Original Article

Comparison of capecitabine-based regimens with platinum-based regimens in Chinese triple-negative breast cancer patients with liver metastasis

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Background: Capecitabine-based chemotherapy (CBC) presents potential value in patients with liver metastasis; platinum-based chemotherapy (PBC) has shown promising benefit in patients with triple-negative breast cancer (TNBC). For TNBC patients with liver metastasis, which treatment strategy is better remains to be further studied. The aim of this study was to report the first real-world data evaluating the efficacy and safety of PBC versus CBC in the first-line treatment in Chinese TNBC patients with liver metastasis.

Methods: TNBC patients with liver metastasis pretreated with anthracyclines/taxanes in 4 institutions of China between January 2010 and December 2019 were included. Objective response rate (ORR), overall survival, treatment pattern, and toxicity profile were assessed between PBC and CBC groups.

Results: A total of 59 TNBC patients with liver metastasis were identified. Among these, 33 were treated with PBC and 26 were treated with CBC. The ORR was higher in the CBC group than in the PBC group (57.7% versus 30.3%, P=0.035). Median overall survival was also greatly improved (19.2 versus 14.4 months, P=0.041). Docetaxel/cisplatin was more likely to be used for PBC, and paclitaxel/capecitabine was the main regimen for CBC. Multivariable Cox regression analysis indicated that CBC was an independent predictor for overall survival after adjustment for baseline factors including age, tumor size, nodal status, prior anthracyclines/taxanes use, and tumor grade (odds ratio =0.51; 95% confidence interval, 0.27–0.98; P=0.042). Adverse events were not different except gastrointestinal tract toxicities, hand-foot syndrome and hematologic toxicity.

Conclusions: For TNBC patients with liver metastasis, capecitabin-based chemotherapy might be more suitable than the platinum-based regimen in the first-line treatment, as measured by objective response rate and overall survival. Further large-scale studies are warranted.

Keywords: Capecitabine; platinum; triple-negative breast cancer (TNBC); liver metastasis

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Introduction

Triple-negative breast cancer (TNBC) refers to the absence of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor-2 (HER-2). It is a specific subtype of breast cancer accounting for 15–20% of all breast cancers (1). TNBC presents a trend of early visceral metastasis, and has poorer prognosis (2). Among patients with metastatic breast cancer (MBC), approximately half will develop liver metastases (LM), and 12% of patients develop metastasis of primary liver cancer (3), leading to liver dysfunction and poor survival (4).

Instead of available target agents, chemotherapy represents the mainstay systemic treatment for metastasis TNBC (mTNBC) (5). Anthracyclines and taxanes are fundamental regimens with proven efficacy in every stage of breast cancer (6). However, for patients with anthracycline/taxanes-pretreated breast cancers, there are no standard regimens currently (7).

For patients with mTNBC, platinum-based chemotherapy (PBC) has shown promising results in increasing preclinical and clinical trials. Platinum can lead to DNA damage, and TNBC is more sensitive to these agents compared to other subtypes of breast cancers. The benefit of platinum regimens was confirmed by several II or III clinical trials (8-10).

For patients with LM, capecitabine-based chemotherapy (CBC) seems to show potential value. Capecitabine is among the drugs of first choice for breast cancer patients resistant to anthracycline or taxane (11). It is activated in the liver and further forms 5-FU in the tumor tissue (12-14), suggesting higher concentration in the liver and the potential benefit for patients with liver metastases (LM).

However, for mTNBC patients with LM, which agents are more suitable is uncertain. In this study, we present the result of the comparison of the PBC and CBC in patients with mTNBC-LM.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4590).

Methods

Patients and data collection

In this study, we retrospectively compared the efficacy and toxicity of CBC and PBC in mTNBC patients with LM. We reviewed the electronic medical records of patients with mTNBC who received systematical chemotherapy at four cancer centers in China (National Cancer Center, Chinese PLA General Hospital, Beijing Chaoyang Hospital, Beijing Sanhuan Cancer Hospital) between January 2010 and December 2019.

Inclusion criteria were as follows for eligible patients: (I) immunohistochemical (IHC) staining method was applied to determine the ER/PgR/HER-2status. Triple negativity breast cancer was defined as the deficiency of expression of ER, PgR, and HER-2. "ER/PgR negative" were defined when less than 1% positive tumor cells were detected with nuclear staining by IHC according to the guidelines of new College of American Pathologists. HER-2 status was evaluated by IHC and fluorescence *in situ* hybridization (FISH). "HER-2 negative" was defined as IHC scoring 0 or 1+ or FISH nonamplied according to the American Society of Clinical Oncology (ASCO) guidelines. (II) Breast cancers patients had initial isolated liver metastasis. (III) Patients received PBC or CBC as the first-line treatment. (IV) Patients had completed treatment records and follow-up information. Finally, 59 eligible TNBC patients with LM were included in this study (*Figure 1*). Initial LM was defined as LM that occurred as the first evidence of metastasis, and isolated LM was characterized by the absence of extrahepatic metastasis.

Patients were further allocated into two groups by their regimens in their salvage chemotherapies: the PBC group and CBC group. PBC referred to chemotherapy that included cisplatin or carboplatin alone or in combination with another regimen. CBC was defined as chemotherapy that included capecitabine alone or in combination with other regimens. Clinical data were collected and analyzed, including demographic characteristics, disease stage at diagnosis, treatment regimens, response to treatment, adverse events, and overall survival.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). It was approved by the Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No.: 15-115/1042). Because of the retrospective nature of the research, the requirement for informed consent was waived.

Response assessment and follow-up

Tumor response was evaluated according to the response evaluation criteria in solid tumors (RECIST) 1.1 guideline, which was classified into four categories: complete response

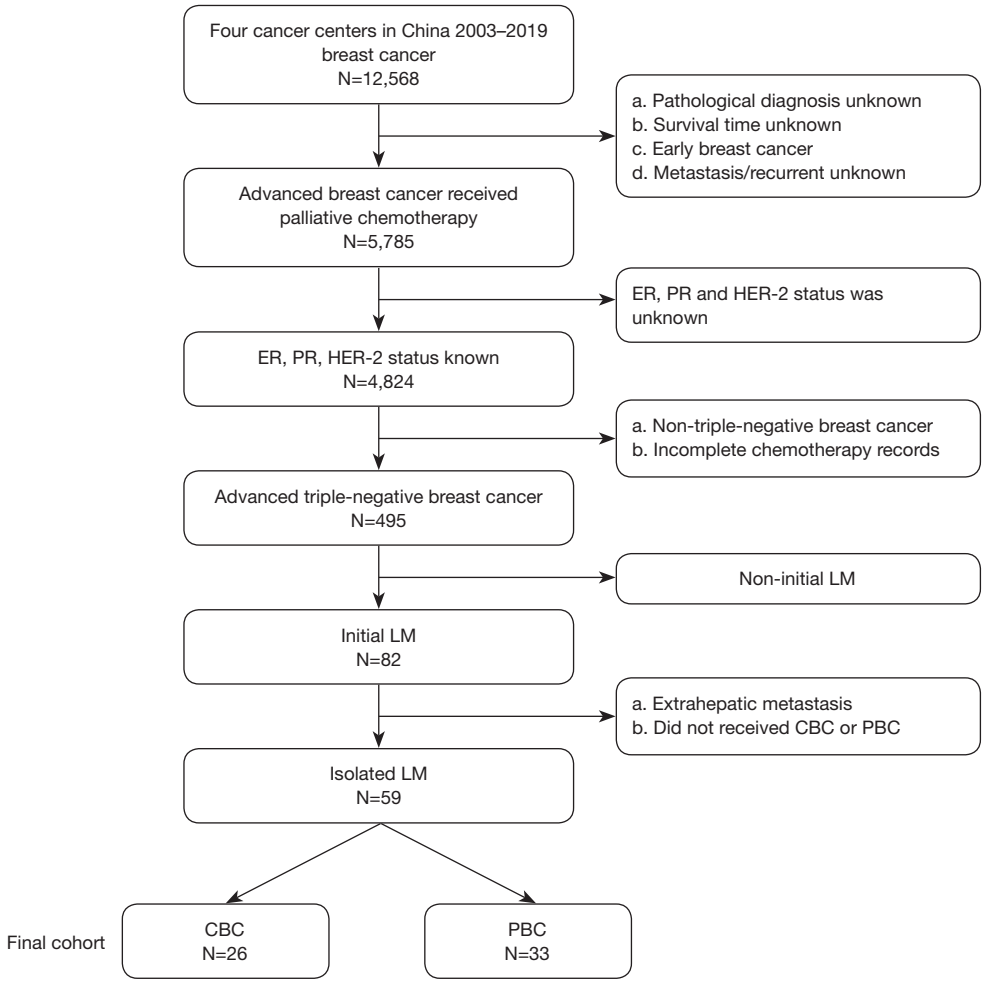

Figure 1 Flow diagram of patient selection.

(CR), partial response (PR), stable disease (SD), and progressive disease (PD). Tumor response to treatment was assessed every 2 cycles during chemotherapy and then every 3 months after chemotherapy. The efficacy of chemotherapy was evaluated in terms of objective response rate (ORR) and overall survival (OS). Adverse events were evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) 4.03.

Statistical analysis

OS was defined as the interval from the time of diagnosis of the liver metastasis to the time of death or until the date of the last follow-up visit. OS was computed according to the Kaplan-Meier method, and compared by the log-rank test. Multivariate survival analysis was performed according to the Cox proportional hazards model. Statistical analysis was performed via SPSS software version 22.0. A P value less than 0.05 was considered to be statistically significant.

Results

Characteristics of patients

We identified 12,568 patients with breast cancer who had available treatment data from 2003 to 2019. Of these patients, 5,785 received palliative chemotherapy for the treatment of metastatic or recurrent breast cancer at four major cancer centers in China (National Cancer Center, Chinese PLA General Hospital, Beijing Chaoyang Hospital, Beijing Sanhuan Cancer Hospital). Of the 5,785 patients, 961 patients with MBC were excluded due to their unknown ER/PgR/HER2 status. Among the remaining patients,

4,329 patients who were not TNBCs or had incomplete chemotherapy records were excluded from this study. Eighty-two patients were diagnosed with initial LM on the basis of abdominal computed tomographic scans or magnetic resonance imaging scans. LM was confirmed pathologically if necessary. Among these, patients who were not isolated LM and did not receive PBC or CBC as the first-line treatment were excluded. Finally, 59 patients were confirmed eligible and included for the final analysis (*Figure 1*).

Patient demographics at baseline are presented in *Table 1*. In total, 59 eligible patients were included in this study between January 2003 and December 2019. Of these patients, 33 patients were treated with PBC, and 26 were treated with CBC. The median age at diagnosis of the two cohorts was 48 [32–73] years and 52 [28–73] years, respectively. Premenopausal patients were dominant in the two groups. All patients had failed treatment with anthracyclines and taxanes. The majority of patients (66.7% for PBC; 53.8% for CBC) presented with pathological T2 tumors, and more than half (54.6% for PBC; 61.6% for docetaxel) had N0/1 axillary nodes. The median Ki67 expression was 40% in PBC and 50% in CBC. Disease-free interval (DFI) was 21.7 months in patients with PBC, similar with that in CBC (P=0.56). Overall, the two groups were well balanced in baseline characteristics.

Chemotherapy regimens

In the PBC group, 19 (57.6%) patients received platinum agents (carboplatin or cisplatin) combined with taxanes (TP), 9 (27.2%) patients were treated with gemcitabine+platinum (GP), and 5 (15.1%) were treated with vinorelbine+platinum (NP). The main strategies of CBC were taxane-containing regimens (TX, n=18, 65.3%), followed by vinorelbine/capecitabine combinations (NX, n=6, 23.1%), and capecitabine monotherapy (X, n=1, 3.8%). Carboplatin was administered at the area under the curve equal to 5 (AUC =5) on the first day every 3 weeks. Cisplatin was given at a dose of 25 mg/m^2/day on the first 3 days every 3 weeks. Capecitabine was delivered at a dose of 1,250 mg/m2 for the first 2 weeks every 21 days. The treatment strategies in the two cohorts are listed in *Table 2*.

Response and survival

The overall response rate (ORR) was 30.3% (10/33) in the PBC group, including 1 complete response (CR, 3.1%) and 9 partial response (PR, 27.3%); 15(45.5%) patients had stable disease (SD) and 8 (24.2%) experienced progressive disease (PD) during the systematic treatment. In the CBC cohort, ORR was 57.7% (15/26), consisting of 1 (3.8%) CR, 14 (53.8%) PR, 8 (30.8%) SD, and 3 (11.5%) PD. There was a significantly higher response rate in patients who received CBC (57.7%) than that in patients who received PBC (30.3%, P=0.035, *Table 3*).

During the follow-up, 42 patients died and 17 patients remained alive. Median OS in the PBC group was 14.4 months (95% CI, 9.9–18.9 months), which was statistically longer than that in the CBC group (19.2 months, 95% CI, 10.7–27.7 months, P=0.041), as illustrated in *Figure 2*. Multivariate Cox proportional hazards analysis was performed to eliminate confounding variables and to clarify whether CBC alone conferred a survival benefit. Univariate analysis was performed to explore potential prognostic factors; all of the variables with P<0.1 were included in the Cox multivariate analysis (*Table 4*). The results indicated that CBC remained an independent predictor for OS after adjustment for baseline factors including age, tumor size, nodal status, prior anthracycline/taxane use, and tumor grade (OR 0.51; 95% CI, 0.27–0.98; P=0.042, *Table 4*).

Toxicity

Major treatment-related adverse effects (TRAEs) are shown in *Table 5*, mainly including vomiting, neutropenia, leucopenia, hand-foot syndrome, hepatic abnormalities, and fatigue. During the treatment, 93.9% of patients treated with PBC had at least one TRAEs compared with 96.2% of those treated with CBC. Gastrointestinal tract adverse events occurred more frequently and were more severe with PBC than CBC at grade 1/2 (P=0.015) and at grade 3/4 (P=0.045). Hand-foot syndrome was more common in the CBP group especially at grade 3/4 (37.2% *vs.* 18.0%, P=0.037). Neutropenia (75.8% *vs.* 38.5%, P=0.004) and leucopenia (78.8% *vs.* 46.2%, P=0.009) at grade 1/2 also occurred more frequently in the PBC group than in the CBC groups. Incidences of diarrhea, fatigue, and hepatic abnormalities were comparable between the two groups. There were no treatment-related deaths in either group. Generally, both treatment strategies were tolerated and quite manageable.

Discussion

Studies focused on mTNBC indicated that capecitabine-based regimens could prolong the survival time (15-17).

Table 1 Baseline characteristics of patient with metastatic triple-negative breast cancer

Demographic	PBC (n=33)	CBC (n=26)	P
Median age (range), yr	48 [32–73]	52 [28–73]	0.84
Menopausal status, n (%)			0.64
Premenopausal	21 (63.6)	15 (57.7)	
Postmenopausal	12 (36.4)	11 (42.3)	
Prior anthracyclines, n (%)			0.61
Neoadjuvant	7 (21.2)	7 (26.9)	
Adjuvant	26 (78.8)	19 (73.1)	
Prior taxanes, n (%)			0.4
Neoadjuvant	7 (21.2)	8 (30.8)	
Adjuvant	26 (78.8)	18 (69.2)	
TNM staging			
Tumor classification, n (%)			0.49
T1	7 (21.2)	6 (23.1)	
T2	22 (66.7)	14 (53.8)	
T3-4	4 (12.1)	6 (23.1)	
Lymph node classification, n (%)			0.47
N0	9 (27.3)	10 (38.5)	
N1	9 (27.3)	6 (23.1)	
N2	10 (30.3)	4 (15.4)	
N3	5 (15.2)	6 (23.1)	
Histological grade, n (%)			0.85
II	26 (78.8)	21 (80.8)	
III	7 (21.2)	5 (19.2)	
DFI (months, range)	21.7 (2.4–121.2)	18.4 (1.2–90.0)	0.56
Number of metastatic organ, n (%)			0.49
Single	13 (39.4)	8 (30.8)	
Multiple	20 (60.6)	18 (69.2)	
Ki67 (median)[a]	40 [10–90]	50 [25–90]	0.53

[a], some of Ki67 index from local hospital were missing. CBC, carboplatin-based chemotherapy; DFI, disease-free interval defined as the time from operation to first relapse; PBC, platinum-based chemotherapy.

Most recent studies showed that PBC in TNBC patients has promising results in increasing preclinical and clinical trials. The platinum-based regimen has higher ORR and better survival than the platinum-free regimen (8-10). However, study focused on TNBC patients with LM is scarce.

With regard to the present study, we compared the efficacy and safety profile of capecitabine-based regimens with platinum-based regimens in TNBC patients with LM. The result demonstrated that the CBC group achieved higher ORR and longer OS than that in the PBC group, with tolerable adverse events except incidence of hand-foot syndrome. To the best of our knowledge, this is the

Table 2 Chemotherapy regimens

PBC (n=33)	Dose and schedules	n (%)	CBC (n=26)	Dose and schedules	n (%)
Gemcitabine/ Cisplatin	DDP 75 mg/m^2 d1, Gem 1.0 g/m^2 d1, 8, Q21d	8 (24.2)	Vinorelbine/ Capecitabine	Cap 1,000 mg/m^2 d1–14, NVB 25 mg/m^2 d1, 8, Q21d	6 (23.1)
Vinorelbine/ Cisplatin	DDP 75 mg/m^2 d1, NVB 25 mg/m^2 d1, 8, Q21d	4 (12.1)	Gemcitabine/ Capecitabine	Cap 1,000 mg/m^2 d1–14, Gem 1.0 g/m^2 d1, Q21d	1 (3.8)
Gemcitabine/ Carboplatin	CBP AUC 5 d1, Gem 1.0 g/m^2 d1, 8, Q21d	1 (3.0)	Docetaxel/ Capecitabine	Cap 1,000 mg/m^2 d1–14, TXT 75 mg/m^2 d1, Q21d	8 (30.8)
Vinorelbine/ Carboplatin	CBP AUC 5 d1, NVB 25 mg/m^2 d1, 8, Q21d	1 (3.0)	Paclitaxel/ Capecitabine	Cap 1,000 mg/m^2 d1–14, PTX 175 mg/m^2 d1, Q21d	10 (34.5)
Docetaxel/ Cisplatin	DDP 75 mg/m^2 d1, TXT 75 mg/m^2 d1, Q21d	11 (33.3)	Capecitabine	Cap 1,250 mg/m^2 d1–14, Q21d	1 (3.8)
Paclitaxel/ Cisplatin	DDP 75 mg/m^2 d1, PTX 175 mg/m^2 d1, Q21d	2 (6.1)			
Docetaxel/ Carboplatin	CBP AUC 5 d1, TXT 75 mg/m^2 d1, Q21d	3 (9.1)			
Paclitaxel/ Carboplatin	CBP AUC 5 d1, PTX 175 mg/m^2 d1, Q21d	3 (9.1)			

AUC, area under the curve; Cap, capecitabine; CBC, capecitabine-based chemotherapy; CBP, carboplatin; DDP, cisplatin; Gem, gemcitabine; NVB, vinorelbine; PTX, paclitaxel; PBC, platinum-based chemotherapy; TXT, docetaxel.

Table 3 Best tumor response to chemotherapy

Tumor response	PBC (n=33, %)	CBC (n=26, %)
CR	1 (3.1)	1 (3.8)
PR	9 (27.3)	14 (53.8)
SD	15 (45.5)	8 (30.8)
PD	8 (24.2)	3 (11.5)

CBC, capecitabine-based chemotherapy; CR, complete response; PBC, platinum-based chemotherapy; PD, progression disease; PR, partial response; SD, stable disease.

first investigation to compare the role of PBC with CBC in TNBC patients with LM.

Our data showed that the ORR (57.7% *vs.* 30.3%, P=0.035) was higher in the CBC group, and the median OS (19.2 *vs.* 14.4 months, P=0.041) was greatly improved compared with the PBC group. These findings are also consist with most other studies supporting a statistically significant benefit on response rates and median OS from capecitabine in anthracycline- and taxane-pretreated MBC (15-17). Results from several meta-analysis showed that capecitabine could significantly improve the survival both in patients with early and advanced breast cancer (18,19). Capecitabine might prolong OS in patients with ER-negative or HER2-negative breast cancer in the first-line treatment. Moreover, adjuvant capecitabine therapy showed effectiveness in triple-negative subgroup (19).

In our study, we found that capecitabine showed an active efficacy in a liver metastatic setting. This observation was in line with the previous studies (20-27). Findings from the study of colorectal cancer patients with LM indicated that the concentration of 5-FU (precursor of capecitabine) in liver metastasis tissue was higher than normal colorectal tissue and reached about 70% of the number in colorectal tumor tissue (20). Possible explanations might be the higher concentration of 5-Fu in the liver (21,22). The chemotherapy response may be influenced by the distribution of drugs and its concentration in tumor tissues. Capecitabine is an oral chemotherapy drug and is

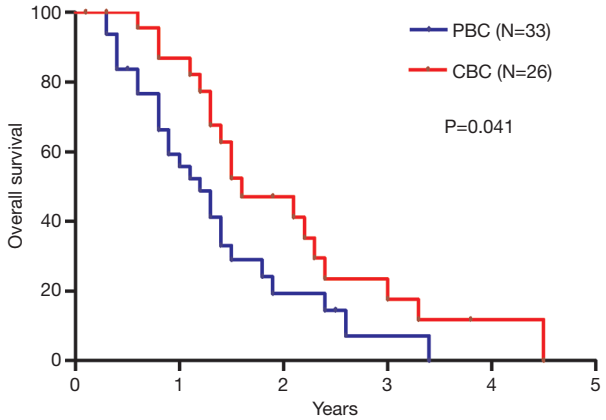

Figure 2 Kaplan-Meier curves of overall survival for patients treated with capecitabine-based chemotherapy (N=26) and platinum-based chemotherapy (N=33).

enzymatically converted into 5-FU in the liver and tumor tissues (23,24). The activity of thymidine phosphorylase (TP) is much higher in normal liver tissues than that in other tissues (25). The benefit of capecitabine-based therapy (CBT) is significantly affected by the activity of TP (26). Another possible explanation might be the maintenance chemotherapy of capecitabine (27). Maintenance chemotherapy refers to the continuous treatment of part of the primary agents in patients after the initial standard treatment, which can significantly prolong the survival time. Capecitabine-based regimens usually ends with the maintenance of capecitabine monotherapy (28,29).

Generally, both strategies were well tolerated and manageable. In the CBC group, the most frequent adverse effects were neutropenia, leucopenia and hand–

Table 4 Univariate and multivariate Cox regression analyses

Variables	Univariate analysis		Multivariate analysis	
	P	HR	P	HR
Age at recurrence, y (≤50 *vs.* >50)	0.4	1.238		
Tumor size, cm (1,2 *vs.* 3,4)	0.42	0.732		
Number of LNM (0,1 *vs.* 2,3)	0.5	0.657		
First-line chemotherapy (CBC *vs.* PBC)	0.05	0.536	0.042*	0.514
Tumor grade (II *vs.* III)	0.38	0.756		
Prior anthracyclines (yes *vs.* no)	0.46	0.733		
Prior taxanes (yes *vs.* no)	0.21	0.593		
Number of metastatic organs (single *vs.* multiple)	0.065	0.537	0.056	

*, P values <0.05. CBC, capecitabine-based chemotherapy; LNM, lymph node metastases; HR, hazard ratio; PBC, platinum-based chemotherapy.

Table 5 Percent frequency of selected treatment-related adverse events

Toxicity	PBC (n=33), No. (%)		CBC (n=26), No. (%)		P (grade 1–2)	P (grade 3–4)
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4		
Vomiting	18 (54.5)	10 (30.3)	6 (23.1)	2 (7.7)	0.015*	0.045*
Neutropenia	25 (75.8)	7 (21.2)	10 (38.5)	4 (15.4)	0.004*	0.57
Hand–foot syndrome	0	0	15 (57.7)	2 (7.7)	<0.001*	<0.001*
Leucopenia	26 (78.8)	6 (18.2)	12 (46.2)	2 (7.7)	0.009*	0.43
Fatigue	11 (33.3)	0	9 (34.6)	0	0.92	NA
Hepatic abnormalities	5 (16.0)	2 (8.0)	5 (20.1)	1 (4.7)	0.68	0.7

*, indicates statistically significant. CBC, capecitabine-based chemotherapy; PBC, platinum-based chemotherapy; NA, not applicable.

foot syndrome. In the PBC group, the incidence of gastrointestinal, leukopenia, and neutropenia adverse events was more common than that of CBC. These results are in line with the previous studies (30-33).

Although the treatment option for breast cancer LM is palliative, different local treatment modalities, such as surgery and stereotactic body radiotherapy (SBRT), have been applied together with systemic chemotherapeutic agents in order to improve outcomes (34,35).

For breast cancer patients with LM receiving metastasectomy, the median 3-, and 5-year survival rates range between 49–94% and 5–78%, respectively (36-39). Findings from a case-matched analysis showed that liver resection combined with systemic treatment resulted in improved OS compared to systemic treatment alone. Median OS of the resection group was 82 months with a 3- and 5-year OS of 81% and 69%, respectively, compared with a median OS of 31 months in the systemic group with a 3- and 5-year OS of 32% and 24%, respectively (40). A systematic review (41) analyzed 956 patients receiving resection of breast cancer LM. The median 3-, and 5-year survival were 52.9% and 33% respectively. Despite some promising reports, surgical resection of BCLM is still controversial because of its invasiveness. In addition, many patients develop unpredictable recurrent disease (42).

SBRT offers an alternative, non-invasive approach for LM, with highly conformal doses delivered to tumor sites and a steep dose gradient, which allows normal liver tissues to be spared. Retrospective and prospective studies have demonstrated the feasibility of SBRT for LM with local control rates ranging from 60–90% at 2 years after treatment (43,44). Findings from a recent study revealed that SBRT might be an effective and safe treatment option in selected breast cancer patients with LM (45). Another study reported that the median OS after SBRT of breast patients with LM was 21 months (46). The patient selection criteria, and optimal dose and fractionation for liver SBRT are still under investigation. Several clinical trials evaluating SBRT on patients with limited MBC are on-going. An on-going randomized phase II/III trial (NCT02364557) studies how well standard of care therapy with stereotactic radiosurgery and/or surgery works and compares it to the standard of care therapy alone in treating patients with breast cancer that has spread to one or two locations in the body (limited metastatic) that are previously untreated. Another phase II/III multi-center randomized randomised controlled trial (The CORE study, NCT02759783) in patients with breast, prostate or non-small cell lung cancer (NSCLC) primary cancer is comparing standard of care with or without SBRT for extra-cranial metastases, and will help to clarify whether SBRT is a viable therapeutic approach for breast cancer metastases.

Our study should be considered in the context of its limitations. First, this was a retrospective study and the sample size was relatively small. Second, TNBC is a heterogeneous disease and treatment response to chemotherapy might vary between basal and non-basal breast cancer. In spite of its limitations, this study provided clinical reference that capecitabine is considerably effective in TNBC with LM, and capecitabine, rather than platinum, might be a better choice in first-line chemotherapy for TNBC patients with LM, if not contraindicated.

In conclusion, our study indicates that CBC, with its acceptable toxicity profile, might be used as an effective alternative treatment in patients with TNBC LM. In the future, studies involving larger number of patients are needed, and more clinical trials could perhaps be carried out.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

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