Apatinib beyond first progression is associated with prolonged overall survival in patients with advanced breast cancer: Results from an observational study

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Abstract. In the present study, the efficacy and safety of a low dose of apatinib in the treatment of patients with advanced breast cancer (ABC) in a real-world setting were assessed, the impact of continuous anti-angiogenic therapy beyond progression was determined and the factors associated with efficacy were evaluated. A total of 63 patients with ABC who were treated with apatinib and for whom several lines of treatment had failed were retrospectively analyzed in Tangshan People's Hospital (Tangshan, China) between January 2016 and October 2022. Apatinib was administered orally combined with chemotherapy, endocrine therapy, targeted therapy or monotherapy at a dose of 250 mg per day. Apatinib administration was continued in certain patients beyond first progressive disease (PD), and these patients were defined as the continued anti-angiogenic treatment beyond first progression (CABF) group, while those who discontinued apatinib were defined as the non-CABF group. In the evaluation of the first efficacy, the objective response rate was 33.3%. A total of 26 patients continued to receive apatinib post-first PD and were allocated to the CABF group. The median overall survival (OS) time of the 63 patients was 16 months. Log-rank univariate analysis revealed that the OS time was significantly associated with molecular subtype (P=0.014), CABF (P=0.004), and the neutrophil-to-lymphocyte ratio (NLR) (P=0.011). Multivariate Cox regression analysis revealed that being in the non-CABF group and a high NLR were independent risk factors for lower OS time (P=0.017 and P=0.041, respectively). These results support the continued administration of low-dose apatinib beyond progression and the use of NLR as an easily accessible prognostic marker in patients with ABC treated with apatinib.

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Introduction

Breast cancer is the most common malignant tumor and the fifth leading cause of cancer-associated mortality worldwide (1). Although it is commonly treated based on the molecular type according to various guidelines, advanced breast cancer (ABC), including recurrent and metastatic breast cancer, is incurable. Angiogenesis significantly impacts the occurrence and development of cancer owing to the ability of new blood vessels to deliver oxygen and nutrients to tumor cells, promoting tumor growth, metastasis and invasion (2,3). Therefore, inhibition of angiogenesis can limit the growth and spread of tumors by preventing the delivery of nutrients, thus starving the tumors (4). Various mouse models have demonstrated that vascular endothelial growth factor (VEGF) induces breast cancer cell proliferation (5). VEGF and VEGF receptor 2 (VEGFR-2) are core participants in pathological angiogenesis, and key targets for the development of drugs against angiogenesis (6,7). Apatinib, as a VEGFR2 inhibitor, has shown moderate efficacy in the treatment of metastatic breast cancer, and is currently used as an option for maintenance salvage therapy following failure of treatment with multiple lines of treatment (8,9). Apatinib combined with dose-dense paclitaxel and carboplatin neoadjuvant therapy was previously shown to significantly improve the pathological complete response rate to 60.9% in patients with triple-negative breast cancer who underwent surgery (10). However, rebound tumor growth occurred when VEGFR tyrosine kinase inhibitor (TKI) treatment was discontinued after the acquisition of resistance, and this growth was ultimately reversed after long-term anti-angiogenic treatment withdrawal (11). Given the poor prognosis of patients with ABC and the difficulty

in the selection of therapeutic regimens following failure of routine treatments, the present study retrospectively analyzed the efficacy of sustained apatinib treatment in patients with ABC in a real-world setting to address the importance of anti-angiogenic treatment and the feature of rebound tumor growth mediated by anti-angiogenic treatment withdrawal.

Materials and methods

Patients and methods. Between January 2016 and October 2022, 74 patients with ABC who were treated with apatinib at Tangshan People's Hospital (Tangshan, China) were screened for inclusion. All patients received at least three lines of standard treatment according to the National Comprehensive Cancer Network (NCCN) guidelines (12). All patients were administered oral apatinib combined with other therapies, such as chemotherapeutic agents, endocrine therapy or targeted therapy. The patients were divided into neutrophil-to-lymphocyte ratio (NLR)-high and -low group, taking the median value of the NLR as the cut off. All patients met the following inclusion criteria: i) Pathologically diagnosed as having breast cancer; ii) underwent multiple lines of line therapy (≥4 lines) according to the NCCN guidelines; iv) had an Eastern Cooperative Oncology Group score of 1-3; v) were of clinical stage IV: vi) (13) possessed a measurable target lesion based on the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria; vii) (14) were treated with oral apatinib for >4 weeks; and viii) had complete routine blood data available for at least 1 week before apatinib treatment. The exclusion criteria were as follows: i) Possessed another malignant tumor; and ii) had incomplete clinical pathological or follow-up data.

Treatment and follow-up. Eligible patients who had received multiple lines of treatment that had failed according to the NCCN guidelines received apatinib orally at a dose of 250 mg daily (one cycle every 4 weeks). Symptomatic treatment was scheduled if a patient exhibited grade II-III adverse events or above until the adverse events remitted to grade 1 or less. Patients received oral apatinib as a monotherapy or combination therapy, including chemotherapy, endocrine therapy, targeted therapy. Certain patients were continued on apatinib, but the combination of antitumor drugs was changed upon first PD, while other patients were switched from the apatinib and combined drug treatment to a different antitumor drug regimen upon first PD; this choice was determined by the physicians based on the patient's toxicity tolerance and the treatment's short-term efficacy.

The primary endpoint was overall survival (OS), calculated from the time of taking apatinib to either death from any cause or the last follow-up. The progression-free survival (PFS1), defined as the time from the beginning of apatinib to first PD. Patients were continued on apatinib combined with other drugs post-PD, such as etoposide, capecitabine, vinorelbine, gemcitabine, albumin paclitaxel, targeted therapy and ulvestrant endocrine therapy, with the aim of addressing persistent anti-angiogenic effects. PFS2 was defined as the time between the first PD to the second PD in next-line therapy or death from any cause. Patients who were continued on apatinib combined with other drugs as a next-line treatment post-first PD were defined as the CABF group, while those who discontinued apatinib were defined as the non-CABF group (Fig. 1).

Follow-up was performed by visits to the clinic, hospital admissions and telephone contact as of December 2022.

Efficacy evaluation. The first endpoint was overall survival (OS), and the secondary endpoints included PFS1, PFS2, PFS, objective response rate (ORR) and safety. Treatment responses were determined according to the RECIST 1.1 criteria. Computed tomography and ultrasound were performed every 4-6 weeks after oral apatinib until PD or patient withdrawal. Adverse events were assessed based on the Common Terminology Criteria for Adverse Events Version 4.0 (15) and graded as 0-4.

Ethics statement. This study was conducted in line with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Tangshan People's Hospital (approval no. RMYY-LLKS-2019-1224).

Statistical analysis. SPSS version 23.0 software (IBM Corp.) was used to conduct all statistical analyses. In the descriptive analysis, quantitative variables are described as the mean and range, while qualitative variables are described as quantity and percentage. Comparisons of the variables were performed using a χ^2 or Fisher's test as appropriate. The normal distribution quantitative variables were described as mean ± standard deviation, and independent t-test was used for inter-group comparison. Survival analysis was conducted using Kaplan-Meier curves. Univariate analysis and log-rank test were performed, and the resulting significant variables were included in further multivariate Cox regression analyses. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical characteristics. A total of 63 patients were enrolled in the present study. The median age of the patients was 53 years (range: 29-78). The research population was entirely female. At first, 55 patients received a combination of apatinib and chemotherapeutic drugs, including capecitabine (20 patients), etoposide (20 patients), vinorelbine (7 patients), gemcitabine (4 patients) and albumin paclitaxel (4 patients). In addition, 4 patients received apatinib monotherapy, 2 patients received apatinib combined with pyrotinib targeting therapy and 2 patients received apatinib combined with endocrine therapy. After the first PD, apatinib was continued in 26 patients (26/63, 41.27%) who were defined as the CABF group. Among them, 6 patients (6/26, 23.08%) received combined therapy with etoposide, 4 patients (4/26, 15.38%) were treated with capecitabine, 2 patients (2/26, 7.69%) were treated with vinorelbine, 3 patients (3/26, 11.54%) were treated with gemcitabine, 4 patients (4/26, 15.38%) were treated with albumin paclitaxel, 6 patients (6/26, 23.08%) were treated with targeted therapy and 1 patient (1/26, 3.85%) received a combination with fulvestrant endocrine therapy. Based on the progression, the other 37 patients were allocated to the non-CABF group; that is, they were switched from apatinib-containing treatment to a new antitumor drug

Table I. Baseline characteristics of the non-CABF (n=37) and CABF (n=26) groups.

Clinical characteristics	Non-CABF	CABF	P-value
Age, years[b]	54.4 (35-78)	51.9 (29-77)	0.801
ECOG, n			0.502
1-2	29	23	
3	8	3	
Molecular subtype			0.645
Luminal (HER2-negative)	13	12	
HER2-positive	9	6	
Triple-negative	15	8	
Menstrual status			0.271
Premenopause	9	9	
Postmenopause	28	17	
Lung metastasis			0.198
Yes	19	17	
No	18	9	
Liver metastasis, n (%)			0.143
Yes	11	12	
No	26	14	
Brain, n (%)			0.495
Yes	7	4	
No	30	22	
Bone, n (%)			0.254
Yes	17	15	
No	20	11	
Serous cavity, n (%)			0.257
Yes	5	6	
No	32	20	
Lymph node, n (%)			0.155
Yes	11	4	
No	26	22	
≥3 organ metastases, n (%)			0.341
Yes	24	19	
No	13	7	
Previous number of treatment lines, n (%)			0.018[a]
4	16	4	
>4	21	22	
Combined therapy, n (%)			0.566
Chemotherapy	31	24	
Endocrine therapy	1	1	
Monotherapy	3	1	
Targeted therapy	2	0	

[a]P<0.05. [b]Median (range). ABC, advanced breast cancer; ECOG, Eastern Cooperative Oncology Group Performance; HER2, human epidermal growth factor receptor 2; PD, progressive disease; CABF, continued anti-angiogenic treatment beyond first progression.

regimen. The detailed clinical differences in the baseline characteristics between the non-CABF and CABF groups of the 63 patients are shown in Table I.

The complete routine blood data of the total 63 patients within 1 week before apatinib treatment are shown in Table II. There was no significant difference between the non-CABF and CABF groups.

Short-term efficacy. As of the cutoff date of December 2022, the median follow-up time was 15.6 months (range,

Table II. Serum characteristics of the patients with ABC before apatinib treatment.

Variables	Median of total	Non-CABF	CABF	P-value
Mean WBC count (x10^9/l)	4.52	5.35±2.25	4.83±1.63	0.321
Neutrophils (x10^9/l)	2.84	3.47±1.73	3.01±1.33	0.254
Lymphocytes (x10^9/l)	1.34	1.44±0.69	1.40±0.54	0.780
NLR	2.1	2.69±1.37	2.35±1.29	0.329
HGB (x10^9/l)	115	112.76±18.39	119.04±16.40	0.168
PLT count (x10^9/l)	235	229.32±84.38	222.23±80.08	0.738

ABC, advanced breast cancer; CABF, continued anti-angiogenic treatment beyond first progression; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; HGB, hemoglobin; PLT, platelet.

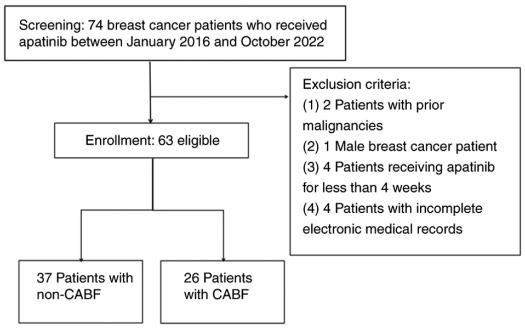

Figure 1. Flowchart of the specific screening process. CABF, continued anti-angiogenic treatment beyond first progression.

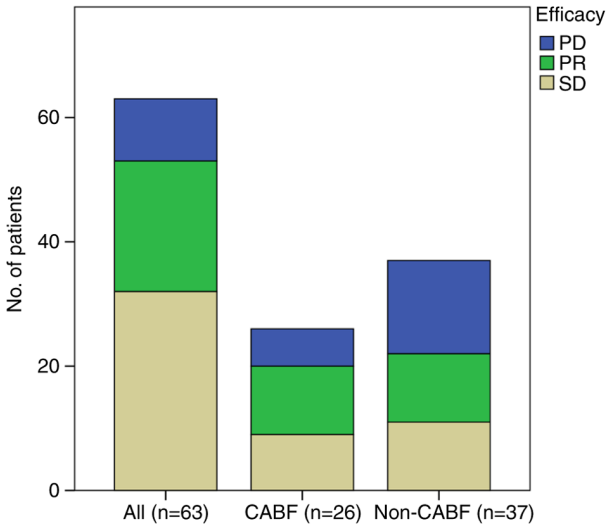

Figure 2. Response of patients treated with apatinib. PR, partial response; SD, stable disease; PD, progressive disease; CABF, continued anti-angiogenic treatment beyond first progression.

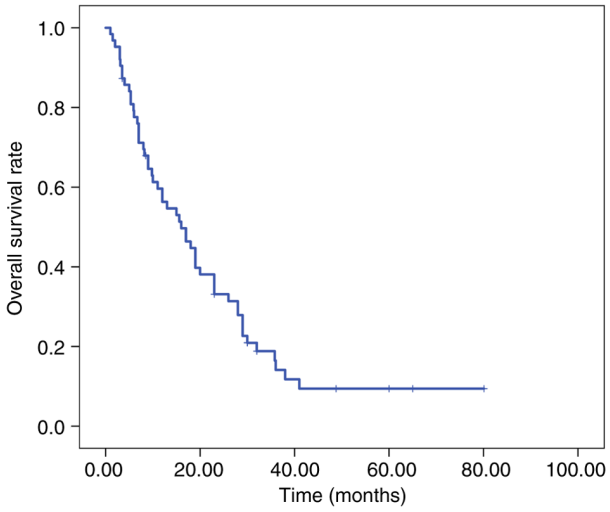

Figure 3. Kaplan-Meier curves of overall survival.

1-80 months). In the first efficacy evaluation, the therapeutic outcomes were PD in 10 patients (10/63, 15.87%), stable disease (SD) in 32 patients (32/63, 50.79%) and partial response (PR) in 21 patients (21/63, 33.33%). The ORR and the disease control rate were 33.3 and 84.1%, respectively. Among the 26 patients who continued oral apatinib treatment, PD was observed in 6 patients (6/26, 23.08%), SD in 9 patients (9/26, 34.62%) and PR in 11 patients (11/26, 42.31%). Of the 37 patients who refused continued apatinib treatment after progression, 40.54% experienced PD (15/37), 29.7% experienced SD (11/37) and 29.7% exhibited a PR (11/37). The best tumor response before and post-first progression is shown in Fig. 2. The overall population median OS time was 16.0 months (95% CI, 9.52-22.48; Fig. 3).

Log-rank univariate analysis for OS. Table III shows results of the univariate analysis of the OS with various clinical parameters in patients with ABC treated with apatinib. The results of the univariate analysis of OS showed statistically significant differences between the three groups in terms of molecular subtype, namely, luminal [human epidermal growth factor receptor 2 (HER2)-negative] (28 months; 95% CI, 16.62-39.38), HER2-positive (6 months; 95% CI, 0.00-12.06) and triple-negative (15 months; 95% CI, 7.89-22.11) (P=0.014). Statistically significant differences were observed in PFS1, PFS2 and OS between the patients in the CABF and non-CABF groups (P<0.05; Fig. 4A-C). The median OS time of the patients in NLR-low group (19 months; 95% CI, 7.76-30.24) was significantly longer than that of the patients in the NLR-high group (9 months; 95% CI, 1.45-16.55) (P=0.011; Fig. 4D).

Table III. Univariate analysis of OS with clinical parameters in patients with ABC treated with apatinib.

	PFS			OS		
Clinical parameter	mPFS1 time, months	χ^2 value	P-value	mOS time, months	χ^2 value	P-value
ECOG PS score		14.031	<0.001		2.153	0.142
1-2	5.96			22.09		
3	2.06			15.79		
Molecular subtype		11.595	0.003		8.541	0.014
Luminal (HER2-negative)	7.17			28.00		
HER2-positive	2.03			6.00		
Triple-negative	3.10			15.00		
Number of treatment cycles		0.049	0.824		0.352	0.553
4	2.07			19.00		
>4	3.10			12.00		
≥3 organ metastases		4.282	0.039		1.359	0.244
Yes	3.03			13.00		
No	4.07			19.00		
Brain metastasis		1.314	0.252		2.216	0.137
Yes	4.06			14.21		
No	5.56			23.79		
Apatinib sustained post-first PD		4.233	0.040		8.446	0.004
CABF	5.70			23.00		
Non-CABF	2.03			12.00		
NLR		6.703	0.010		6.491	0.011[a]
Low	4.43			19.00		
High	2.00			9.00		
Hemoglobin		4.812	0.028		2.024	0.155
Low	2.13			12.00		
High	4.83			19.00		
Platelet count		0.330	0.566		0.125	0.723
Low	3.10			15.60		
High	4.03			17.00		
Secondary hypertension		0.455	0.500		0.651	0.420
Yes	4.83			19.00		
No	3.03			12.00		
Proteinuria		9.954	0.002		2.126	0.145
Yes	12.2			19.00		
No	3.03			15.60		

OS, overall survival; PFS, progression-free survival; ABC, advanced breast cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; HER2, human epidermal growth factor receptor 2; PD, progressive disease; CABF, continued anti-angiogenic treatment beyond first progression; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell count; m, median.

Multivariate Cox regression analysis. The results of the multivariate logistic regression analysis showed that CABF and NLR were independent predictive factors for OS (Table IV).

Adverse events. The overall incidence of grade ≥3 adverse events was low, with no cases of death caused by adverse events. Adverse events primarily included secondary hypertension, hand-foot syndrome, oral cavity mucositis, secondary proteinuria, fatigue and diarrhea, with no cases of gastrointestinal bleeding. Grade 2 or above adverse events were dominant in all patients and could be alleviated after symptomatic treatment or dose adjustment of apatinib (Table V).

Discussion

Angiogenesis, the process by which new blood vessels are formed from pre-existing vasculature, has been implicated in the growth, progression and metastasis of cancer, and

Table IV. Multivariable analysis of overall survival with significant clinical parameters in patients with advanced breast cancer treated with apatinib.

Clinical parameters	B	SE	Wald	df	P-value	Exp(B)
Molecular subtype	0.157	0.155	1.028	1	0.311	1.170
CABF	-0.712	0.299	5.656	1	0.017	0.491
NLR	0.581	0.284	4.169	1	0.041	1.787

CABF, continued anti-angiogenic treatment beyond first progression; NLR, neutrophil-to-lymphocyte ratio; SE, Standard error; df, degree of freedom.

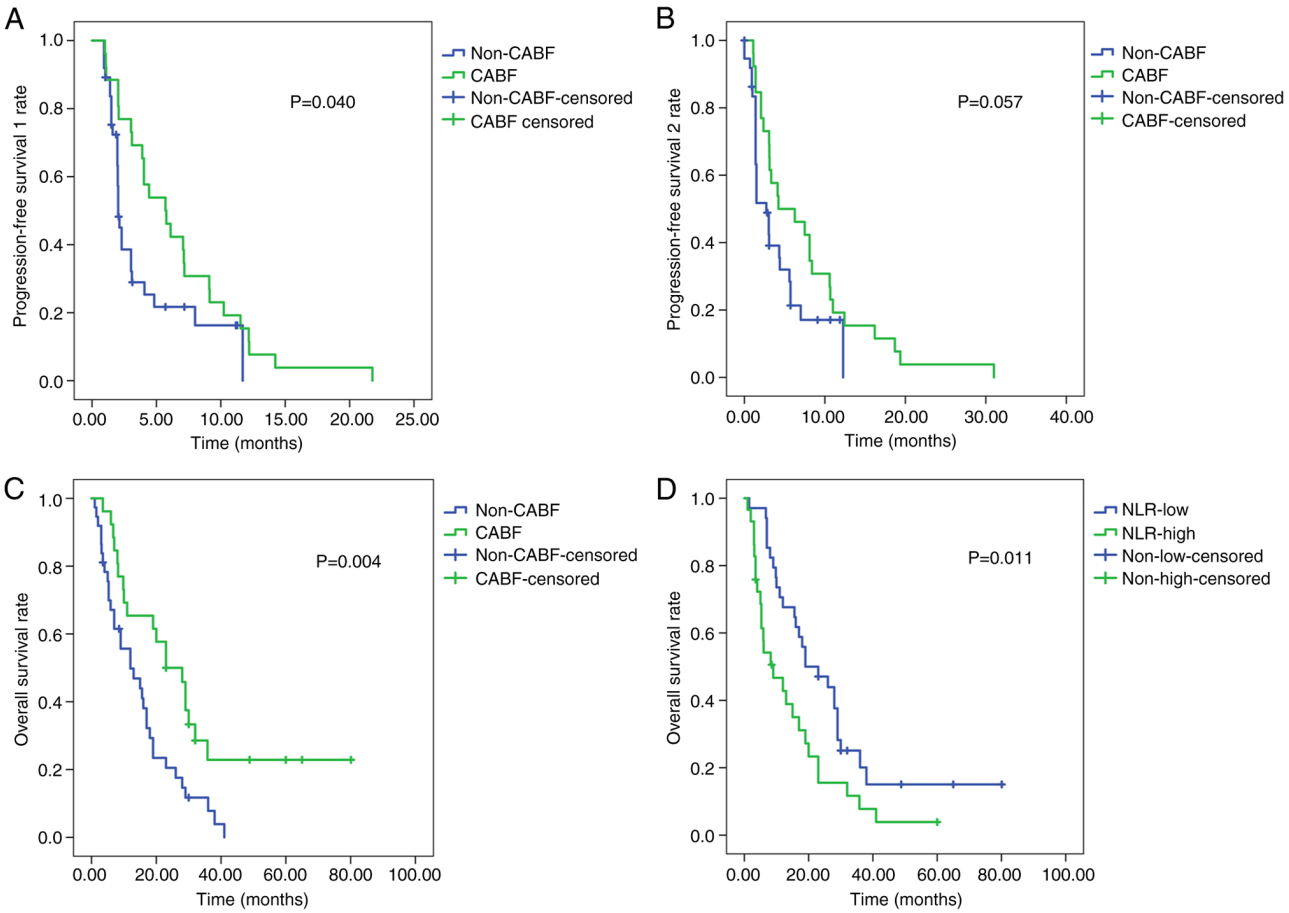

Figure 4. Kaplan-Meier curves of PFS1 (A) PFS2 (B) and OS (C) of patients in the CABF and non-CABF groups. Kaplan-Meier curves of OS (D) of patients in the NLR-low and NLR-high groups. CABF, continued anti-angiogenic treatment beyond first progression; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; OS, overall survival.

tumor angiogenesis has been explored as a key therapeutic target for decades (16). Several trials have shown that adding bevacizumab to paclitaxel significantly improves the PFS time of patients with HER2-negative metastatic breast cancer (mBC) (17-19). Moreover, a meta-analysis of the E2100, AVADO and RIBBON-1 studies suggested that bevacizumab combined with chemotherapy as a first-line treatment for mBC significantly improved the ORR and PFS time, but did not improve OS time in patients with increased grade 3-4 adverse effects (20). However, the results of another meta-analysis suggested that use of chemotherapy with bevacizumab as an adjuvant, considering its favorable effects on clinical outcomes, was a preferred therapeutic option for patients with MBC, for whom the disease must be rapidly treated (21).

Apatinib, a anti-angiogenic TKI with moderate adverse events, can suppress angiogenesis, tumor growth and metastasis by inhibiting the phosphorylation of VEGFR2 and blocking downstream signaling pathways (22). Apatinib has been clinically used in patients with refractory ABC and is considered an efficient treatment for patients with mild adverse effects (23,24). In the present real-world study, a PR was observed in 21 patients (21/63, 33.33%) and SD was observed in 32 patients (32/63, 50.79%), with mild adverse effects (grades 1-2), such as secondary hypertension, hand-foot syndrome, oral cavity mucositis,

Table V. Incidence of the main adverse events related to apatinib.

Adverse effects	Grade I-II, n (%)	Grade III-IV, n (%)
Hematology		
Neutropenia	22 (34.9)	4 (6.3)
Thrombocytopenia	12 (19.0)	1 (1.6)
Non-hematology		
Secondary hypertension	19 (30.2)	3 (4.8)
Hand-foot syndrome	17 (27.0)	1 (1.6)
Fatigue	21 (33.3)	2 (3.2)
Secondary proteinuria	7 (11.1)	0 (0.0)
Oral cavity mucositis	8 (12.7)	0 (0.0)
Diarrhea	11 (17.5)	0 (0.0)

secondary proteinuria, fatigue and diarrhea, with no cases of gastrointestinal bleeding. In addition, the enrolled patients had been heavily treated according to NCCN guidelines, and it was difficult to formulate a standard therapeutic schedule for them. Apatinib-containing treatment may be a promising therapeutic strategy for patients with ABC who have developed multidrug resistance to traditional chemotherapeutic agents.

However, tumor vascular rebound or increased growth has been reported following treatment discontinuation (25). These withdrawal-mediated tumor growth rebounds were found to decrease following long-term periods of discontinuation (11,26). Evidence suggests that in certain circumstances, continuing therapy beyond disease progression can result in antitumor activity (27,28). After first-line treatment with bevacizumab with chemotherapy, maintenance of bevacizumab treatment until disease progression or unacceptable levels of toxicity is a reasonable strategy to improve and maintain the clinical response, increase the time to progression, extend OS time, relieve tumor-related symptoms and delay the use of aggressive therapies, without compromising a patient's quality of life (28). The TANIA trial demonstrated that maintaining bevacizumab after the first and second PD led to improved second-line PFS times, which may be associated with increased redundancy of angiogenic pathways in the later stages in patients with ABC who were pretreated with bevacizumab (29). Low-dose apatinib has been shown to have a moderate effect in patients with ABC (9,23,24). However, to the best of our knowledge, no previous study has investigated apatinib rechallenge in patients with ABC. In the present study, of the 26 patients who continued to take apatinib after the first PD, 9 patients achieved SD and 11 achieved a PR. Univariate analysis revealed that apatinib sustained after the first PD was significantly associated with PFS1 and PFS2, and in some cases, even OS. Additionally, CABF was also an independent risk factor for OS, as shown by the results of the multivariate Cox regression analysis. This demonstrated that there was a rebound in tumor growth during the interval of anti-angiogenic therapy. Low-dose apatinib offers improved survival in patients with ABC and retains its antitumor activity even beyond disease progression.

Anti-angiogenic therapy not only reduces the formation of new blood vessels, which are essential for cancer growth and metastasis, but also reprograms the immune microenvironment of the tumor (30). Neutrophils produce various angiogenic molecules and an equally wide range of anti-angiogenic molecules (31). Neutrophils accumulate in the peripheral blood of patients with cancer, especially in those with advanced-stage disease, and a high circulating NLR is a robust biomarker of poor clinical outcomes in various types of cancer (32). As an easily accessible prognostic marker, a high NLR has been reported to be associated with a poor prognosis in breast cancer in several studies (33-35). Apatinib, as a moderate anti-angiogenic TKI, has been used in patients with refractory ABC in the clinic, but to the best of our knowledge, no association with NLR has been reported. Moreover, patients with hepatocellular carcinoma treated with apatinib with a low pretreatment NLR have been reported to have significantly longer OS and PFS times than those with a high pretreatment NLR (36). In the present study, using the median NLR as a cutoff, the patients in the NLR-low group showed a longer median OS time than those in the NLR-high group (19 vs. 9 months). This was likely due to low-dose apatinib alleviating hypoxia and remodeling the immunosuppressive tumor microenvironment to make it more permissive for antitumor immunity (37). In this manner, the drugs can be efficiently delivered to promote the release of new tumor antigens, increase the immune response and eventually improve the therapeutic outcome.

The results of the univariate analysis showed that the mean OS times of patients with luminal (HER2-negative), triple-negative, and HER2-positive molecular subtypes were 28, 15 and 6 months, respectively, but the results were not statistically significant. This may be since more HER2-positive patients in the CABF group had additional HER2 targeting therapy; nevertheless, only 2 patients (2/15) were treated with HER2 targeting therapy during first-line treatment with apatinib. Furthermore, 27.9% of the HER2-positive patients showed high VEGFR2 expression (38). According to a recent case report (39), two patients with multi-line anti-HER2 treatment failure who underwent apatinib and anti-HER2 combination treatment still had PFS times of 8.4 and 10.6 months; this suggests that apatinib can restore the HER2-targeting sensitivity and improve survival, but does not suggest abandoning the use of HER2-targeted therapy.

The present study was an observational trial in the real world and thus has associated limitations, such as a small sample size, a lack of diversity in the patient population and a lack of randomized design. However, a real-world study is more complicated and closer to clinical reality than a prospective study. Future studies with a larger cohort of patients are needed to verify these findings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JW contributed to the design of the study, the analysis and interpretation of data, and the first draft of the manuscript. JJ, XY and JL performed the data collection and analysis, and revised the manuscript. ZY contributed to the design of the study, analysis and interpretation of data, and revised the manuscript. All authors have read and approved the final manuscript. JW, JJ, JL, XY and ZY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This study was conducted in line with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of Tangshan People's Hospital (Tangshan, China) approved the study and waived the requirement for written informed consent (approval no. MYY-LLKS-2019-1224).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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