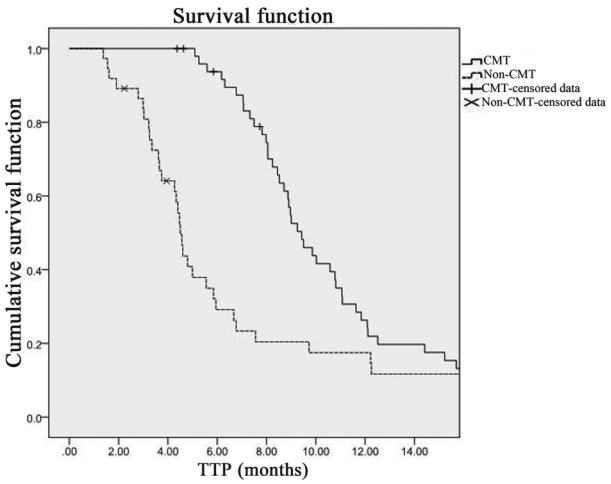

Figure 1. Median time to progression (TTP) of the CMT *vs* non-CMT group (group-censored data). The median TTPs after combination chemotherapy were 4.11 months (95%CI = 3.34-4.87 months) for the CMT patients (n = 50) and 2.0 months (95%CI = 1.63-2.38 months) for the non-CMT patients (n = 37). CMT: capecitabine maintenance therapy. Cox regression analysis (P = 0.039).

7.2, 25.9, and 10.8%, respectively. In the 50 CMT patients, the incidence of gastrointestinal side effects, leukopenia and PPE was 66, 70, 64%, while the grade III-IV incidence of these adverse reactions was 4, 20, and 8%. In the non-CMT group, the incidence of gastrointestinal side effects, leukopenia and PPE was 67.6, 73, 62.2%; the incidence of grade III-IV events was 5.4, 24.3, and 10.8%. Overall, there were no significant differences of the adverse reactions between the CMT and non-CMT groups (Table 5). In this study, therapy was discontinued in 8.6% of the patients due to adverse reactions (12/139), and dose reduction or dose delay of capecitabine was necessary in 3.6% (5/139). The frequency of dose adjustments in the CMT was 10% (5/50), including dose reduction or delay, which could be reversed after symptomatic treatments. During the study period, no patients died from therapy-related adverse reactions and no serious adverse events occurred.

Discussion

Chemotherapy plays an important role in the treatment of advanced breast cancer; the effectiveness of first-line combination chemotherapies is up to 60-80% (2,20,21). In

Table 2. Correlation of MTTP with clinical pathological characteristics.

Sub-group	N	MTTP (months)	P	HR	95%CI
With/without CMT			0.004	1.95	1.24-3.07
CMT	50	9.43			
Non-CMT	37	4.50			
First line/multiple-line chemotherapy			0.056	1.46	0.99-2.15
First-line chemotherapy	80	7.33			
Second- or multiple-line chemotherapy	43	4.99			
ER/PR level			0.179	1.32	0.88-1.99
Positive	87	6.18			
Negative	36	5.95			
Her-2 level			0.495	1.14	0.78-1.68
Positive	47	6.18			
Negative	70	5.95			
Unknown	6				
Menstrual status			0.455	1.16	0.79-1.71
Premenopausal	83	7.00			
Postmenopausal	40	5.26			
DFS			0.126	1.37	0.92-2.05
≤3 years	49	5.55			
>3 years	54	6.31			
Palliative treatments	20				
With/without gut metastasis			0.147	1.37	0.90-2.08
Without	34	8.05			
With	89	5.59			
Number of metastatic lesions			0.510	1.14	0.78-1.66
≤2	76	5.95			
>2	47	6.18			

MTTP: median time to progression; CMT: capecitabine maintenance therapy; ER/PR: estrogen receptor/progesterone receptor; DFS: disease-free survival. The Log-rank test was used for analyses.

Table 3. Multivariate Cox regression analysis of median time to progression.

Clinicopathological characteristics	Wald	RR	P	95%CI
With/without capecitabine maintenance therapy	12.994	2.676	0.000	1.567-4.569
First-line/multiple-line chemotherapy	6.379	2.260	0.012	1.200-4.254
Menstrual status	3.888	1.905	0.049	1.004-3.614

the present study, we found that ORR, DCR and CBR of the first-line chemotherapy were 55.0, 91.3, and 63.8% and were 26.5, 79.1, and 37.2% for the second-line chemotherapy. The differences in outcome between first- and second-line chemotherapies achieved or almost achieved statistical significance (Table 4). On the other hand, there were various follow-up treatment strategies for metastatic breast cancer patients after response to combined chemotherapy: continuing combination chemotherapy until disease progression or intolerance, replacement of the therapy regimens, or maintenance therapy with a single agent used in the initial, combined chemotherapy. Research has shown that maintenance therapy could significantly prolong the MTTP (19 *vs* 8 months) compared with the control group in complete remission patients, but toxic side effects were also increased (22). Therefore, which chemotherapy drug should be chosen for maintenance therapy after initial treatment with a combination of drugs is still a clinical issue.

This study summarized the efficacy and safety of CMT in patients after initial disease control status using a first-line capecitabine-based combination chemotherapy. The results suggest that CMT resulted in a better therapeutic efficacy for advanced breast cancer treatments, with an MTTP of 9.43 months, which was longer than that of the non-CMT group (4.5 months, $P = 0.004$). While the ORRs in the two groups (58 *vs* 51.4%, $P = 0.538$) were well matched, 86% CMT patients, but only 54.1% in the non-CMT group ($P = 0.001$), enjoyed clinical benefits (CBR) for more than 6 months, which suggested that CMT can extend the therapeutic efficacy after an initial combination

Table 4. Correlation analysis between ORR, DCR and CBR with clinical pathological characteristics.

Sub-group	ORR (%)	n/N	P	DCR (%)	n/N	P	CBR (%)	n/N	P
With/without CMT			0.538						0.001
With CMT	58.0	29/50					86.0	43/50	
Without CMT	51.4	19/37					54.1	20/37	
First-line/multiple-line chemotherapy			0.002			0.056			0.005
First-line	55.0	44/80		91.3	73/80		63.8	51/80	
Second- or multiple-line chemotherapy	26.5	11/43		79.1	34/43		37.2	16/43	
ER/PR level			0.969			0.852			0.877
Positive	44.8	39/87		87.4	76/87		54.0	47/87	
Negative	44.4	16/36		86.1	31/36		55.6	20/36	
Her-2 level			0.912			0.815			0.788
Positive	44.7	21/47		87.2	41/47		53.2	25/47	
Negative	45.7	32/70		85.7	60/70		55.7	39/70	
Menstrual status			0.965			0.907			0.489
Premenopausal	44.6	37/83		86.7	72/83		56.6	47/83	
Postmenopausal	45.0	18/40		87.5	35/40		50.0	20/40	
DFS			0.590			0.629			0.645
≤3 years	42.0	21/49		83.7	41/49		51.0	25/49	
>3 years	48.1	26/54		87.0	47/54		55.6	30/54	
With/without gut metastasis			0.626			0.394			0.159
Without	41.2	14/34		91.2	31/34		64.7	22/34	
With	46.1	41/89		85.4	76/89		50.6	45/89	
Number of metastatic lesions			0.995			0.625			0.223
≤2	44.7	34/76		21	67/76		55.3	42/76	
>2	44.7	21/47		85.3	40/47		53.2	25/47	

ORR: objective response rate; DCR: disease control rate; CBR: clinical benefit rate; CMT: capecitabine maintenance therapy; ER/PR: estrogen receptor/progesterone receptor; DFS: disease-free survival. The Pearson chi-square test was used for analyses.

Table 5. Therapy-related adverse reactions.

Classification of adverse reactions	CMT (n = 50)		non-CMT (n = 37)		P	
	n (%)	III/IV (%)	n (%)	III/IV (%)	n	III/IV
Adverse reactions of the hematological system						
Leukopenia	35 (70%)	10 (20%)	27 (73%)	9 (24.3%)	0.762	0.629
Decrease of platelets	6 (12%)	1 (2%)	5 (13.5%)	1 (2.7%)	0.834	0.829
Non-hematological adverse reactions						
Gastrointestinal side effects	33 (66%)	2 (4%)	25 (67.6%)	2 (5.4%)	0.966	0.757
Abnormal liver function	3 (6%)	1 (2%)	3 (8.1%)	0 (0%)	0.701	0.387
PPE	32 (64%)	4 (8%)	23 (62.2%)	4 (10.8%)	0.860	0.654

CMT: capecitabine maintenance therapy; III/IV: grade III/IV leukopenia; PPE: palmar-plantar erythrodysesthesia. The Pearson chi-square test was used for statistical analyses.

therapy. The MTTP of the 50 CMT patients was 4.11 months, while tumors of 3 patients (6%) continued to shrink, reaching PR; 38 patients (76%) maintained the therapeutic efficacy of the initial combined chemotherapy at the first evaluation. The ORR, DCR and CBR of 6, 82, 48%, respectively, were similar to those reported in the literature (3), and 6 patients continued the CMT for more than 1 year. Twelve patients who did not develop PD still continued CMT at the time of data cutoff.

The feasibility of using other drugs for maintenance treatment of recurrent or metastatic breast cancer should also be evaluated, because for metastatic breast cancer with positive hormone receptors (i.e., ER/PR), endocrine drugs can also be used for maintenance therapy. In addition, HER2-targeting drugs, such as trastuzumab and lapatinib have also been selected as maintenance therapy for breast cancer patients with positive HER2 receptors (23). A few prospective clinical trials have obtained results showing that continuous application of trastuzumab until disease progress offers clinical benefits, suggesting that the progression-free survival of patients can be prolonged with anti-HER2-targeted therapy after progression of the disease (24). In this study, 16 of the 37 non-CMT patients received an endocrine maintenance therapy consistent with their ER/PR and Her-2 receptor statuses. The hormone receptor-positive patients were first considered to accept chemotherapy in case of a failed previous endocrine therapy or a low ER/PR-positive ratio. If the benefit of an endocrine maintenance therapy was thought to be greater than or equal to chemotherapy, endocrine maintenance therapies were considered as first treatment choice, but the MTTP of these patients was only 2.27 months, which was significantly less than that of the CMT group. Based on our safety analysis of capecitabine as maintenance treatment, there were no significant differences of hematological and non-hematological toxicity between the CMT and non-CMT groups, which suggests that CMT did not increase toxicity effects, and has a favorable safety profile.

Taken together, we should first consider breast cancer as ''chronic disease'' for the development of treatment options and not only focus on first-line chemotherapy regimens, but also on maintenance therapies to be considered after response to first-line medications. Continuous maintenance therapy is recommended with a single chemotherapy agent being administered after initial response to combination chemotherapy. Furthermore, anti-tumor treatment is long-term medication, and the choice of drugs should be based on patient compliance. Therefore, the ideal chemotherapy drug should be effective as monotherapy, the toxicity should be low, and it should be easy to use over the long term, like the oral capecitabine used in this study. A limitation of this analysis is the small sample size, but the results warrant additional phase III clinical trials and comparison with alternative, effective maintenance therapy drugs.

In summary, CMT extended the therapeutic efficacy of primary, combined chemotherapy, and ensured good quality of life for patients, thereby making it a new option for a second-line maintenance medication for advanced breast cancer therapy.

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