



RETRACTED: A Phase II, Single-Arm Study of Apatinib and Oral Etoposide in Heavily Pre-Treated Metastatic Breast Cancer

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Introduction: We performed this clinical trial to evaluate the efficacy and safety of apatinib and oral etoposide in patients with HER2-negative locally advanced or metastatic breast cancer (MBC).

Methods: Patients with HER2-negative MBC previously treated with anthracycline and taxanes and failed ≥ 1 prior chemotherapy regimens were recruited. The starting dose of apatinib was 500 and 425 mg in patients with ECOG scores of 0–1 and 2, respectively. The etoposide capsules were given at 50 mg/m² on days 1 to 10 for 21 days. The primary end point was objective response rate (ORR). Secondary end points included progression-free survival (PFS), disease control rate (DCR), overall survival (OS), and safety.

Results: Thirty-one eligible patients were enrolled. The median follow-up time was 11 months. The median PFS for all patients was 6.9 months [95% confidence interval (CI) 6.0–7.9], and 6.9 months (95% CI 5.3–8.6) and 6.6 months (95% CI 1.4–11.7) for patients with apatinib 425 and 500mg once daily, respectively. The ORR was 35.5% (11/31). The DCR was 87.1% (27/31). The median OS was 20.4 months (95% CI 11.4–29.3). The median PFS of patients who had hypertension and proteinuria was longer than that for those without hypertension and proteinuria. The most common grade 3/4 treatment-related AEs were hypertension (12/31, 38.7%), fatigue (3/31, 9.7%), thrombocytopenia (3/31, 9.7%).

Conclusion: Apatinib combined with etoposide capsules is effective and tolerable in heavily pretreated, metastatic HER2-negative breast cancer patients. A lower apatinib dose provide equivalent efficacy and reduced toxicity.

Clinical Trial Registration: <https://clinicaltrials.gov/>, identifier NCT03535961.

Keywords: apatinib, breast cancer, angiogenesis, HER2-negative, oral etoposide

INTRODUCTION

Breast cancer is the most common malignant tumor and the second leading cause of cancer-related death in women worldwide (1). The median survival time of patients after metastasis is 9 months to 3 years (2, 3). In China, HER2-negative breast cancer accounts for approximately 65% of all breast cancers (4). There is no specific targeted drug for this type of breast cancer. The treatment for HER2-negative metastatic breast cancer, especially in second and later lines, requires more new drugs or combined regimens.

Tumor angiogenesis is closely related to tumor growth and metastasis, and antiangiogenic strategies are some of the most important strategies for metastatic breast cancer. Bevacizumab has shown some efficacy in the treatment of metastatic breast cancer, and chemotherapy as a first-line and second-line treatment for HER2-negative metastatic breast cancer has significantly extended median progression-free survival (PFS) (5, 6). Preclinical studies have shown that antiangiogenic drugs combined with chemotherapy can improve the efficacy of chemotherapeutic drugs and reverse the resistance of tumor cells (7–9), which indicates this combination therapy may be a potential treatment.

Apatinib is an oral small molecule tyrosine kinase inhibitor (TKI) that selectively inhibits vascular endothelial growth factor receptor 2 (VEGFR2), which exhibits some efficacy in triple-negative and non-triple-negative metastatic breast cancer by monotherapy (10, 11). Oral etoposide is one of the options for patients with metastatic breast cancer, achieving a median PFS of 5 months and a median overall survival (OS) of 16 months with manageable toxicity (12). We suppose that apatinib and etoposide capsules are effective and tolerable in patients with breast cancer.

Therefore, this study aimed to explore the efficacy and safety of apatinib combined with etoposide capsules in pre-treated metastatic HER2-negative breast cancer patients from the NCT03535961 trial.

MATERIALS AND METHODS

Study Design and Participants

Patients included in the trial were 18-to-75-year-old females with histologically or cytologically diagnosed HER2-negative locally advanced or metastatic breast cancer who received at least one regimen of chemotherapy after metastasis, including taxane and anthracycline, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. The patients had measurable lesions as defined by the Response Evaluation

Criteria In Solid Tumors (RECIST) (v 1.1). Patients who had previously received small molecule anti-angiogenic TKIs and patients with uncontrolled hypertension were excluded from the trial.

The study was approved by the Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences and performed in accordance with the Declaration of Helsinki. Every patient signed written informed consent.

Procedures

The starting dose of apatinib was 500 and 425 mg in patients with ECOG scores of 0–1 and 2, respectively, and apatinib was taken orally each day. The etoposide capsules were given at 50mg/m² on days 1 to 10 for 21 days per cycle. The tumor response was evaluated every 6 weeks according to RECIST v1.1 until the disease progressed or intolerable adverse reactions occurred. Blood pressure was monitored twice a day for the first 3 weeks and at least once a day after blood pressure stabilized. Routine blood and urine tests were performed weekly, physical examinations were performed every 3 weeks, liver and kidney functions were monitored, and electrocardiograms and tumor marker tests were performed every 6 weeks.

Dosage adjustment was recommended if hematological toxicity above grade 3 or non-hematological toxicity above grade 2 (except for hair loss) occurred, including withdrawal and reduction.

The first reduced dose was 425 mg/day and the second reduced dose was 250 mg/day for patients with an apatinib starting dose of 500 mg. Patients with a starting dose of 425 mg were adjusted to 250 mg/day first and 250 mg every other day second. The first and second adjustments of etoposide dose were 35 mg/m² on d1–10 and 35 mg/m² on day 1–7, respectively. When adverse reactions of grade 3 and above occurred, dose adjustments were made according to the protocol. When adverse reactions were of grade 2 or below, researchers were allowed to adjust the doses according to the specific conditions. Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) 4.0.

Outcome

The primary endpoint was the objective response rate (ORR), and the secondary endpoints were the disease control rate (DCR), PFS, OS, safety. The PFS duration was defined as the interval between the initiation of treatment and the last follow-up in patients with disease progression (PD) or to death from any cause, whichever occurred first. The OS was defined as the interval between the initiation of treatment and death for any reasons.

Statistical Analysis

Simon's two-stage design with a one-sided $\alpha = 0.05$ and 80% test efficiency was used to determine the number of patients that needed to be enrolled (13). Previous studies have shown that the ORR of apatinib monotherapy for patients with metastatic non-triple-negative breast cancer is 16.7%, and the ORR of etoposide capsule monotherapy is 21.3% (10, 14). We estimated that the response rate of apatinib combined with etoposide was 40%. Under such conditions, at least 2 of 10 patients needed to

Abbreviations: MBC, metastatic breast cancer; HER2, human epidermal growth factor receptor 2; VEGFR2, vascular endothelial growth factor receptor 2; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria In Solid Tumors; PFS, progression free survival; OS, overall survival; ORR, objective response rate; DCR, disease control rate; CI, confidence interval; AE, adverse event; HR, hazard ratio; PR, partial response; SD, stable disease; CTCAE, Common Terminology Criteria for Adverse Events.

respond for the trial to move to the next stage. Another 21 patients needed to be recruited in the second stage, for a total of 31 patients. If 10 or more patients responded to this therapy, the regimen would be considered a success.

Patients receiving ≥ 1 cycle of apatinib were included for survival and safety analysis. PFS and OS were estimated based on a Kaplan-Meier curve. A log-rank test was used to compare the median progression free survival (PFS) in different subgroups. Factors with $p < 0.1$ in the Kaplan-Meier single factor analysis were included in the Cox regression model for analysis. SPSS 23.0 and GraphPad Prism 7.0 were used for data analysis.

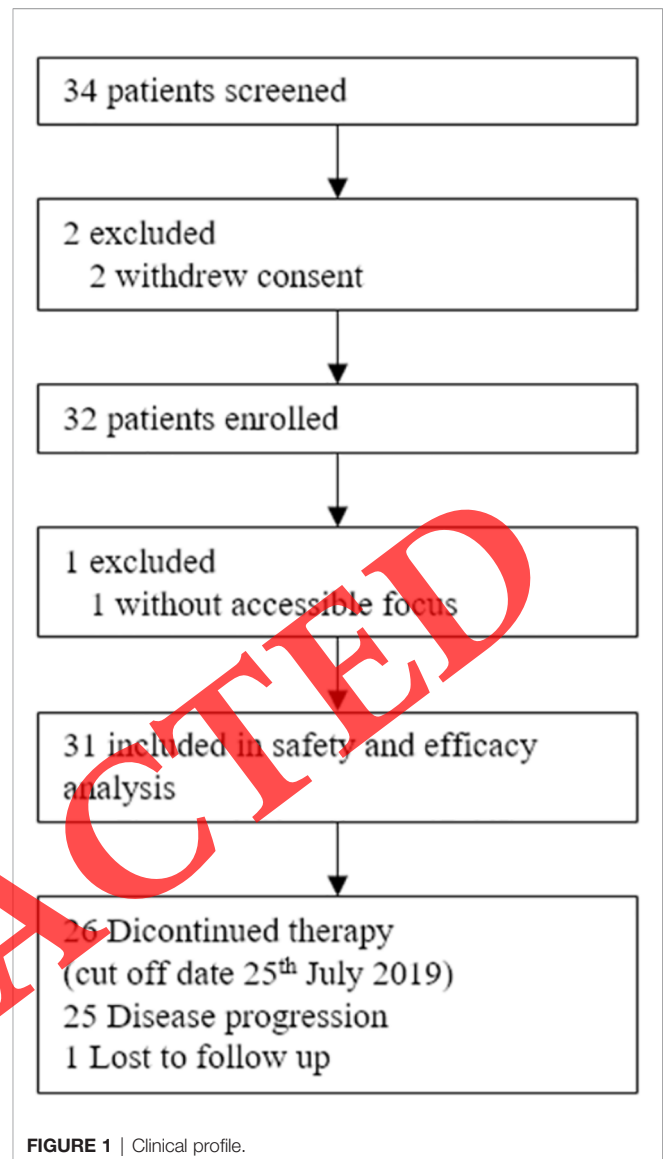
RESULTS

Thirty-four patients were screened from May 1st, 2017 to May 1st, 2019. Two patients withdrew their informed consent. Because one patient had only bone metastases and no measurable lesions, 31 patients were included in the final survival and safety analyses (Figure 1). The basic clinicopathological and median PFS data are shown in Table 1.

Efficacy

The median follow-up time was 10.3 months [95% confidence interval (CI) 3.5–24.3]. All patients had breast invasive ductal carcinoma, with a median age of 47 years (34–65). Treatment was discontinued in twenty-five patients due to disease progression, and six patients continued to receive treatment until the cutoff day. According to the RECIST version 1.1, no patients achieved a complete response in this study, eleven patients (35.5%) achieved a partial response (PR), the ORR was 35.5% (11/31), 16 (51.6%) patients achieved stable disease (SD) (Table 2), and twenty-two patients (71.0%) patients had tumor shrinkage of different degrees (Figure 2). The DCR was 87.1% (27/31), the median PFS was 6.9 months (95% CI 6.0–7.9) (Figure 3), and the clinical efficacy of initial apatinib doses of 500 and 425mg in patients is shown in Table 2.

Sixteen (51.6%) patients with an ECOG score of two received an apatinib dose of 425 mg, and fifteen (48.4%) patients with an ECOG score of 0–1 received an apatinib dose of 500 mg; the median PFS was 6.9 months (95% CI 5.3–8.6m) and 6.6 months (95% CI 1.4–11.7), ($p=0.56$), respectively, which has no statistical significance. The median PFS of hormone receptor-positive and hormone receptor-negative patients was 7.4 months (95% CI 6.0–8.8) and 3.1 months (95% CI 1.0–5.2, $p=0.04$), respectively. There was no significant difference in median PFS between patients with and without visceral metastasis ($p=0.82$). There were eleven (35.5%), eleven (35.5%), and nine (29.0%) patients who had received 1, 2, and 3 chemotherapy regimens, respectively. Their median PFS values were 6.6 months (95% CI 3.4–9.7), 6.9 months (95% CI 0.4–13.4) and 7.0 months (95% CI 3.6–10.5, $p=0.82$), respectively. The results of the subgroup analysis are shown in Table 2. Factors with $p < 0.1$ in the univariate analysis were included in the multivariate analysis, and the hazard ratio (HR) of hormone receptor status on median PFS was 2.4 months (95% CI 0.9–6.1; $p=0.08$), which reach a



marginal statistical significance. The results of the subgroup analysis are shown in Table 1.

As of the date of data analysis, seventeen patients were still alive, with a median OS of 20.4 months (95% CI 11.4–29.3).

Safety

Most of the adverse events were mild to moderate (Table 3) and were well controlled after treatment. The most common grade 3–4 adverse events were hypertension (38.7%), fatigue (9.7%), and thrombocytopenia (9.7%). No adverse events related death or serious adverse events was reported. Grade 3–4 hypertension in patients was reduced to below 140/90 mmHg after receipt of antihypertensive drugs.

Twelve (38.7%) patients experienced apatinib dose reductions due to adverse events. Of these, five patients were in the apatinib 500 mg group (one with neutropenia, one with hypertension, one with hand-foot syndrome, and two with fatigue), of which four patients experienced twice dose reductions, and seven patients were in the

TABLE 1 | Patients characteristics and median progression free survival (mPFS) in subgroups.

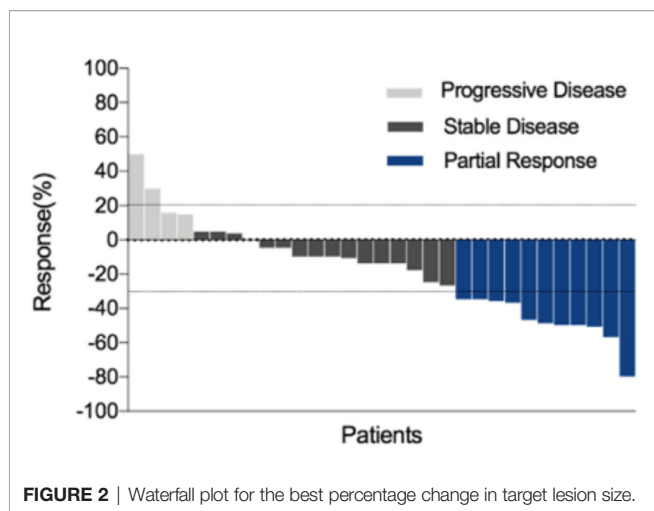
Overall	All patients enrolled (%)	mPFS (months, 95%CI)	P Value
Number	31	6.9 (6.0–7.9)	
Age	47 (34–65)		
≥50	14 (45.2)	7.0 (2.8–11.2)	0.65
<50	17 (54.8)	6.4 (4.4–8.5)	
Hormone receptor status			
Positive	19 (61.3)	7.40 (6.0–8.8)	0.04
Negative	12 (38.7)	3.13 (1.0–5.2)	
Axillary lymph node metastasis			
Positive	22 (71.0)	4.4 (0.0–13.9)	0.21
Negative	9 (29.0)	6.9 (6.1–7.8)	
TNM stage			
I	3 (9.7)	14.73	0.16
II	17 (54.8)	7.03 (6.0–8.0)	
III	11 (35.5)	4.00 (0.0–8.9)	
ECOG performance status			
0–1	16 (51.61)	6.93 (5.27–8.60)	0.56
2	15 (48.39)	6.56 (1.41–11.73)	
Metastasis site			
No visceral	10 (32.3)	7.03 (4.7–9.3)	0.82
Visceral	21 (67.7)	6.57 (3.4–9.7)	
Lines of chemotherapy			
2	11 (35.5)	6.57 (3.4–9.7)	0.82
3	11 (35.5)	6.93 (0.4–13.4)	
≥4	9 (29.04)	7.03 (3.6–10.5)	
Apatinib dose			
425mg	15 (48.4)	6.93 (5.3–8.6)	0.56
500mg	16 (51.6)	6.56 (1.4–11.7)	
Apatinib dose reduction			
No	12 (38.7)	5.83 (2.7–9.0)	0.59
Yes	19 (61.3)	7.40 (1.8–13.0)	
Hypertension			
No	7 (22.6)	2.60 (2.2–3.0)	0.02
Yes	24 (77.4)	7.4 (6.0–8.4)	
Hand-foot skin reaction			
No	17 (54.8)	6.9 (5.1–8.7)	0.46
Yes	14 (45.2)	6.6 (2.1–11.0)	
Proteinuria			
No	16 (51.6)	4.00 (0.1–7.9)	0.04
Yes	15 (48.4)	8.10 (2.4–13.9)	
Mucositis			
No	25 (80.7)	6.57 (5.0–8.2)	0.79
Yes	6 (19.3)	11.53	

TABLE 2 | Clinical response to apatinib and oral etoposide therapy.

Treatment efficacy	Total	Apatinib 500mg (n=16)	Apatinib 425mg (n=15)
	n (%)	n (%)	n (%)
Partial response	11 (35.5)	7 (43.8)	4 (26.7)
Stable disease	16 (51.6)	8 (50.0)	8 (53.3)
Disease progression	4 (12.9)	1 (6.3)	3 (20.0)
Overall response	11 (35.5)	7 (43.8)	4 (26.7)
Disease control	27 (87.1)	15 (93.8)	12 (80.0)
median PFS(m)	6.9 (6.0-7.9)	6.6 (1.4-11.7)	6.9 (5.3-8.6)

425 mg group (one with thrombocytopenia, one with hypertension, one with asthenia, two with proteinuria, and two with hand-foot reaction) and received one apatinib dose reduction. Eleven (35.5%) patients had their doses modified during or at the end of the first cycle, and five (16.1%) (four patients had a second dose reduction) had their doses modified at the end of the second cycle. Two patients underwent dose adjustment for etoposide capsules.

A stratified analysis of each adverse event suggested that the occurrence of hypertension and proteinuria may be a positive predictor of response. We found that the median PFS in patients with hypertension was significantly longer than that in patients without hypertension [7.4 months (95% CI 6.0–8.44) versus 2.6 months (95% CI 2.2–3.0), HR 0.28 (95% CI 0.1–0.8), $p=0.022$]; median PFS was also significantly longer in patients with



proteinuria than those without proteinuria [8.1 months (95% CI 2.4–13.9) versus 4.0 months (95% CI 0.1–7.9), HR 0.38 (95% CI 0.15–0.94), $p=0.036$] (Figures 4A, B).

DISCUSSION

This study firstly explored the application of apatinib combined with etoposide capsules in locally advanced and metastatic HER2-negative breast cancer. In this study, the ORR was 35.5%, the median PFS was 6.9 months, and the median OS was 20.4 months.

The median PFS associated with apatinib monotherapy for metastatic non-triple-negative breast cancer and triple-negative breast cancer was 4.0 months (95% CI 2.8–5.2) and 3.3 months (95% CI 1.7–5.0), respectively (10, 11). In previous studies, the median PFS associated with etoposide monotherapy for advanced

breast cancer was between 2.6 and 5.0 months, and the median OS was between 11.0 and 24.0 months (12, 14–16). Although this study has limitations in comparison with other studies directly, it can be seen from the data that the median PFS and median OS were longer in patients who received apatinib and etoposide capsules than in those who received either one of the two drugs alone.

Antiangiogenic drugs combined with chemotherapy increased the PFS in locally advanced and metastatic HER2-negative breast cancer after second-line treatment. The results of this study are equivalent to or even better than those of similar studies. In the RIBBON-2 study, the median PFS was 7.2 months in patients with metastatic HER2-negative breast cancer using standard chemotherapy regimens combined with bevacizumab for the second-line treatment (6). Treatment with gemcitabine or capecitabine combined with sorafenib yielded a median PFS of 3.4 months as a first-line treatment after metastasis in breast cancer patients (17). Most of the antiangiogenic drugs and chemotherapy drugs tested so far have obtained a small benefit in terms of the median PFS, but no clinical benefit of OS has been seen yet. However, the occurrence of adverse events is greatly increased, which has substantially limited the use of such regimens in clinical practice. In this study, we achieved a median PFS of 6.9 months and a median OS of 20.4 months. The response was comparable to or even better than that in similar studies, and the adverse events were manageable that no bleeding or febrile neutropenia occurred. At the same time, Chinese scholars have shown that apatinib combined with etoposide capsules has achieved good results in advanced ovarian cancer, in which the median PFS was 8.1 months, the ORR reached 54.3% (19/35), and the toxicities were well tolerated (18). In addition, apatinib and etoposide capsules are administered orally, which reduces the duration and the cost of hospitalization, so this combination is suggested to be one of the treatment options for patients with locally advanced and metastatic breast cancer.

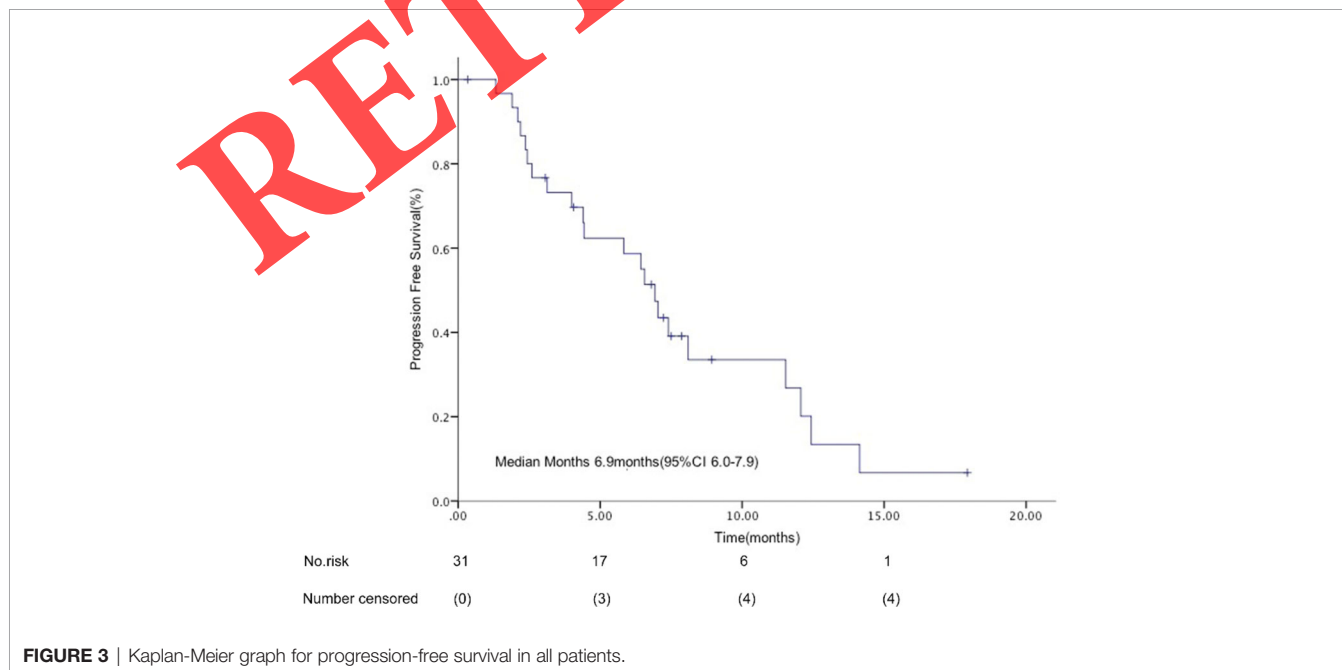


TABLE 3 | Treatment-related adverse events in the safety population.

Adverse event	Apatinib 500mg (n=16)			Apatinib 425mg (n=15)		
	Total	Grade 1–2 (%)	Grade 3–4 (%)	Total	Grade 1–2 (%)	Grade 3–4 (%)
Non-Hematological						
hypertension	12 (75.0)	4 (25.0)	8 (25.8)	12 (80.0)	8 (53.3)	4 (26.7)
Proteinuria	10 (62.5)	10 (62.5)	0	5 (33.3)	4 (26.7)	1 (6.7)
Hand-foot syndrome	13 (81.3)	13 (81.3)	0	5 (33.3)	5 (33.3)	0
Mucositis	5 (31.4)	5 (31.4)	0	1 (6.7)	1 (3.2)	0
Fatigue	8 (50.0)	6 (37.5)	2 (12.5)	3 (20.0)	2 (6.5)	1 (3.2)
Diarrhea	0 (0)	0	0	1 (6.7)	1 (6.7)	0
Vomiting	11 (68.8)	10 (62.5)	1 (6.3)	7 (46.7)	7 (46.7)	0
Nausea	12 (75.0)	11 (68.8)	1 (6.3)	10 (66.7)	10 (66.7)	0
Alopecia	7 (43.8)	7 (43.8)	0	5 (33.3)	5 (33.3)	0
Hyperbilirubinaemia	3 (18.8)	3 (18.8)	0	2 (13.3)	2 (13.3)	0
Aminotransferase increased	6 (37.5)	6 (37.5)	0	2 (13.3)	1 (6.7)	1 (6.7)
Hematological						
Neutropenia	14 (87.5)	13 (81.3)	1 (6.3)	10 (66.7)	9 (60.0)	1 (6.67)
Anemia	2 (12.5)	2 (12.5)	0	3 (20.0)	3 (20.0)	0
Thrombocytopenia	4 (25.0)	3 (18.8)	1 (6.3)	5 (33.3)	3 (9.7)	1 (6.67)

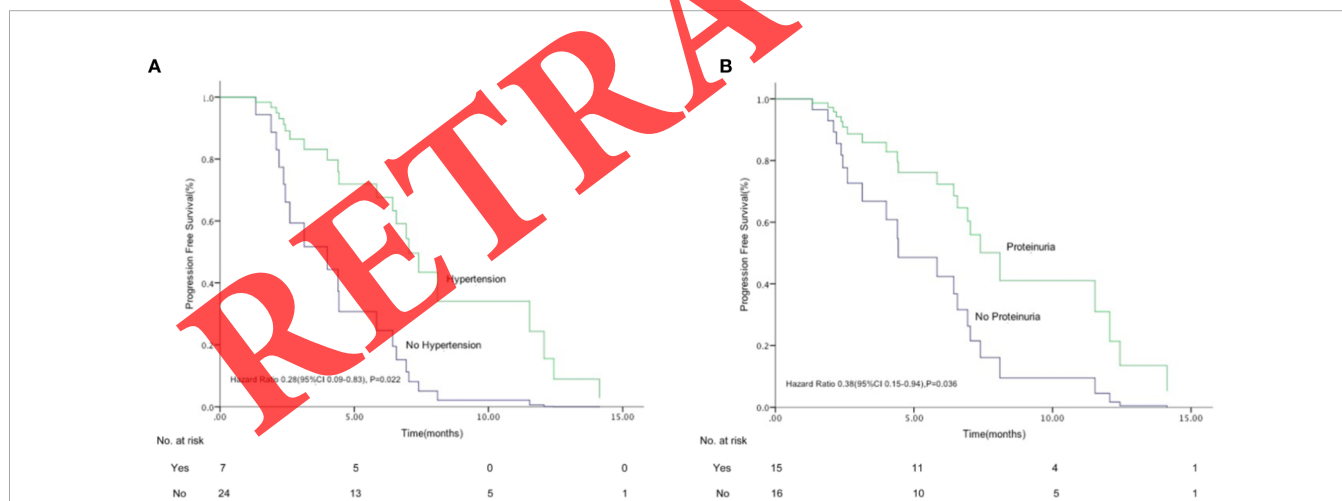


FIGURE 4 | Kaplan-Meier graph for progression-free survival in patients who had hypertension **(A)** and proteinuria **(B)** ($n=31$). **(A)** Median progression free survival (PFS) in patients with hypertension was significantly longer than that in patients without hypertension [7.4 months (95% CI 6.0–8.4) versus 2.6 months (95% CI 2.2–3.0), hazard ratio (HR) 0.28 (95% CI 0.09–0.83), $p = 0.022$]. **(B)** Median PFS was also significantly longer in patients with proteinuria than those without proteinuria [8.1 months (95% CI 2.4–13.9) versus 4.0 months (95% CI 0.1–7.9), HR 0.38 (95% CI 0.15–0.94), $p = 0.036$].

In this study, different starting doses of apatinib were given on the basis of the patient's ECOG score. There was no significant difference in the median PFS (6.6 months vs. 6.9 months, $p=0.56$) in the 500 mg group and 425 mg group, but fewer adverse events were observed in the 425 mg group. Therefore, we recommend 425mg

apatinib as the starting dose for combination therapy. In addition, there was no significant difference in the median PFS between patients treated in the second-line, third-line, or further in this study protocol ($p=0.82$), indicating that apatinib and etoposide capsules can be used in patients who progress after multiline treatment.

In previous studies, the single dose of apatinib was 500–850 mg once per day. We observed in our clinical practice that some patients were intolerant to the 500 mg dose in the combination strategy of chemotherapy and apatinib. Therefore, we administered 500 mg once daily to patients with superior physical status and 425 mg once daily to patients with relatively worse status. For etoposide capsules, previous clinical research has recommended 50 mg–60 mg/m² for 14 consecutive days or 10 days in a 21-day cycle. We learned from clinical experience that most patients were unable to tolerate the dosage. Considering that our research protocol used a combination treatment, we choose the 50 mg/m²/d on d1–10 and a 21-day cycle as the starting dose for etoposide. Nonetheless, 38.7% of apatinib was taken in reduced doses due to intolerable adverse events.

It is worth noting that this study showed that the occurrence of hypertension and proteinuria may be a positive predictor for efficacy. Previous studies have shown that the occurrence of adverse events such as hypertension and proteinuria may be one of the predictive markers for the efficacy of antiangiogenic drugs. In a clinical study of sunitinib in advanced renal cell carcinoma (19), patients with hypertension had longer PFS and OS than patients without hypertension (median OS 41.6 *versus* 16.4 months, $p < 0.0001$, median PFS 12.9 *versus* 5.6 months, $p < 0.0001$, respectively). A cohort study of patients with metastatic gastric cancer treated with apatinib showed that the median PFS was prolonged by 24.5 days (86.5 *versus* 62 days) in patients who developed adverse reactions such as hypertension, proteinuria, and hand-foot syndrome within 4 weeks of taking the drug, and the median OS was extended by 2.2 months (20). In our study, further analysis showed that the median PFS was prolonged by 4.8 months in patients with hypertension receiving apatinib and etoposide ($p = 0.022$), and the median PFS in patients with proteinuria was extended by 4.1 months ($p = 0.036$), but there was no statistically significant difference in overall survival. The trends of adverse reactions and curative effects in this study are consistent with previous studies, and it is worth expanding the sample size for further research.

This study did have some limitations. First, the number of patients enrolled was small, and there was a lack of control cases. Second, there might be bias in the population because this is a single-arm, single-center clinical trial.

In summary, this study demonstrates that apatinib combined with etoposide capsules has a good effect in the second-line treatment of HER2-negative locally advanced and metastatic breast cancer with tolerable adverse reactions, suggesting that the combination deserves further phase III clinical research.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be available from the corresponding author by request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PY proposed ideas and designed studies study concepts, and review manuscript. Conception and design were performed by BX, PY, JW, and FM. All authors have contribution in collection and assembly of data. Data analysis and interpretation were done by NH, AZ, YS, JY, and XW. NH was a major contributor in writing the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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