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Anlotinib in combination with metronomic chemotherapy in HER2-negative metastatic breast cancer: an observational and retrospective study

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Abstract

Anti-angiogenesis offers an important treatment strategy for metastatic breast cancer (MBC). Metronomic chemotherapy (MCT) provides antiangiogenic effects without increased toxicities, making it good partner for antiangiogenic therapy. We conducted the present retrospective study to evaluate the efficacy and safety of anlotinib plus MCT for HER2 negative MBC. Patients with HER2 negative MBC who received metronomic chemotherapy (Vinorelbine (NVB), Capecitabine (CAPE), Etoposide (VP-16)) with anlotinib were retrospectively analyzed from Jan 2019 to Dec 2021. The primary end point was progression free survival (PFS). Secondary end points included objective response rate (ORR), disease control rate (DCR), overall survival (OS) and safety. 48 patients with HER2 negative MBC were enrolled. 19 (39.6%) patients received NVB, 17 (35.4%) patients received CAPE and 12 (25.0%) patients received VP-16. The overall ORR and DCR were 8.3% (4/48) and 87.5% (42/48) respectively. The median PFS was 5.6 months (95% CI 4.3-7.0 months), and the median OS was 25.2 months (95% CI 20.2-30.1 months). The patients with age ≥ 50 (5.3 vs. 7.7 months, $P=0.014$, HR = 0.407) and pathologic grade 1 or 2 (6.2 vs. 3.2 months, $P=0.023$, HR = 2.471) had significantly longer PFS. The patients with hormone receptor (HR) positive (5.3 vs. 7.7 months, $P=0.004$, HR = 0.206) and pathologic grade 1 or 2 (6.2 vs. 3.2 months, $P=0.020$, HR = 3.882) had significantly longer OS. The incidence of all grades adverse events (AEs) was 56.3% (27/48) and grade 3–4 AEs was 12.5% (6/48). Within the context of real-world clinical practice, anlotinib in combination with metronomic chemotherapy provides a well-tolerated and effective treatment option for HER2-negative MBC, which warrants further investigation in the future.

Keywords Metastatic breast cancer, Anlotinib, Metronomic chemotherapy, Anti-angiogenesis, Safety

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Introduction

Neo-angiogenesis is one of the typical hallmarks of cancer, crucial for tumor growth, invasion, and metastasis. Anti-angiogenic therapies have emerged as a critical strategy for treating various metastatic cancer [1], such as colorectal cancer, lung cancer, and gastric cancer [2, 3]. However, the efficacy of anti-angiogenic therapies in metastatic breast cancer (MBC) remains unclear [4, 5]. Studies have shown that bevacizumab can improve progression-free survival (PFS), but its impact on overall survival (OS) is still controversial [6, 7]. The advent of small-molecule tyrosine kinase inhibitors (TKIs) has marked a significant advancement in oncology, offering promising therapeutic outcomes for a spectrum of malignancies. Anlotinib, an active inhibitor for vascular endothelial growth factor receptor (VEGFR) 1–3, platelet-derived growth factor receptor (PDGFR) 1–4, fibroblast growth factor receptor (FGFR) 1–4 and c-Kit, had shown therapeutic effects in various solid tumors [8, 9]. A phase II study has previously demonstrated the objective efficacy and tolerable toxicity of anlotinib monotherapy in heavily pretreated, human epidermal growth factor receptor 2 (HER2)-negative MBC [10]. Anlotinb in combination with chemotherapy could significantly enhance the tumor response rate according to another retrospective study [11].

Metronomic chemotherapy (MCT), first proposed by Hanahan and Kerbel, utilizes a continuous low-dose chemotherapy regimen to suppress tumor angiogenesis [12, 13]. As its demonstrated potential of MCT in breast cancer by evidence of efficacy and tolerability, recent international guidelines have endorsed MCT as a viable treatment option for MBC [14, 15]. An innovative therapeutic approach involves the combination of MCT with VEGF inhibitors to augment antiangiogenic effects. Preclinical studies suggested that the synergistic use of continuous low-dose topotecan combined with TKIs showed therapeutic advantages, particularly for metastatic triple-negative breast cancer (TNBC) [16]. Furthermore, the combination of MCT with bevacizumab has yielded promising results in MBC management, with a modest increase in treatment-related adverse event [17–19].

This study aims to investigate the therapeutic efficacy and safety of anlotinib in combination with MCT in the treatment of HER2-negative MBC patients within the context of real-world clinical practice, seeks to provide a new treatment option for MBC patients.

Patients and methods

Patients

From Jan 2019 to Dec 2021, HER2-negative MBC patients who received metronomic chemotherapy combined with anlotinib in Peking University Cancer Hospital and National Cancer Center were screened. The main inclusion criteria: (1) Patients with pathological confirmed of metastatic breast cancer and progressed after first line chemotherapy or endocrine therapy. (2) Whether the biopsy of the metastatic sites or the primary tumor was HER2- (estrogen receptor (ER) and/or progesterone receptor (PR) positivity was defined as ≥1% and HER2 positivity was defined as immunohistochemical score of 3+or fluorescence in situ hybridization (FISH) (+) (according to ASCO/CAP 2013 Guidelines). (3) Received anlotinib and metronomic chemotherapy, including Capecitabine (CAPE), Vinorelbine (NVB), Etoposide (VP-16), with dose escalation or discontinuation permitted due to poor tolerability. (4) patients undergo at least one physician's directed clinical evaluation after administration of the drug, including physical examination, ultrasonography, computed tomography, and magnetic resonance imaging. The main exclusion criteria included: (1) The patients had no efficacy evaluation. (2) Patients were lost to follow-up before disease progression.

Study design

This is a real-world study. In this study, patients received anlotinib 10 mg orally once daily on day 1 to 14 every 3 weeks and metronomic chemotherapy with NVB 40–50 mg 3 times per week, CAPE 1000 mg twice daily or 500 mg three times a day, VP-16 25–50 mg day 1 to 14 every three weeks until disease progression, intolerable toxicity or death.

Efficacy and safety assessment

All patients underwent imaging examinations every 2–3 months after treatment to evaluate clinical efficacy. The efficacy was evaluated according to Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 [20]. The efficacy assessment is divided into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The objective response rate (ORR) is the sum of the proportions in CR and PR. The disease control rate (DCR) is sum of the CR, PR and SD. PFS is defined as the time interval from the start of first-line chemotherapy to cancer progression, mortality from any cause. OS refers to the time from the start of randomization to death from any cause. The toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Follow-up is made based on the patients' medical history, including but not limited to the date of the last outpatient visit, the date of hospitalization, and the date of laboratory examination at our center. Telephone follow-up was performed for patients who had not seen a doctor for more than 6 months. The follow-up deadline is April 15, 2023.

Statistical analysis

The patients' characteristics was summarized with descriptive statistics. ORR and DCR among different groups were compared by Pearson's chi squared test or Fisher's exact test. Survival curves of patients were estimated by the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards model was used to verify the factors significantly related to PFS and OS. Variables with P-values less than 0.05 in univariate analyses were included in multivariate Cox models to identify independent prognostic factors. A value of two-tailed $P<0.05$ was defined as statistically significant difference. Statistical analysis was performed using SPSS 22.0 software (SPSS Inc., IL, US).

Results

Clinicopathological characteristics

48 patients with HER2-negative MBC who received anlotinib plus metronomic chemotherapy were included. 19 (39.6%) patients received NVB, 17 (35.4%) patients received CAPE and 12 (25.0%) patients received VP-16. The median age was 50 years (range 25–70) old. In total, hormone receptor (HR) positive patients accounted for 56.3% (27/48) and 43.8% (21/48) patients were TNBC. Most of the patients had serious metastasis and was heavily treated. 39 (81.3%) patients had visceral metastasis and 18 (37.5%) had more than 2 metastatic sites. 33 (67.8%) had received more than 1-line previous chemotherapy. The clinicopathological characteristics are summarized in Table 1.

Response rate

In this study, no patients achieved a CR, with 4 (8.3%) patients achieved PR, 38 (79.2%) patients reached SD and 6 (12.5%) patients reached PD. The ORR and DCR were 8.3% (4/48) and 87.5% (42/48) respectively (Table 2). Then we analyzed the differences in ORR and DCR with respect to age (< 50 vs. ≥ 50), HR status (positive vs. negative), pathologic grade (1–2 vs. 3), visceral metastasis (visceral vs. non-visceral), number of metastatic sites (1–2 vs. ≥ 3), prior anti-angiogenesis after metastasis (Yes vs. No), lines of chemotherapy after metastasis (< 3 vs. ≥ 3), lines of systematic treatment after metastasis (< 4 vs. ≥ 4) and metronomic chemotherapy regimen (NVB vs. CAPE vs. VP-16). The patients with lines of chemotherapy after metastasis < 3 had higher DCR than those with lines of chemotherapy after metastasis ≥ 3 (96.7% vs. 72.2%, $P=0.022$), but the difference in ORR between the two groups was not statistically significant (10.0% vs. 5.6%, $P=1.000$) (Table 2).

PFS and OS and prognostic factors for PFS and OS

With the median follow-up of 22.8 months (3.2–51.0 months) until April 15, 2023, all of 48 patients progressed, 20 patients died due to tumor progression. The median PFS was 5.6 months (95% CI 4.3-7.0 months), and the median OS was 25.2 months (95% CI 20.2–30.1 months), respectively. In the univariate analysis, the patients with age ≥ 50, pathologic grade 1 or 2, visceral metastasis or metronomic chemotherapy regimen with CAPE had significantly longer PFS ($P=0.009$, $P=0.039$, $P=0.020$ and $P=0.014$, respectively) (Fig. 1A, B, C and D). The patients with HR-positive or pathologic grade 1 or 2 had significantly longer OS ($P=0.003$ and $P=0.006$) (Fig. 2A and B).

Then we analyzed these factors in the Cox regression analysis. The patients with age ≥ 50 (5.3 vs. 7.7 months, $P=0.014$, HR = 0.407) and pathologic grade 1 or 2 (6.2 vs. 3.2 months, $P=0.023$, HR = 2.471) had significantly longer PFS. The patients with HR-positive (5.3 vs. 7.7 months, $P=0.004$, HR = 0.206) and pathologic grade 1 or 2 (6.2 vs. 3.2 months, $P=0.020$, HR = 3.882) had significantly longer OS.

Safety

The incidence of adverse events (AEs) upon treatment was summarized in Table 3. The most common AEs of any grade were secondary hypertension (18/48, 37.5%), hand-foot syndrome (8/48, 16.7%), leukopenia (7/48, 14.6%), neutropenia (7/48, 14.6%), anemia (7/48, 14.6%), elevated liver enzymes (6/48, 12.5%), thrombocytopenia (5/48, 10.4%), nausea or vomiting (3/48, 6.3%), diarrhea (1/48, 2.1%), proteinuria (1/48, 2.1%). The most common grade 3–4 AEs were secondary hypertension (5/48, 10.4%).

8 (16.7%) of the 48 patients had dose reduction due to secondary hypertension induced by anlotinib. The reasons for drug discontinuation or temporary interruption were hand-foot syndrome (1/48, 2.1%), neutropenia (1/48, 2.1%) and anemia (1/48, 2.1%). The three groups with different metronomic chemotherapy regimen had same AE profiles, while the group with CAPE had higher hand-foot syndrome (7/19, 36.8%).

Discussion

Plenty of clinical trials have confirmed the therapeutic efficacy of anti-angiogenic agents including bevacizumab and small-molecule TKIs in various solid tumors [21]. Anlotinib exerts its effects by inhibiting various pathways involving VEGFR/FGFR/PDFGR to hinder tumor angiogenesis, while also inhibit cell proliferation and metastasis. In recent years, its application in MBC has been widely studied. A single-arm, perspective phase II study firstly explored the efficacy and safety of anlotinib monotherapy in the treatment of heavily pre-treated, HER2-negative MBC. It reported that anlotinib monotherapy achieved an ORR of 15.4%, a DCR of 80.8%, and a median PFS of 5.22 months (95%CI, 2.86–6.24) in HER2-negative MBC patients who had failed treatment after at least one

Table 1 Clinicopathologic characteristics of patients

Characteristics	*n*(%)	CAPE (*n* = 19)	NVB (*n* = 17)	VP-16 (*n* = 12)	*P*
Age median(range)	50 (27–74)	48 (32–74)	50 (27–74)	52 (44–68)	
Histology					
IDC	46 (95.8)	18 (94.7)	17 (100.0)	11 (91.7)	0.714*
ILC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Others	2 (4.2)	1 (5.3)	0 (0.0)	1 (8.3)	
Grade					
1 or 2	35 (72.9)	14 (73.7)	13 (76.5)	8 (66.7)	0.027*
3	9 (18.8)	1 (5.3)	4 (23.5)	4 (33.3)	
Unknown	4 (8.3)	4 (21.1)	0 (0.0)	0 (0.0)	
HR					
Negative	21(43.8)	3 (15.8)	8(47.1)	10(83.3)	0.001
Positive	27(56.3)	16(84.2)	9(52.9)	2 (16.7)	
De novo stage IV breast cancer					
No	38 (79.2)	17(89.5)	12(70.6)	9(75.0)	0.325*
Yes	10 (20.8)	2 (10.5)	5 (29.4)	3(25.0)	
DFS					
≤ 60moths	26 (68.4)	10(58.8)	9(75.0)	7(77.8)	0.552*
>60moths	12 (31.6)	7 (41.2)	3(25.0)	2(22.2)	
Visceral metastasis					
No	9 (18.8)	3 (15.8)	3 (17.6)	3(25.0)	0.806*
Yes	39 (81.3)	16(84.2)	14(82.4)	9(75.0)	
Number of sites of metastasis					
< 3	30 (62.5)	11(57.9)	12(70.6)	7(58.3)	0.746*
≥ 3	18 (37.5)	8 (42.1)	5 (29.4)	5(41.7)	
Prior chemotherapy after metastasis					
Taxanes	36 (75.0)	15(78.9)	14(82.4)	7(58.3)	0.369*
Anthracyclines	10 (20.8)	7(36.8)	1(5.9)	2(16.7)	0.079*
CAPE/NVB/Gem	28 (58.3)	12(63.2)	9(52.9)	7(58.3)	0.825
Platinum	13 (27.1)	7(36.8)	4(23.5)	2(16.7)	0.503*
Others	12 (25.0)	2(10.5)	4(23.5)	6(50.0)	0.064*
Prior endocrine therapy after metastasis					
No CDK4/6i	36 (75.0)	11(57.9)	14(82.4)	11 (91.7)	0.095*
CDK4/6i	12 (25.0)	8 (42.1)	3 (17.6)	1(8.3)	
Prior anti-angiogenesis after metastasis					
No	38 (79.2)	16(84.2)	13 (76.5)	9(75.0)	0.738*
Yes	10 (20.8)	3 (15.8)	4 (23.5)	3(25.0)	
Lines of chemotherapy after metastasis					
1st line	15 (31.3)	6(31.6)	4 (23.5)	5(41.7)	0.354*
2nd line	15 (31.3)	7(36.8)	7(41.2)	1 (8.3)	
>2nd line	18 (37.5)	6(31.6)	6(35.3)	6(50.0)	
Lines of endocrine therapy after metastasis					
1st line	10 (38.5)	6 (40.0)	3(33.3)	1(50.0)	0.934*
2nd line	9 (34.6)	5(33.3)	4 (44.4)	0 (0.0)	
>2nd line	7 (26.9)	4(26.7)	2(22.2)	1 (50.0)	
Lines of systematic treatment after metastasis					
< 4	25 (52.1)	8 (42.1)	9(52.9)	8 (66.7)	0.410
≥ 4	23 (47.9)	11(57.9)	8(47.1)	4 (33.3)	

Note: NVB: Vinorelbine; CAPE: Capecitabine; VP-16: Etoposide

prior chemotherapy regimen [10]. Retrospective studies demonstrated the therapeutic potential of anlotinib monotherapy or combination therapy in later-line treatment of MBC patients in China [11, 22]. In particular, the combination therapy achieved better clinical and survival outcomes. A real-word study reported the combination of anlotinib with chemotherapy obtained a median PFS of 5.0 months (95%CI, 4.0–6.0) [22]. Another recent

Table 2 Efficacy of anlotinib combined with MCT in HER2-negative MBC patients

Parameter	ORR	*P*	DCR	*P*	Median PFS (95%CI) (months)	*P*	Median OS (95%CI) (months)	*P*
Total	8.3%		87.5%		5.6 (4.3-7.0)		25.2 (20.2–30.1)	
Age								
< 50	12.0%	0.610*	88.0%	1.000*	5.3 (4.0-6.5)	0.009	19.3 (14.2–24.5)	0.302
≥ 50	4.3%		87.0%		7.7 (4.5–10.7)		24.0 (23.8–28.1)	
HR								
Negative	0.0%	0.121*	81.0%	0.383*	4.2 (2.5-6.0)	0.194	18.5 (13.6–23.4)	0.003
Positive	14.8%		92.6%		7.0 (3.8–10.1)		-	
Pathological grade								
1 or 2	11.4%	0.566*	85.7%	1.000*	6.2 (4.5-8.0)	0.039	26.0 (19.0-32.9)	0.006
3	0.0%		88.9%		3.2 (2.6–3.8)		10.8 (7.0-14.6)	
Visceral metastasis								
No	0.0%	1.000*	77.8%	0.312*	4.2 (2.7–5.8)	0.020	18.7 (8.8–28.6)	0.481
Yes	10.3%		89.7%		7.0 (4.0-9.9)		25.2 (19.1–31.2)	
Number of sites of metastasis								
< 3	6.7%	0.624*	93.3%	0.179*	5.9 (4.3–7.5)	0.623	22.7 (17.7–27.7)	0.593
≥ 3	11.1%		77.8%		5.5 (4.2–6.7)		26.0 (15.1–36.8)	
Prior anti-angiogenesis after metastasis								
No	7.9%	1.000*	86.8%	1.000*	6.2 (4.2–8.2)	0.122	25.2 (19.1–31.2)	0.214
Yes	10.0%		90.0%		3.5 (1.9-5.0)		18.5 (9.8–27.1)	
Lines of chemotherapy after metastasis								
< 3	10.0%	1.000*	96.7%	0.022*	5.9 (2.4–9.4)	0.678	25.2 (16.4–33.9)	0.469
≥ 3	5.6%		72.2%		5.5 (4.2–6.7)		19.4 (15.5–23.3)	
Lines of systematic treatment after metastasis								
< 4	0.0%	0.046*	88.0%	1.000*	5.3 (3.0-7.5)	0.931	19.4 (14.6–24.1)	0.093
≥ 4	17.4%		87.0%		6.0 (4.8–7.2)		-	
Metronomic chemotherapy regimen								
CAPE	10.5%	0.661*	94.7%	0.304*	8.4 (4.1–12.8)	0.014	-	0.079
NVB	11.8%		88.2%		3.5 (2.9-4.0)		19.4 (5.4–33.3)	
VP-16	0.0%		75.0%		4.4 (2.4–6.5)		18.7 (13.1–24.3)	

Note: ORR: objective response rate; DCR: disease control rate; OS: overall survival; HR: hormone receptor; NVB: Vinorelbine; CAPE: Capecitabine; VP-16: Etoposide; *: Fisher exact test

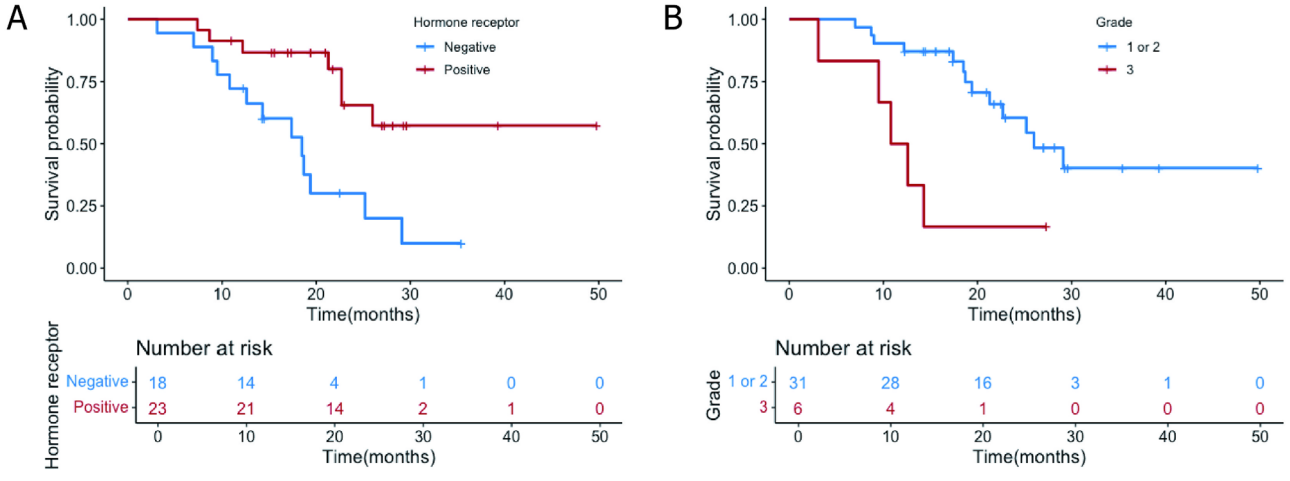

Fig. 1 Kaplan–Meier analysis of progression-free survival (PFS). 1 **A**. The PFS in different age groups. **1**B. The PFS in different Grade groups. **1** C. The PFS in visceral metastasis groups. 1D. The PFS in different MCT regimens groups

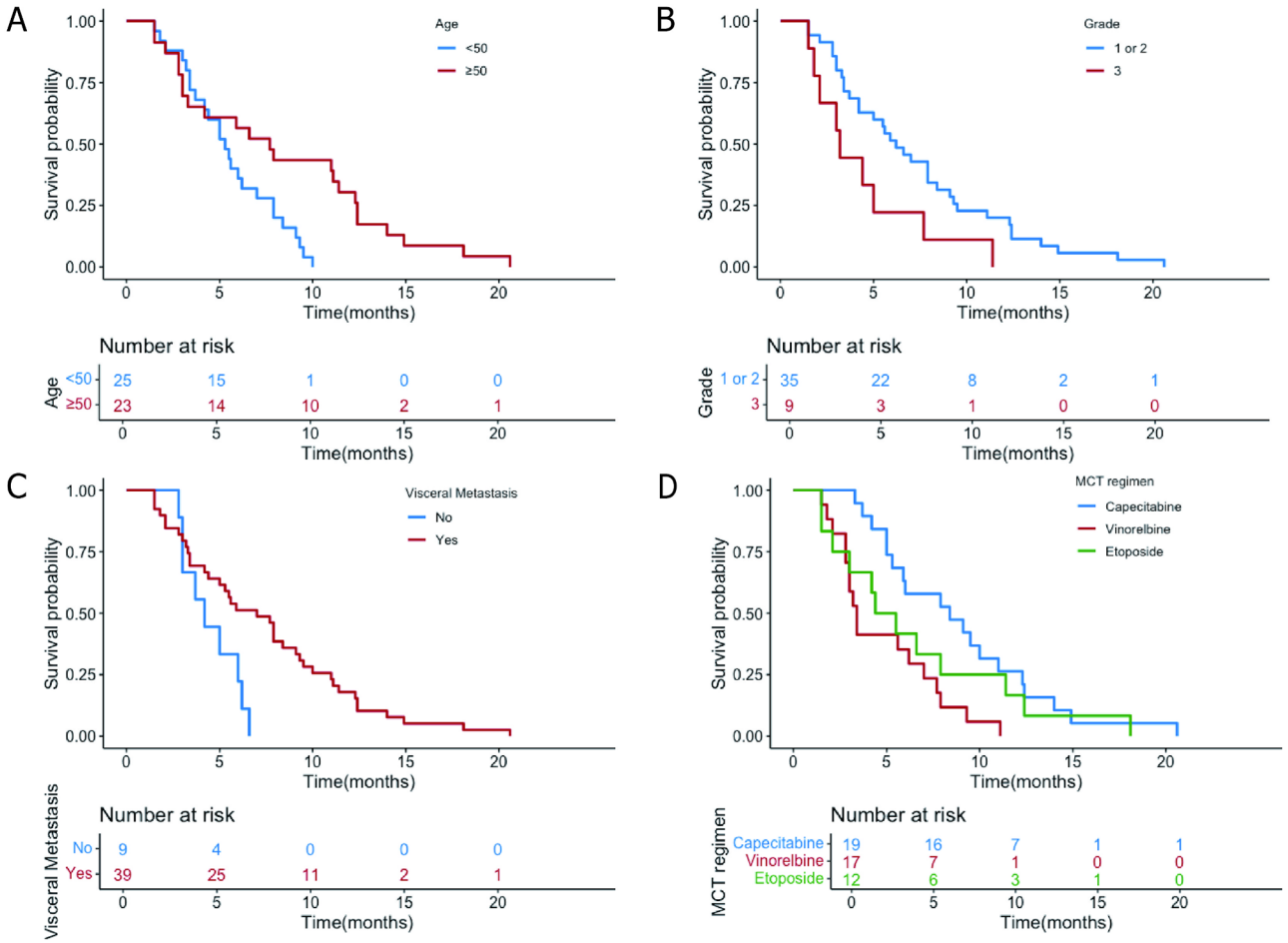

Fig. 2 Kaplan–Meier analysis of overall survival (OS). 2 **A**. The OS in groups with different hormone receptor status. 2**B**. The OS in groups with different grades

Table 3 Treatment-related adverse events

Treatment regimen	***n*** **= 48**		**CAPE (*n* = 19)**		**NVB (*n* = 17)**		**VP-16 (*n* = 12)**	
Adverse Events	All Grade (n, %)	≥ Grade3 (n, %)	All Grade (n, %)	≥ Grade3 (n, %)	All Grade (n, %)	≥ Grade3 (n, %)	All Grade (n, %)	≥ Grade3 (n, %)
Non-hematologic								
Secondary hypertension	18(37.5)	5(10.4)	8 (42.1)	2 (10.5)	7(41.2)	2(11.8)	3(25.0)	1(8.3)
Hand-foot syndrome	8(16.7)	1(2.1)	7 (36.8)	1 (5.3)	1 (5.9)	0	0	0
Proteinuria	1(2.1)	0	0	0	1 (5.9)	0	0	0
Nausea or Vomiting	3(6.3)	0	1 (5.3)	0	2(11.8)	0	0	0
Diarrhea	1(2.1)	0	0	0	1 (5.9)	0	0	0
Hematologic								
Leukopenia	7(14.6)	1(2.1)	2 (10.5)	0	3 (17.6)	1 (5.9)	2(16.7)	0
Neutropenia	7(14.6)	1(2.1)	2 (10.5)	0	3 (17.6)	1 (5.9)	2(16.7)	0
Anaemia	7(14.6)	1(2.1)	1 (5.3)	0	3 (17.6)	0	3(25.0)	1(8.3)
Thrombocytopenia	5(10.4)	0	1 (5.3)	0	1 (5.9)	0	3(25.0)	0
Elevated liver enzymes	6(12.5)	0	1 (5.3)	0	2(11.8)	0	3(25.0)	0

Note: NVB: Vinorelbine; CAPE: Capecitabine; VP-16: Etoposide

study retrospectively analyzed the efficacy and safety of anlotinib-contained therapy in patients with MBC. The combination of anlotinib with chemotherapy had the best clinical effect (DCR: 79.3%) in MBC patients and achieved a promising median PFS of 7.83 months (95% CI, 2.416–9.104) in HER2-negative MBC patients [11]. Recent findings suggest that the combination of anlotinib with eribulin may be a promising therapeutic option for

HER2-negative locally recurrent or metastatic breast cancer. In particular, for HER2-negative patients who had previously received anthracycline or paclitaxel-based chemotherapy, the combination regimen could significantly improve median PFS to 5.1 months (*versus* 3.5 months, $p=0.04$) compared to eribulin alone, with common adverse effects mainly related to chemotherapy [23]. Overall, anlotinib combined with chemotherapy has demonstrated promising efficacy and survival benefits in heavily pre-treated patients with HER2-negative MBC. However, the increased risk of adverse effects remains a clinical challenge.

The concept of MCT was initially introduced in 2000, involving the continuous use of very low-dose chemotherapeutic agents with no prolonged drug-free period, which is noted for its safety profile. It works through multiple mechanisms, including cytotoxic effects, immunomodulation, angiogenesis inhibition, and tumor stroma regulation. These mechanisms make MCT suitable for combination with antiangiogenic agents. The previous study showed that the combination of MCT (CTX, 50 mg once daily and CAPE, 500 mg thrice daily) and bevacizumab (10 mg/kg every 2 weeks) had CBR 68% and mTTP 10.5 months with minimal toxicity [24]. A multicenter, randomized phase III study compared the efficacy and safety of bevacizumab (10 mg/kg every 2 weeks) in combination with either paclitaxel (90 mg/ m^2 on days 1, 8, and 15 every 4 weeks) or metronomic chemotherapy of CTX (50 mg once daily) and CAPE (500 mg thrice daily) in HER2-negative MBC in first-line setting. The DCR was 79% in the paclitaxel group versus 64% in the MCT group, with median PFS of 10.3 months and 8.5 months, respectively ($p=0.83$). The MCT group experienced significantly less hair loss and numbness, and treatment costs were similar [17]. Montagna et al. evaluated the efficacy and safety of metronomic CTX (50 mg once daily) and CAPE (500 mg thrice daily) combined with bevacizumab and anlotinib in 26 primary HER2-negative MBC patients. Among 24 evaluable patients, the CBR was 75% and the mTTP was 10.8 months. Toxicity was generally mild with rare grade 3–4 toxicities [25]. In another phase I study, 23 pretreated MBC patients received treatment of vandetanib combined with metronomic CTX (50 mg once daily) and MTX (2.5 mg twice daily on day 1 and 2 every week), which showed modest clinical efficacy with a CBR of 25% and frequent grade 3–4 adverse events [26].

In our study, the combination of anlotinib with metronomic chemotherapy achieved an ORR of 8.3% (4/48) and a DCR of 87.5% (42/48). The median PFS was 5.6 months (95% CI: 4.3–7.0 months), and the median OS was 25.2 months (95% CI: 20.2–30.1 months). These results suggest that anlotinib combined with MCT shows potential efficacy in patients with HER2-negative MBC, comparable to previous studies. We noticed the ORR we obtained was lower than the ORR, but we think the results were still clinically meaningful. For breast cancer patients with metastatic disease, treatment priorities have shifted toward reducing side effects, improving quality of life, and prolonging survival while maintaining therapeutic efficacy. The combination of regimens of anti-angiogenic therapy and MCT were all orally administrated being more convenient for patients, the higher DCR and promising survival outcomes provides them a sustained and effective treatment option in later-line treatment. We also compared the efficacy of anlotinib combined with different MCT regimens. Patients who received anlotinib plus metronomic CAPE, NVB, and Vp-16 achieved a median PFS of 8.4 months (95%CI, 4.1–12.8 months), 3.5 months (95%CI, 2.9-4.0 months) and 4.4 months (95%CI, 2.4–6.5 months), respectively. MCT regimen with CAPE showed significantly longer median PFS in univariate analysis, though this was not confirmed in Cox regression analysis. A retrospective study by Cazzaniga et al. reported median PFS of 7.2 months, 10.7 months, and 4.4 months for metronomic VRL, CAPE, and CTX monotherapy, respectively [27]. Based on these findings, anti-angiogenic therapy combined with metronomic capecitabine appears to achieve better survival outcomes. However, evidence-based data remain insufficient, and larger studies are needed to determine the optimal drug and dosing schedule in the future.

Endocrine therapy remains the first choice for HR-positive MBC, the addition of targeted agents such as CDK4/6 inhibitors has significantly improved patient outcomes and prognosis [28–30]. However, patients who progress after endocrine therapy still require chemotherapy with limited available options currently. In our study, 25 h-positive MBC patients received the treatment of anlotinib and MCT. While there was no significant difference in ORR and DCR between HR-positive and HR-negative groups, the median PFS for the HR-positive group was 6.5 months, significantly longer than 4.2 months in the HR-negative group. These findings suggest that anlotinib combined with MCT provides an effective, convenient, and affordable later-line treatment option for HR-positive MBC patients after endocrine resistance.

The most common adverse events of anti-angiogenic drugs are secondary hypertension, proteinuria, and hand-foot syndrome. Usually, most of these toxicities can be mitigated by dose adjustments and discontinuation. In this study, the majority of patients had grade 1–2 adverse events related to anlotinib. The incidence and severity of secondary hypertension, proteinuria, and hand-foot syndrome are consistent with previous relevant clinical trials [31]. No increased chemotherapy-related adverse events have been reported. These findings suggest the well-tolerated toxicity of the combined anti-angiogenic therapy and MCT, which are expected to improve treatment

compliance and quality of life in patients with metastatic disease.

We acknowledge limitations in the present study. Firstly, the sample size was small, thus limits the generalizability of the findings. Secondly, it is an observational and exploratory retrospective study, which limits its evidence level. Thirdly, it is a single-arm study and lacks control over treatment variables. It is difficult to isolate the effects of the combination therapy and potentially introduces bias. The findings of this study were only preliminary confirmation of the feasibility and safety of combination of anti-angiogenesis drugs and MCT. Further large-scale, retrospective or prospective clinical trials with comparative arm of MCT are warrants in the future to validate the results of this study. It will bring higher level evidence-based medical evidence if randomized controlled clinical trials could be carried out in the future.

Conclusion

Within the context of real-world clinical practice, anlotinib in combination with metronomic chemotherapy including Vinorelbine, Capecitabine, and Etoposide, achieved potential efficacy and well-tolerated toxicity for the treatment of patients with HER2-negative MBC. Our findings suggest anti-angiogenic therapy combined with metronomic chemotherapy provide an alternative treatment strategy and was effective, convenient, and affordable. This combination therapy warrants further validation in the future.

Abbreviations

AEs	Adverse events
CAPE	Capecitabine
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete response
DCR	Disease control rate
ER	Estrogen receptor
VP-16	Etoposide
FGFR	Fibroblast growth factor receptor
FISH	Fluorescence in situ hybridization
HR	Hormone receptor
HER2	Human epidermal growth factor receptor 2
MBC	Metastatic breast cancer
MCT	Metronomic chemotherapy
ORR	Objective response rate
OS	Overall survival
PR	Partial response
PDGFR	Platelet-derived growth factor receptor
PR	Progesterone receptor
PFS	Progression-free survival
PD	Progressive disease
RECIST	Response Evaluation Criteria in Solid Tumor
SD	Stable disease
TNBC	Triple-negative breast cancer
TKIs	Tyrosine kinase inhibitors
VEGFR	Vascular endothelial growth factor receptor
NVB	Vinorelbine

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Author contributions

B.S., Q.L., and H.P.L. planned the research; B.S., Q.L., J.X.L., G.H.S., L.J.D., H.F.J., Y.Y., H.W., J.W. and X.R.L. collected and organized the patient data; B.S., Q.L. and J.X.L.analyzed the data; B.S., Q.L. and J.X.L. wrote the paper. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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Data availability

The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Peking University Cancer Hospital ethical committee (No. 2021YJZ98) in accordance with the Declaration of Helsinki. All patients voluntarily participated and provided written informed consent.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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