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ORIGINAL RESEARCH

Anlotinib or Bevacizumab Combined with Taxane/Capecitabine for the Second-Line or Subsequent Treatment of HER-2 Negative Metastatic Breast Cancer: A Retrospective Cohort Study

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Background: Anlotinib and bevacizumab have demonstrated efficacy in treating HER-2 (human epidermal growth factor receptor 2)-negative metastatic breast cancer (MBC), yet no comparative studies have been conducted to access their effectiveness in MBC patients. Accordingly, this study aimed to evaluate the safety and effectiveness of anlotinib versus bevacizumab when combined with taxane/capecitabine for second-line or subsequent treatment of HER-2-negative MBC.

Methods: Patients with pathologically confirmed HER-2-negative MBC that underwent second-line or subsequent treatment of anlotinib or bevacizumab plus taxane/capecitabine between April 2020 and October 2021 were retrospectively reviewed. Outcomes including the objective response rates (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) were analyzed.

Results: A total of 130 patients were included for this study, with 67 in the anlotinib + chemotherapy group and 63 in the bevacizumab + chemotherapy group. The ORRs were 40.30% for the anlotinib + chemotherapy group and 30.16% for the bevacizumab + chemotherapy group (P = 0.27), while the DCRs were 86.57% and 69.84%, respectively (P = 0.03). Patients in the anlotinib + chemotherapy group showed significantly longer median PFS and OS compared to the bevacizumab + chemotherapy group (mPFS: 8.57 vs 5.90 months, HR 0.55 [95% CI 0.36–0.85], P = 0.04; mOS: 22.76 vs 16.50 months, HR 0.63[95% CI 0.43–0.93], P = 0.02). The most common treatment-related adverse events (TRAE) were grade 1/2 alopecia, peripheral neuropathy, hypertension, and granulocytopenia, with both groups exhibiting tolerable TRAE profiles.

Conclusion: In this retrospective analysis, anlotinib combined with taxane/capecitabine demonstrated a manageable safety profile. This regimen was associated with improved DCR, PFS, and OS compared to bevacizumab plus chemotherapy in patients with HER2-negative MBC. These findings suggest that anlotinib may represent a promising therapeutic option for patients for whom ADC drugs are inaccessible or unsuitable; however, further prospective, randomized studies are warranted to confirm.

Keywords: anlotinib, breast cancer, angiogenesis, taxane, capecitabine

Introduction

Breast cancer (BC) is the leading cancer in prevalence and mortality among women, with 2.3 million diagnoses and 666,000 deaths recorded globally in 2022 alone.[1] Classification into five subtypes based on gene expression profiling is crucial for targeted treatment strategies.[2] HER-2 positive BC benefits from targeted therapies like Herceptin, small molecule tyrosine kinase inhibitors (TKIs), and antibody-drug conjugates (ADCs).[3] HER-2 negative BC comprises Hormone receptor (HR)-positive her-2 negative BC and as well as triple negative breast cancer (TNBC),[4] with HR-positive HER-2-negative BC responding to endocrine therapies including tamoxifen and aromatase inhibitors,[3] and CDK4/6 inhibitors. With ongoing

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advances in treatment, for patients with HR-positive, HER2-negative breast cancer with visceral crisis or endocrine resistance, beyond systemic chemotherapy options, sacituzumab govitecan (SG) (targeting TROP2), trastuzumab-deruxtecan (T-DXd) (for HER2-low disease), and PAM pathway inhibitors have become recommended second-line and beyond treatment regimens.[5] However, when ADCs are inaccessible, unsuitable, or disease has progressed, systemic chemotherapy options A and B remain comparable. However, when ADCs are inaccessible, unsuitable, or disease progresses, systemic chemotherapy options for post-endocrine therapy progression are similar to TNBC patients. Chemotherapy remains the primary treatment for these patients, yet the efficacy is relatively limited. Novel therapies like PARP inhibitors, PAM pathway inhibitors and immunotherapies are subject to some limitations and require biomarker screening,[6] leaving many BC patients' needs unmet. This study focuses on exploring the therapeutic value of anti-angiogenic agents combined with chemotherapy for HR-positive, HER2-negative breast cancer and triple-negative breast cancer with visceral crisis or endocrine resistance, in situations where ADC is unavailable, unsuitable, or disease has progressed. Vascular endothelial growth factor (VEGF), crucial for tumor angiogenesis, is 7-fold higher in VEGF levels in BC tumors than in paracancerous tissues.[7] Preclinical studies showed that anti-angiogenic drugs combined with chemotherapy can overcome chemoresistance, improving treatment outcomes. The first anti-angiogenic drug, bevacizumab, has received approval for advanced BC, as well as liver, colorectal, and non-small cell lung cancer. It improves objective response rate (ORR) and progression-free survival (PFS) in HER-2-negative metastatic breast cancer (MBC) patients, although it does not extend patient OS.[8] Despite the US FDA withdrawing its indication for BC, and the 2022 NCCN guidelines removing its recommendation, ESMO continues to recommend it. Prior to 2022, for HR-positive, HER2-negative, and triple-negative breast cancers opting for systemic chemotherapy, combining a single-agent chemotherapy with an anti-angiogenic agent also constituted a treatment option. Other anti-angiogenic drugs like sunitinib,[9,10] ramucirumab,[11] and sorafenib[12] showed inadequate clinical benefits. Apatinib showed some efficacy in Chinese clinical trials but was limited by treatment-related toxicity.[13]

These breast cancers require novel antiangiogenic agents due to issues such as limited overall survival (OS) prolongation and a high incidence of antiangiogenic-associated adverse events. Anlotinib, targeting VEGFR, c-Kit, PDGFR, and FGFR, has shown efficacy and manageable toxicity in treating various solid tumors, including thyroid, small cell, and non-small cell lung cancers,[14] and has NMPA approval for these indications. In recent years, increasing evidence has emerged to support the efficacy of anlotinib in treating breast cancer. A Phase II study demonstrated anlotinib's efficacy as second-line or subsequent treatment for HER-2-negative advanced BC patients who failed prior treatments.[15] Several clinical studies have demonstrated the effectiveness of combining anlotinib with chemotherapy against metastatic breast cancer, while also showing that the toxicity is tolerable. These exploration has primarily focused on HER2-negative advanced breast cancer,[16] though it has also extended to the neoadjuvant[17] and combination with immunotherapy.[18,19] This study retrospectively evaluates the safety and effectiveness of the combination of anlotinib plus taxane/capecitabine versus bevacizumab plus taxane/capecitabine, based on data from our clinical center over recent years.

Materials and Methods

Patients

As this was a retrospective cohort study, a formal sample size calculation was not performed a priori. The study enrolled a total of 130 patients, which constituted all consecutive eligible patients with HER2-negative metastatic breast cancer who received either anlotinib or bevacizumab combined with taxane/capecitabine as second-line or subsequent therapy at our institution between April 2020 and October 2021. The detailed inclusion criteria were as follows: (1) aged 18–75 years; (2) patients with HER-2-negative BC who had failed at least one standard treatment underwent treatment after metastasis or relapse; (3) patients who were treated with anlotinib or bevacizumab combined with taxane or capecitabine; and (4) patients who had Eastern Cooperative Oncology Group (ECOG) scores of 0–1 and measurable lesions per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. This study was approved by the Ethics Committee of The Affiliated Yantai Yuhuangding Hospital of Qingdao University (Ethics approval #2022-276), conducted according to the principles of the Declaration of Helsinki, and written informed consent was obtained from all patients to participate in this study. All patients provided informed consent for the off-label use of anlotinib or bevacizumab.

Study Design and Procedures

Treatment Allocation: The choice between anlotinib and bevacizumab was primarily based on physician discretion, considering factors such as drug availability during the study period, patient comorbidities (eg, baseline hypertension, proteinuria risk profile), patient preference after detailed discussion of potential toxicities, and out-of-pocket payment considerations.

Based on actual treatment for BC, patients were categorized into two groups: anlotinib + chemotherapy (taxane paclitaxel or capecitabine) and bevacizumab + chemotherapy (taxane paclitaxel or capecitabine). Anlotinib, administered orally at a dose of 12 mg q.d. daily for 14 days per cycle, was adjusted to 10 mg or 8 mg dose in cases of intolerable toxicity. Bevacizumab was intravenously administered at a dosage of 10 mg/kg every three weeks according to Chinese Society of Clinical Oncology (CSCO) Guideline. Chemotherapy regimens consisted of capecitabine, docetaxel, nab-paclitaxel, or paclitaxel, dosed at 1000 mg/m^2 orally twice per day (days 1–14) every 3 weeks, 75–100 mg/m^2 i.v. every 3 weeks, 260 mg/m^2 i.v. every 3 weeks, and 175 mg/m^2 i.v. every 3 weeks. Hospital medical records and imaging systems were used to assess patient clinical characteristics. PFS and overall survival (OS) were analyzed through outpatient visits and telephone follow-ups. Follow-up and OS Data Capture: We employed a multi-source approach to ensure accurate OS data: 1) Regular review of hospital electronic medical records; 2) Cross-referencing with regional death registries; 3) Active telephone follow-ups conducted by trained research staff. The loss-to-follow-up rate was 4.6% (Unable to Contact = 6/130 patients), which is relatively low and helps mitigate potential bias. Adverse events were identified based on inpatient and outpatient medical records for each treatment cycle.

Effectiveness and Safety Analysis

To ensure objectivity and consistency, all baseline and follow-up imaging studies were independently reviewed by two experienced radiologists who were blinded to the patient's treatment group assignment. Assessments were performed using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). In cases of discrepancy between the two initial reviewers, a final consensus was reached through discussion with a third senior radiologist. The primary effectiveness measures included ORR, disease control rate (DCR), PFS and OS. ORR is calculated as the sum of the percentage of patients achieving CR and PR. DCR is the sum of the proportion of patients with CR, PR and stable disease (SD). PFS is defined as the duration from treatment initiation to disease progression or death from any cause. OS is the duration from treatment initiation to death from any cause. Safety analysis were performed for patients who received at least one treatment as per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE 5.0).

Statistical Analysis

SPSS v26.0 (SPSS, Inc., IL, USA) was used for all statistical testing. Categorical data are presented as frequencies with percentages, while continuous data are reported as medians with ranges. Chi-square test were applied to analyze differences in baseline data for second-classified or unordered multiclassified indicators, and the rank-sum test was used for ordered multiclassified indicators. Pearson chi-squared tests were used to compare ORRs and DCRs among groups. Kaplan-Meier curves were used to assess median PFS and OS (mPFS and mOS), with two-sided long-rank tests used for group comparisons. Cox proportional regression model was applied to estimate hazard ratios with 95% confidence intervals (CIs). A p-value of less than 0.05 was considered statistically significant.

Handling of Missing Data: For baseline characteristics, the percentage of missing data was minimal (<2% for any variable) and was handled using complete-case analysis, as the impact on results was deemed negligible. This information has been added as a footnote to Table 1.

Multiple Testing: For the primary comparisons of ORR, DCR, PFS, and OS between the two main groups, no adjustment for multiple testing was applied, as these were pre-specified primary and secondary endpoints. All subgroup analyses are considered exploratory and were not adjusted for multiple comparisons; their results should be interpreted as hypothesis-generating.

Table 1 Patient Characteristics

Variable	Anlotinib +Chemotherapy	Bevacizumab+ Chemotherapy	p-value
Total (n=130)	67	63	
Age			
< 65	50(74.6%)	53(84.1%)	0.18
≥ 65	17(25.4%)	10(15.9%)	
ECOG			
0	15(22.4%)	23(36.5%)	0.08
1	52(77.6%)	40(63.5%)	
Hormone receptor			
Positive	40(59.7%)	33(52.4%)	0.40
Negative	27(40.3%)	30(47.6%)	
Type of metastatic site			
Non-visceral	14(20.9%)	29(46.0%)	0.00
Visceral	53(79.1%)	34(54.0%)	
Number of metastatic sites			
1	6(9.0%)	8(12.7%)	0.17
2	21(31.3%)	25(39.7%)	
≥3	40(59.7%)	30(47.6%)	
Neoadjuvant			
Yes	7(10.4%)	16(25.4%)	0.03
No	60(89.6%)	47(74.6%)	
Breast surgery			
No	8(12.0%)	11(17.5%)	0.65
Breast conserving surgery	9(13.4%)	7(11.1%)	
	50(74.6%)	45(71.4%)	
Adjuvant chemotherapy			
Yes	49(73.1%)	39(61.9%)	0.17
No	18(26.9%)	24(38.1%)	
Adjuvant endocrine therapy			
Yes	40(59.7%)	34(54.0%)	0.51
No	27(40.3%)	29(46.0%)	
Previous lines of systematic treatment			
1	15(22.4%)	37(58.7%)	<0.001
≥2	52(77.6%)	26(41.3%)	
Previously applied paclitaxel			
Yes	60(89.6%)	61(96.8%)	0.10
No	7(10.4%)	2(3.2%)	
Chemotherapy			
Pooled taxanes	35(52.2%)	33(52.4%)	0.66
Capecitabine	32(47.8%)	30(47.6%)	

Notes: Missing data for all variables were minimal (<2%) and were handled using complete-case analysis.

Results

Patient Characteristics

A total of 130 patients were included for this study, with 67 in the anlotinib + chemotherapy group and 63 in the bevacizumab + chemotherapy group (Figure 1). Of these, 72 had HR-positive BC and 58 had TNBC. The median follow-up intervals were 34.3 months for the anlotinib + chemotherapy group and 36.5 months for the bevacizumab + chemotherapy group, respectively. Among these patients, 56.15% had HR-positive disease, and all were diagnosed with MBC. There were no differences in patient age (P = 0.18), ECOG (P = 0.08), hormone receptor (P = 0.40), number of metastatic sites (P = 0.17), breast surgery (0.65), adjuvant chemotherapy (0.17), adjuvant endocrine (P = 0.51) or combined chemotherapy drugs (0.66), between the two groups. However, the anlotinib + chemotherapy group had

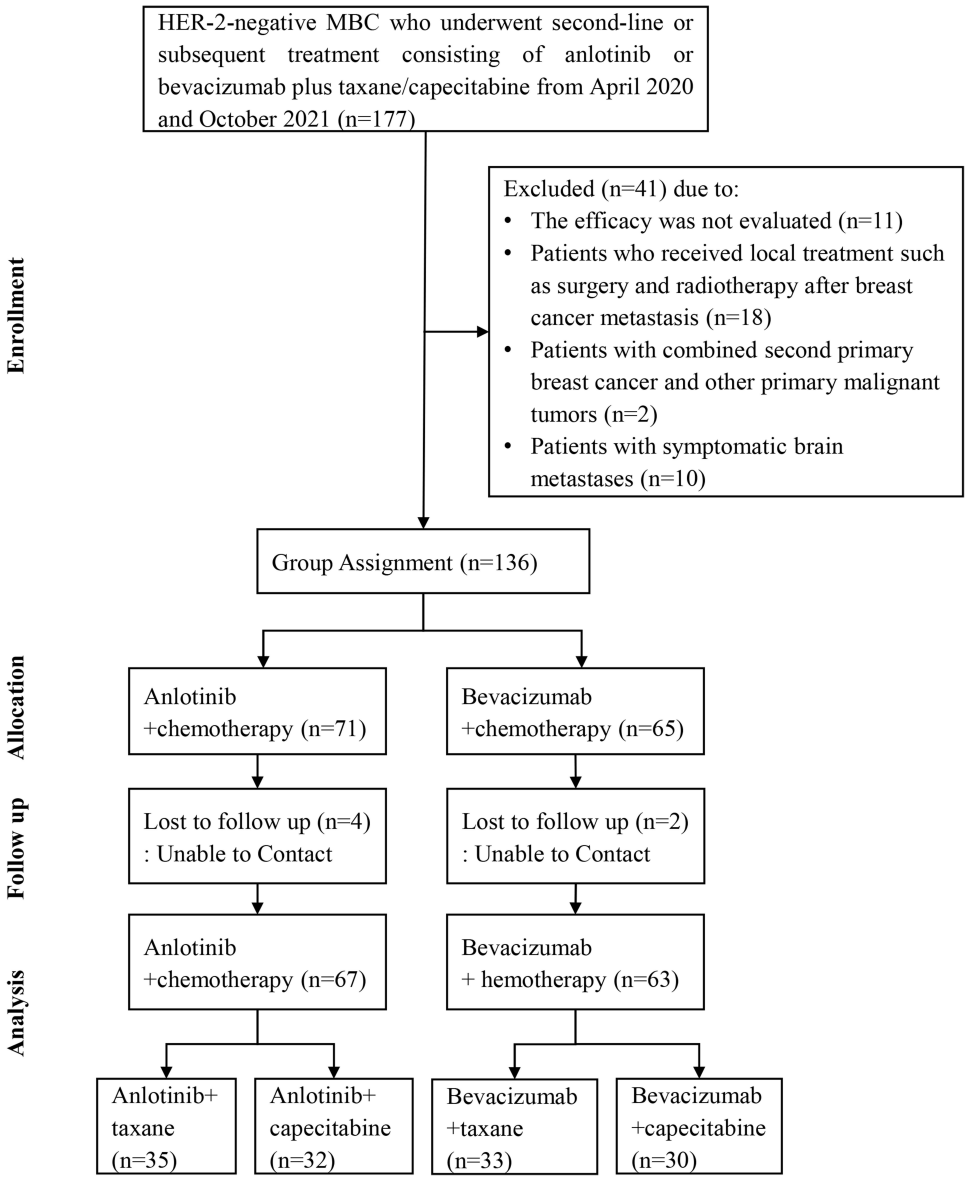

Figure 1 Flow chart. Diagram indicating participant numbers and disposition throughout the study period.

a higher proportion of patients with visceral metastases and those undergoing subsequent therapy, indicating a slightly poorer patient quality in this group. Detailed patient baseline characteristics were shown in Table 1.

Treatment Effectiveness

As of the February 1, 2024 cut-off date, 1 patient (1.49%) in the anlotinib + chemotherapy group and 0 (0%) in the bevacizumab + chemotherapy group were undergoing. OS events were recorded for 54 (80.6%) patients in the anlotinib + chemotherapy group and 55 (87.3%) patients in the bevacizumab + chemotherapy group, with 7 patients lost to follow-up. The median treatment cycles were 8 (range 2–8) for the anlotinib + chemotherapy group and 7 (range 1–8) for the bevacizumab + chemotherapy group.

The ORRs were 40.30% for the anlotinib + chemotherapy group and 30.16% for bevacizumab + chemotherapy group (P = 0.27), with a significant difference in the DCRs between the groups (86.57% vs 69.84%, P = 0.03) (Table 2). Patients treated with anlotinib + chemotherapy exhibited a significantly longer mPFS compared to those administered bevacizumab + chemotherapy (8.57 vs 5.90 months, HR 0.55 [95% CI 0.36–0.85], P = 0.04) (Figure 2A). The median

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Table 2 Effectiveness Outcomes in Patients Treated with Anlotinib +chemotherapy or Bevacizumab+chemotherapy

Tumor Response	Anlotinib+Chemotherapy (n=67)		Bevacizumab+Chemotherapy (n=63)		p-value
	No.	%	No.	%	
CR	2	2.98%	0	0	
PR	25	37.31%	19	30.16%	
SD	31	46.26%	25	39.68%	
PD	9	13.4%	19	30.16%	
ORR (CR+PR)	27	40.29%	19	30.16%	0.272†
DCR (CR+PR+SD)	58	86.56%	44	69.84%	0.032†

Notes: †Pearson chi-square analyses were used to compare ORRs and DCRs between the Anlotinib + Chemotherapy and Bevacizumab + Chemotherapy groups.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

PFS in group anlotinib + taxane, anlotinib+ capecitabine, bevacizumab + taxane, and bevacizumab + capecitabine were: 10.01 (95% CI 7.73–12.29), 6.78 (95% CI 5.27–8.29), 6.84 (95% CI 5.26–8.42), 4.87 (95% CI 3.80–5.94), respectively (Figure 2B).

Patients treated with anlotinib + chemotherapy had a significantly prolonged mOS compared to the bevacizumab + chemotherapy group (22.76 vs 16.50 months, HR 0.63[95% CI 0.43–0.93], P = 0.02) (Figure 3A). The median OS in group anlotinib + taxane, anlotinib+ capecitabine, bevacizumab + taxane, and bevacizumab + capecitabine were: 24.78 (95% CI 19.66, 29.89), 18.81 (95% CI 15.46–22.17), 16.71 (95% CI 13.87–19.55), 16.41 (95% CI 13.04–19.78), respectively (Figure 3B).

In multivariate Cox regression models for both PFS and OS, we adjusted for key potential confounders, including the number of prior lines of systematic treatment, ECOG status, neoadjuvant therapy, radiotherapy, previously applied paclitaxel, and type of metastatic site (visceral vs non-visceral). Univariate cox regression analysis showed a 40% reduction in the risk of progression in the anlotinib + chemotherapy group compared with the bevacizumab + chemotherapy group [HR (95% CI) = 0.60 (0.42–0.85)] (Table 3). After adjusting for confounders in the multivariate analysis, there was still a significant difference in PFS between the two groups (P = 0.01), with a 45% reduction in the risk of progression in the anlotinib + chemotherapy group [HR (95% CI) = 0.55 (0.36–0.85)] (Table 3).

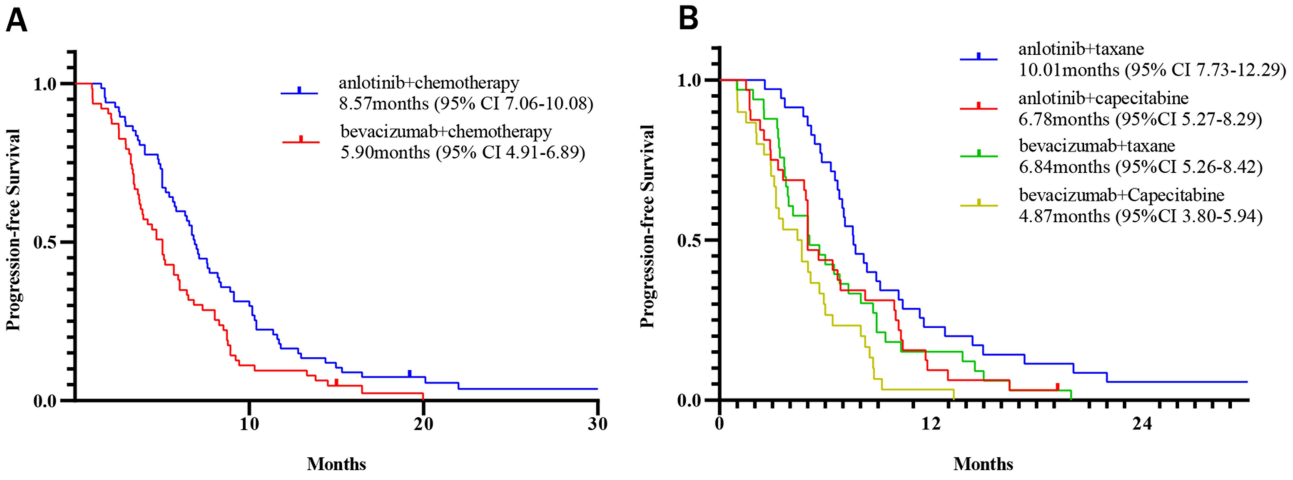

Figure 2 Analysis of PFS outcomes in patients treated with anlotinib + chemotherapy or bevacizumab + chemotherapy. (**A**) mPFS in BC patients administered anlotinib + chemotherapy or bevacizumab + chemotherapy. (**B**) mPFS in BC patients administered anlotinib + taxane, anlotinib + capecitabine, bevacizumab + taxane and bevacizumab + capecitabine. Log-rank tests were used to compare mOS values among groups. The HR and 95% CI values were estimated using Cox proportional hazards models.
Abbreviations: HR, hazard ratio; CI, confidence interval; PFS, progression-free survival.

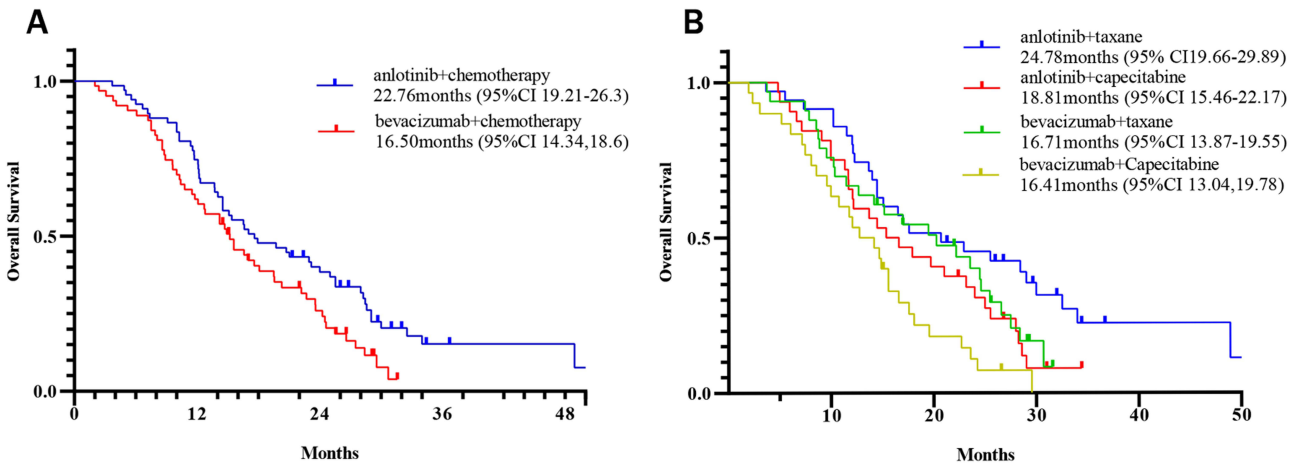

Figure 3 Analysis of OS outcomes in patients treated with anlotinib + chemotherapy or bevacizumab + chemotherapy. (**A**) mOS in BC patients administered anlotinib + chemotherapy or bevacizumab + chemotherapy. (**B**) mOS in BC patients administered anlotinib + taxane, anlotinib + capecitabine, bevacizumab + taxane and bevacizumab + capecitabine. Log-rank tests were used to compare mOS values among groups. The HR and 95% CI values were estimated using Cox proportional hazards models.
Abbreviation: OS, overall survival.

The analysis of OS was similar with that of PFS, with a 37% reduction in the risk of progression in the anlotinib + chemotherapy group compared with the bevacizumab + chemotherapy group [HR (95% CI) = 0.63 (0.43–0.93)]. After adjusting for six confounders, there was still a significant difference in OS between the two groups (P = 0.007), with a 46% reduction in the risk of death in the anlotinib + chemotherapy group versus the bevacizumab + chemotherapy group [HR (95% CI) = 0.54 (0.34–0.84)] (Table 4).

Patients under 65 years of age, with an ECOG score of 0, visceral metastases, four or more treatment lines, hormone receptor-negative status, and HER2 (human epidermal growth factor receptor 2) low expression appeared to gain the most benefit from the combination of anlotinib and chemotherapy. In the anlotinib + chemotherapy group, two patients achieved complete remission (CR) with imaging-confirmed brain and liver metastases, respectively. Five of the 25 patients in partial remission (PR) of the anlotinib + chemotherapy group had brain metastases that shrank by more than 30%. Figure 4 shows the swimming plots for the best response in OS (months). Exploratory subgroup analyses were

Table 3 Univariate and Multivariate Analyses for Progression-Free Survival

Variables	Univariate analysis	
	HR (95% CI)	**P value**
Anlotinib/bevacizumab +chemotherapy	0.60(0.42–0.85)	0.00
	Multivariate analysis	
	HR (95% CI)	**P value**
Anlotinib/bevacizumab +chemotherapy	0.55 (0.36–0.85)	0.01
Previous lines of systematic treatment	1.74(1.13–2.68)	0.01
ECOG	0.88(0.56–1.38)	0.57
Neoadjuvant	0.96(0.58–1.59)	0.86
Radiotherapy	1.16(0.75–1.81)	0.50
Previously applied paclitaxel	0.63(0.34–1.17)	0.14
Type of metastatic site	1.36(0.89–2.08)	0.15

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio;

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Table 4 Univariate and Multivariate Analyses for Overall Survival

Variables	Univariate analysis	
	HR (95% CI)	**P value**
Anlotinib/bevacizumab +chemotherapy	0.63(0.43–0.93)	0.19
	Multivariate analysis	
	HR (95% CI)	**P value**
Anlotinib/bevacizumab +chemotherapy	0.54 (0.34–0.84)	0.007
Previous lines of systematic treatment	0.76 (0.49–1.174)	0.22
ECOG	1.43 (0.91–2.23)	0.13
Neoadjuvant	0.74 (0.43–1.26)	0.26
Radiotherapy	1.2 (0.76–1.90)	0.43
Previously applied paclitaxel	1.00(0.53–1.90)	1.00
Type of metastatic site	0.68 (0.45–1.03)	0.07

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; receptor.

performed (Supplementary Figure 1); however, due to the limited cohort size, these results are not powered for definitive conclusions and are presented in the Supplementary Materials for interested readers.

Safety

In both groups, the most common treatment-related adverse events (TRAEs) were Grade 1 and 2, including granulocytopenia, alopecia, hypertension, and peripheral neuropathy. Anlotinib-treated patients were more susceptible to suffer from pharyngalgia (19.4% vs 4.8%), oral mucositis (14.9% vs 6.4%), and elevated TSH levels (31.3% vs 0%), while proteinuria was more common among individuals treated with bevacizumab (11.1% vs 4.5%). Mucositis and

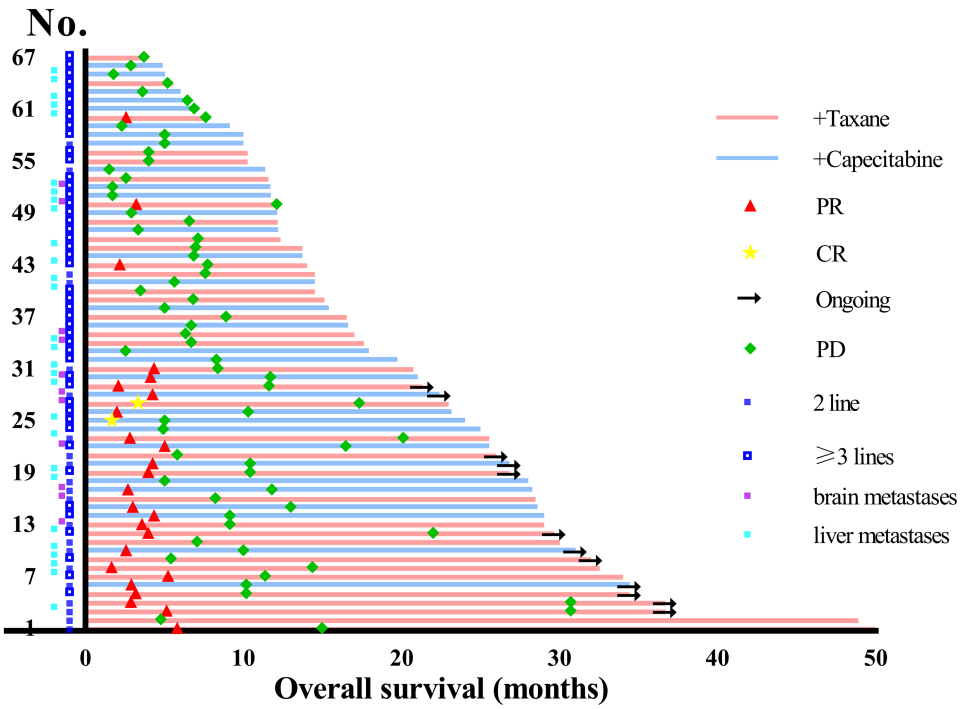

Figure 4 Tumor response in individual patients of anlotinib + chemotherapy group. Swimming plot illustrating the duration of response.
Abbreviations: CR, complete response; PR, partial response; PD, progressive disease.

Table 5 Treatment-Related Adverse Events

Adverse Events	All Grades		Grade 3/4	
	Anlotinib+ Chemotherapy	Bevacizumab+ Chemotherapy	Anlotinib+ Chemotherapy	Bevacizumab+ Chemotherapy
Fatigue	26(38.8%)	27(42.9%)	3(4.48%)	2(3.2%)
Anorexia	32(47.8%)	31(49.2%)	5(7.46%)	7(11.1%)
Weight loss	18(26.9%)	13(20.6%)	5(7.46%)	4(6.3%)
Pharyngalgia	13(19.4%)	2(3.2%)	3(4.48%)	0(0%)
Mucositis oral	10(14.9%)	4(6.4%)	3(4.48%)	0(0%)
Cough	10(14.9%)	0(0%)	3(4.48%)	0(0%)
Hand-foot syndrome	21(31.3%)	13(20.6%)	11(16.42%)	7(11.1%)
Urinary tract infection	3(4.5%)	0(0%)	0(0%)	0(0%)
Hematuria	5(7.5%)	4(6.3%)	0(0%)	0(0%)
Proteinuria	3(4.5%)	7(11.1%)	0(0%)	2(3.2%)
Hypertension	37(55.2%)	36(57.1%)	8(11.94%)	9(14.3%)
TSH elevation	21(31.3%)	0(0%)	0(0%)	0(0%)
Hypothyroidism	5(7.5%)	0(0%)	0(0%)	0(0%)
Alanine aminotransferase	13(19.4%)	16(25.4%)	3(4.48%)	7(11.1%)
Aspartate aminotransferase	8(11.9%)	7(11.1%)	0(0%)	2(3.2%)
Granulocytopenia	54(80.6%)	52(82.5%)	5(7.46%)	11(17.5%)
Thrombocytopenia	8(11.9%)	7(11.1%)	3(4.48%)	4(6.3%)
Anemia	21(31.3%)	20(31.7%)	0(0%)	0(0%)
Alopecia	40(59.7%)	40(63.5%)	13(19.40%)	13(21%)
Sensory neuropathy	35(52.2%)	36(57.1%)	5(7.46%)	11(17.5%)

pharyngalgia in the anlotinib group were primarily managed with supportive care (eg, oral rinses, analgesics), and dose reductions were implemented in cases of Grade 3 events (3 patients, 4.48%). TSH elevation (anlotinib group) was monitored closely, and none required treatment interruption; it was managed expectantly or with endocrinology consultation. Proteinuria (bevacizumab group) was monitored via urinalysis; for persistent Grade 2 or any Grade 3 events, temporary suspension or discontinuation was considered per guidelines (2 patients, 3.2%, had Grade 3 proteinuria leading to treatment discontinuation). Among the patients treated with anlotinib + chemotherapy, 12 underwent dose reductions to 10 or 8 mg due to intolerable toxicities. Except for hair loss, most TRAEs were well-controlled, with no serious TRAEs or treatment-related deaths during follow-up (Table 5).

Discussion

This study is the first retrospective comparison between anlotinib plus taxane/capecitabine with bevacizumab plus taxane/capecitabine as a second-line or subsequent treatment for HER-2-negative MBC. Our findings revealed that the ORRs and DCRs were higher in the anlotinib + chemotherapy group compared to the bevacizumab + chemotherapy group. Moreover, the mPFS and mOS were significantly longer in the anlotinib + chemotherapy group. These results highlight the potential therapeutic advantage of anlotinib plus chemotherapy for patients with pretreated HER-2 negative advanced BC. Regarding the baseline characteristics, it is important to acknowledge that patients in the anlotinib group presented with a higher disease burden, including a greater proportion of visceral metastases and more heavily pretreated status, factors typically associated with poorer prognosis. The observation that this group nonetheless achieved superior survival outcomes creates an apparent paradox. However, the significant improvement in both PFS and OS for the anlotinib group persisted even after rigorous multivariate adjustment for these key prognostic imbalances (Table 3 and Table 4). This suggests that the treatment effect of anlotinib may be substantial enough to overcome these negative baseline prognostic factors. We speculate that the multi-targeting nature of anlotinib, inhibiting not only VEGFR but also PDGFR, FGFR, and c-Kit, might confer a broader anti-angiogenic and direct anti-tumor effect, potentially leading to enhanced efficacy even in challenging clinical scenarios such as visceral metastases. Nonetheless, despite comprehensive

statistical adjustments, the potential for residual confounding inherent to retrospective studies cannot be entirely ruled out, and this finding should be interpreted within this context. Subgroup analyses further revealed that patients treated with anlotinib plus taxane exhibited the longest PFS (10.01 months) and OS (24.78 months). Prior research focused on the bevacizumab-based treatment for advanced BC have shown the combination of bevacizumab and paclitaxel exhibit the best therapeutic efficacy.[20]

For HR-positive HER2-negative advanced BC progresses following endocrine-based treatment, treatment options are limited, with chemotherapy being the primary choice and no standardized regimens for second-line or subsequent treatment, a situation also seen in TNBC.[21] The E2100 study demonstrated that first-line treatment with bevacizumab plus paclitaxel resulted in a 6-month prolongation of PFS.[22] However, other Phase III trials, such as AVADO[23] and RIBBON-1,[20] only detected a 1-month extension of PFS in patients treated with bevacizumab plus chemotherapy, without any OS benefits. Analyses of bevacizumab combined with chemotherapy revealed that bevacizumab plus weekly paclitaxel yielded the best outcomes, yet it did not correlate with improved quality of life or OS in randomized clinical trials or meta-analyses.[8] Consequently, the NCCN guidelines recommend the use of bevacizumab plus paclitaxel selectively, based on specific patient contexts.

Bevacizumab and other monoclonal antibody therapeutics face certain limitations, including the potential for immunogenicity, the requirement for their intravenous administration, and their potential to cause autoimmunity following extended treatment.[24] In contrast, as a small molecule drug, anlotinib is not subject to these limitations. Mechanistically, anlotinib inhibits the activation of VEGFR, PDGFR, FGFR, and c-Met, thereby preventing angiogenesis.[25] It exerts antitumor effects on cancer stem cells by suppressing of NF-κB pathway signaling, in addition to its anti-angiogenic activity.[26] Preclinical analyses have shown that anti-angiogenic drug treatment can induce tumor vascular normalization, thus enhancing drug delivery efficiency[27] and improving anti-tumor efficacy across a range of solid tumors.[28] Appropriate drug combinations may achieve superior antitumor outcomes, and some reports have demonstrated combination therapeutic efficacy when anlotinib was administered together with chemotherapy, immunotherapy in some cancers.[29–31] In recent years, anlotinib has demonstrated favorable efficacy and tolerability in breast cancer-related studies, whether administered as monotherapy[15] or in combination with eribulin,[16,32] metronomic chemotherapy,[33] or immunotherapy.[18,19] A study have confirmed the efficacy of anlotinib or in combination with DDP and elucidates the mechanism behind anlotinib's effectiveness, highlighting its role in inhibiting the JAK2/STAT3 pathway.[34] Actually, the application of anlotinib in BC treatment is currently under exploration, with some basic research indicating that anlotinib inhibits the proliferation, migration and invasion, and induces apoptosis of BC cells.[35]

There are also case reports and clinical studies evaluating the efficacy of anlotinib as monotherapy or in combination with chemotherapy or immunotherapy in MBC. A phase II study on anlotinib monotherapy in previously treated BC patients indicated efficacy in HER-2-negative MBC,[15] but further efficacy studies are warranted. Observations indicate that anlotinib plus eribulin[32] or QB2450[36] could be an alternative treatment for HER2-negative locally advanced or MBC. These studies suggest a therapeutic role for anlotinib in HER-2-negative MBC, but more evidence-based medical support is necessary. Accordingly, the present study was performed to compare anlotinib plus chemotherapy with bevacizumab plus chemotherapy as a second-line or subsequent treatment for patients with HER-2-negative MBC. These analyses revealed that the DCR were higher in the anlotinib group than in the bevacizumab group, with significantly longer PFS and OS outcomes for anlotinib-treated patients as compared to those treated with bevacizumab. Additionally, we also found that anlotinib may have therapeutic effects on BC patients with brain metastases. However, these findings are based on a very small number of cases and must be considered preliminary and anecdotal. They serve to generate a hypothesis for future investigation rather than to draw any firm conclusions. Further research is required to determine whether its mechanism of action is similar to that observed in lung cancer.[37]

The treatment landscape for HER2-negative metastatic breast cancer is rapidly evolving with the emergence of antibody-drug conjugates (ADCs), which have redefined therapeutic standards. For instance, the pivotal DESTINY-Breast04 trial established trastuzumab deruxtecan (T-DXd) as a new standard for patients with HER2-low disease, demonstrating a median PFS of 8.8 months and a median OS of 22.9 months in the overall population.[38] Similarly, the ASCENT trial[39] highlighted the efficacy of sacituzumab govitecan (SG) in triple-negative breast cancer −2. While the efficacy of these ADCs is remarkable, their accessibility can be limited by high cost, specific toxicity profiles (such as interstitial lung disease with T-DXd,[40] and regulatory approval processes in certain regions. In this context, our study

suggests that the combination of anlotinib and chemotherapy, which yielded a median PFS of 8.57 months and a median OS of 22.76 months, presents a viable and important therapeutic alternative. This regimen may be particularly valuable for patients who have progressed on or are ineligible for ADC therapy, or for those treated in healthcare settings with limited access to these novel agents.

Beyond direct effects on angiogenesis, the interplay between anti-angiogenic agents, chemotherapy, and the tumor microenvironment (TME) may significantly influence treatment outcomes. The TME is a complex ecosystem where stromal and immune cells interact with cancer cells, profoundly affecting tumor behavior and therapeutic response.[41] Within this network, extracellular vesicles (EVs) have emerged as critical mediators of metabolic reprogramming and intercellular communication. They can transfer pro-angiogenic factors, oncogenic signals, and drug-efflux pumps, potentially conferring resistance to both chemotherapy and targeted agents.[41] Anti-angiogenic therapy, by promoting vascular normalization, may enhance chemotherapy delivery and efficacy initially.[27] However, the impact on EV-mediated crosstalk remains an area of active investigation. It is plausible that the broader kinase inhibition profile of anlotinib (targeting VEGFR, PDGFR, FGFR) compared to bevacizumab might more effectively suppress the production or cargo of pro-tumoral EVs from various cellular components within the TME, thereby disrupting these resistance pathways and contributing to the observed survival benefit. Furthermore, the development of drug resistance often involves non-genetic adaptation through cancer cell plasticity. As comprehensively reviewed by Chatterjee et al, phenotypic switching allows cancer cell subpopulations to transiently enter a drug-tolerant persistent state, enabling survival under therapeutic pressure.[42] This dangerous duet between plasticity and resistance could modulate the feedback loops targeted by anti-angiogenic therapy. Tumor cells might evade VEGF pathway inhibition by activating alternative transcriptional programs and survival pathways. The multi-targeting nature of anlotinib, simultaneously inhibiting several receptor tyrosine kinases often implicated in these adaptive responses (eg, FGFR, PDGFR), might potentially hinder this escape mechanism more effectively than single-target VEGF blockade, limiting the tumor's ability to switch phenotypes and acquire resistance.[25,26] This provides a compelling, albeit speculative, mechanistic hypothesis for the superior long-term efficacy of anlotinib observed in our study.

To systematically decipher such complex resistance mechanisms, high-throughput functional genomics approaches like CRISPR screening have become indispensable. These technologies can pinpoint genetic determinants of therapeutic resistance on an unbiased, genome-wide scale, as demonstrated in studies identifying novel genes conferring resistance to targeted therapies like trametinib.[43] Applying similar strategies in breast cancer models treated with anlotinib or bevacizumab could future identify predictive biomarkers and rational combination partners to overcome resistance.

Finally, the future of cancer therapy is undoubtedly shifting towards more personalized and precise strategies, with an increasing focus on the immune microenvironment and molecular drivers of individual tumors.[44] In this evolving landscape, anti-angiogenic agents like anlotinib and bevacizumab are likely to find their niche not merely as pure anti-vascular agents, but as integral components of combination regimens that modulate the TME, overcome adaptive resistance, and synergize with other modalities like immunotherapy. Our findings contribute to this future by highlighting the potential of a multi-targeted TKI in a specific clinical context, paving the way for further research into patient selection based on TME characteristics and molecular profiling to maximize clinical benefit. In our study, we also identified the clinical applications of anlotinib in MBC included monotherapy, combination immunotherapy, and combination chemotherapy. In addition to taxane and capecitabine, the chemotherapy combination included agents such as gemcitabine, vinorelbine, and eribulin, all of which are recommended for HER-2 negative MBC. Because of the limited number of cases of MBC treated with other drugs in combination with anlotinib, we did not include them in our study. Our analyses confirmed the potential value of anlotinib combined with chemotherapy for HER-2-negative MBC patients. Clinical trials are currently enrolling patients to assess the efficacy of anlotinib ina combination with capecitabine and immunotherapy in BC. In future studies, we will specifically examine the safety and effectiveness of combining anlotinib and immunotherapy in this patient population.

This study is subject to some limitations. First, this was a retrospective study without a strict design, potentially introducing bias to our conclusions. Second, due to the retrospective collection of patients' prior treatment data, baseline imbalances existed in factors such as the number of prior treatment lines and visceral metastases. Moreover, patient enrollment for this study occurred between 2020 and 2021, a period when ADC drugs were not yet available as a treatment option. So the advantages of combining the anti-angiogenic drug anlotinib with chemotherapy are only applicable to patients for whom ADC drugs are inaccessible or unsuitable Finally, the sample size was modest, which limited the statistical power for subgroup analyses.

Conclusions

In this retrospective study of patients treated within a specific historical period (2020–2021, prior to the widespread adoption of ADCs), anlotinib combined with chemotherapy showed superior DCR, PFS, and OS compared to bevacizumab plus chemotherapy in HER2-negative MBC. However, these findings are derived from a retrospective analysis and require validation in prospective, randomized trials. In the current era where ADCs represent a standard of care for many patients, the definitive value and positioning of this anlotinib-based regimen remain to be fully established. It may represent a therapeutic option for patient populations with limited access to ADCs, for whom ADCs are unsuitable, or following disease progression on ADC therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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