ORIGINAL RESEARCH

Efficacy and safety of anlotinib combined with chemotherapy in the treatment of metastatic triple negative breast cancer

Yeqiang Qian[1], Hefang Wu[1], Lu Gao[1],*

[1]Department of Oncology, Zongyang County People's Hospital, 246700 Tongling, Anhui, China

*Correspondence
lu_gao1226@163.com
(Lu Gao)

Abstract

In order to explore the efficacy of anlotinib combined with chemotherapy in the treatment of metastatic triple negative breast cancer, 100 patients with triple negative breast cancer who met the screening criteria were divided into two groups according to the random number table method. One group was treated with albumin bound paclitaxel and cisplatin chemotherapy as the conventional chemotherapy group, and the other group was treated with anlotinib Hydrochloride Capsules on the basis of the conventional chemotherapy group. Both groups were treated for 6 cycles. After half a year of treatment, compared with the conventional chemotherapy group, the Orr and CBR of the combined drug treatment group were significantly increased, and the levels of bone sialoprotein (BSP), prolactin (PRL), insulin like growth factor-1 (IGF-1) and angiopoietin-2 (Ang-2) were significantly decreased, the difference was statistically significant. There were no serious adverse events in the two groups during the treatment, and there was no significant difference in the incidence of adverse reactions between the two groups; The deadline for follow-up of all patients was June 2023, and the follow-up time was 8–36 months. The medianProgression-free survival (PFS) of patients in the conventional chemotherapy group was 29.38 months (95% CI: 26.918–31.842), and the median PFS of patients in the combined drug treatment group was 33.72 months (95% CI: 32.417–35.023). There was a statistically significant difference in survival between the two groups (Log rank = 4.072, p = 0.044). The curative effect of anlotinib combined with chemotherapy in the treatment of metastatic triple negative breast cancer is significant, which can effectively reduce the level of relevant serum factors, has high safety, and is helpful to improve the survival of patients.

Keywords

Triple negative breast cancer; Anlotinib; Chemotherapy; Safety; Efficacy

1. Introduction

According to the World Health Organization, breast cancer (BC) accounted for up to 2.26 million of the 19.29 million new cancer cases in 2020, surpassing lung cancer as the most prevalent cancer worldwide [1]. BC is the most common malignancy among Chinese women. Approximately 40,000 newly reported BC cases in China every year, and its prevalence is on the rise [2, 3]. A subtype of BC, triple negative BC (TNBC), accounts for 15%–20% of all BC cases and has the poorest prognosis. TNBC is highly invasive, heterogeneous and recurrent, and is typically diagnosed at an advanced stage. TNBC lacks a specific and effective therapeutic target, so chemotherapy is the primary treatment [4, 5]. A combination of anthracycline and paclitaxel is recommended for TNBC chemotherapy. However, this regimen leads to early drug resistance, cytotoxicity and cardiotoxicity and fails to delay TNBC recurrence and metastasis [6]. Combining plat-

inum with other pharmacological treatments has been the focus of TNBC research in recent years, demonstrating favorable clinical efficacy by targeting TNBC's highly invasive and metastatic characteristics [7, 8]. Moreover, antiangiogenic agents have been proposed as a possible treatment for TNBC since angiogenesis is crucial to tumor growth, nutrient supply and metastasis [9]. Anlotinib, as a novel small molecule receptor tyrosine kinase inhibitor, inhibits angiogenesis and tumor progression by blocking the phosphorylation of vascular endothelial growth factor (VEGR)2/3, thereby inhibiting VEGR2/3-mediated signaling. The drug also inhibits angiogenesis by selectively binding to cancer cell surface specific receptors, such as platelet-derived growth factor receptors and fibroblast growth factor receptors [10, 11]. Research on arotinib and chemotherapy in TNBC is relatively limited at present. To fill a gap in the current literature, this study compared conventional chemotherapy with an arotinib combination to examine the efficacy and safety of this scheme for TNBC,

providing evidence support for this approach to metastatic cancer treatment.

2. General data and methods

2.1 Patient data

Patients with relapsed metastatic BC admitted for treatment at our hospital between March 2020 and May 2022 were included in this study. Inclusion criteria: (1) Females aged 18–75 years; (2) Diagnosed as metastatic BC by histology or cytology and confirmed as TNBC by pathology or radiological examination and tumor tissue immunohistochemistry (IHC) [12]; (3) Eastern Cooperation Oncology Group (ECOG) score of 0–2 with a life expectancy of >3 months; (4) Normal organ functions; (5) Complete clinical data and voluntary study participation. Exclusion criteria: (1) Pregnant or breastfeeding; (2) Comorbid with neurological or central nervous system disorders affecting normal communication; (3) Conditions that impact the oral administration and absorption of the study drug, such as dysphagia, gastrointestinal resection, prolonged diarrhea or immune enteropathy; (4) History of uncontrollable hypertension, hematological disease, heart (myocardial infarction and heart failure), liver or kidney dysfunction; (5) Has contraindications for the study chemotherapeutic drugs and their ingredients, such as a pre-treatment peripheral blood neutrophil count of $<1500/mm^3$.

100 patients were selected based on the eligibility criteria and divided into the conventional chemotherapy group (n = 50) and combination therapy group (n = 50) using a random number table. Patients in the conventional chemotherapy group had a mean age of 55.11 ± 10.85 years. There were 14 cases of stage IIIb TNBC, 36 cases of stage IV TNBC, 38 cases of invasive ductal carcinoma, and 12 cases of invasive lobular carcinoma. Metastases were found in 19 patients as lymph nodes and soft tissue metastases, 15 as lung metastases, 13 as liver metastases, and 3 as bone metastases. Patients in the combination therapy group had a mean age of 54.78 ± 11.31 years. There were 17 cases of stage IIIb TNBC, 33 cases of stage IV TNBC, 34 cases of invasive ductal carcinoma, and 16 cases of invasive lobular carcinoma. Metastases were found in 16 patients as lymph node and soft tissue metastases, 21 as lung metastases, 9 as liver metastases, and 4 as bone metastases. Both groups had comparable clinical characteristics.

2.2 Methods

All patients undergo routine vital sign monitoring, blood routine, liver and kidney function, coagulation function and other blood tests, as well as targeted lesion nuclear magnetic resonance imaging (MRI), computed tomography (CT) or ultrasound imaging examinations. For diagnosed tumors, imaging examinations can assist in determining the possibility of surgical resection and feasible surgical methods, thereby improving the detection rate of lesions and tumor staging. Conventional vital sign monitoring, hematology tests (*e.g.*, complete blood counts, liver/kidney function tests and coagulation tests), and radiological examinations (*e.g.*, magnetic resonance imaging (MRI) and computed tomography (CT)) of the target lesion were performed on all patients. Imaging examinations can improve the detection rate of lesions and tumor staging accuracy for diagnosed tumors. This will help determine the possibility of surgical resection and feasible surgical methods. The conventional chemotherapy group received albumin-bound paclitaxel and cisplatin. Albumin-bound paclitaxel (CSPC Pharmaceutical Group Co., Ltd., Shijiazhuang, Hebei, China, NMPA approval no. H20183044, 100 mg) was administered at a dose of 260 mg/m^2 *via* intravenous infusion (30 min) once every 3 weeks. If severe neutropenia (Absolute Neutrophil Count (ANC) $<500/mm^3$ for 1 or more weeks) or severe sensory neurotoxicity is observed during treatment, the dose of paclitaxel should be reduced to 220 mg/m^2 in subsequent treatment. The dose of paclitaxel will need to be reduced to 180 mg/m^2 if the adverse reactions persist after dose reduction. Grade 3 sensory neurotoxicity should be withheld, and treatment may be resumed at a lower dose after the neurotoxicity improves to grade ≤ 2. Cisplatin injection solution (Nuoxi, Hansoh Pharmaceutical Group, Co., Ltd., Lianyungang, Jiangsu, China, NMPA approval no. H20040813, 6 mL: 30 mg) was administered at 20 mg/m^2 body surface area once daily for 5 consecutive days or at 30 mg/m^2 body surface area for 3 days. The prevention of cisplatin-induced nephrotoxicity requires adequate hydration. 2000 mL of isotonic glucose solution was administered *via* intravenous drip 12 h before cisplatin injection. 3000–3500 mL of isotonic saline or glucose solution was given on the day of cisplatin injection. To achieve a daily urine volume of 2000–3000 mL, potassium chloride, mannitol and furosemide were also administered. The combination therapy group received conventional chemotherapy plus anlotinib hydrochloride capsules (Focus V, Chia Tai Tianqing Pharmaceutical Group Co., Ltd., Lianyungang, Jiangsu, China, NMPA approval no. H201820004, 12 mg). Anlotinib is recommended at 12 mg, take orally once a day before breakfast for 2 consecutive weeks followed by 1 week of discontinuation (*e.g.*, 21-day cycle). Anlotinib was administered until disease progression or adverse reactions occurred. A missed dose during the treatment period is skipped if the next dose is less than 12 h away. Among the main adverse reactions that lead to dose reductions are abnormal liver function, hand and foot skin reactions, hypertension, fatigue, diarrhea, anorexia, proteinuria, *etc*. For patients to tolerate treatment, dose adjustments should be made according to the severity of adverse reactions. The adjustment method is to adjust the dose for the first time: 10 mg, once a day, continuously for 2 weeks, stop for 1 week, and then adjust the dose for the second time: 8 mg, in the same method as the first adjustment. Upon finding put that the patient can't tolerate an 8 mg dose, the medication will be discontinued permanently. Anlotinib is permanently discontinued if it is still intolerable at 8 mg. Safety is assessed every cycle, and efficacy every 2 cycles. The chemotherapy course lasted 6 cycles.

2.3 Outcome measures

2.3.1 Efficacy evaluation

Changes in patient conditions were assessed at 6 months post-treatment using the Response Evaluation Criteria in Solid Tumors [13]. Efficacy was classified as complete remission (CR): Shortest diameter of all target and non-target lesions and

their pathologic lymph nodes are <100 mm; Partial response (PR): ≥30% decrease in sum of longest diameters (SLD) of target lesions; Progressive disease (PD): ≥20% increase in SLD of target lesions or new lesions; Stable disease (SD): Neither sufficient shrinkage to quality for PR nor sufficient increase to quality for PD.

Progression-free survival (PFS) is the time from treatment initiation to PD, death or follow-up loss. Overall survival (OS) is the time from randomization to death or follow-up loss. Objective response rate (ORR) is the percent of patients who achieve CR and PR. Clinical benefit rate (CBR) is the percent of patients who achieve CR, PR and SD after treatment.

2.3.2 Detection of serological markers

Morning venous blood sample was collected from patients' elbow before and 6 months after treatment. Blood samples were centrifuged to obtain serum, which was used for measuring the levels of bone sialoprotein (BSP), prolactin (PRL), insulin like growth factor-1 (IGF-1) and angiopoietin-2 (Ang-2). BSP, IGF-1 and Ang-2 were measured by enzyme-linked immunosorbent assay (BSP ELISA kit: Guangdong Gucon Biotech Co., Ltd., Beijing, China, catalogue #K4222; IGF-1 and Ang-2 ELISA kits: Cusabio Biotech Co., Ltd., Jinan, Shandong, China, catalogue #CSB-E13766h and CSB-E04500h). RPL was detected using a magnetic particle-based chemiluminescence immunoassay (Beijing North Institute of Biotechnology Co., Ltd., approval no. YSYJX2013-2400417). Normal range of each indicator: BSP, 0~15 μg/L; PRL <20 μg/L; IGF-1, 49~551 μg/mL; Ang-2, 20~60 pg/mL.

2.3.3 Comparison of adverse reactions

The incidences of adverse reactions including skin itching, diarrhea, nausea and vomiting were recorded and compared between the two groups.

2.3.4 Survival

Patient survival after treatment was monitored by bi-monthly clinic visits or telephone.

2.4 Statistical analysis

After quantitative processing of all data, SPSS 23.0 (SPSS Inc., Chicago, IL, USA) was used for processing and analysis. Counting data such as gender, clinical stage, tumor type, metastasis type, clinical efficacy, and adverse reactions were expressed as number of cases (percentage) by chi square test. Quantitative data such as average age and serological indicators of patients were verified for normal distribution and expressed as sample mean using independent sample t-test. Kaplan Meier was used to plot the patient survival curve, with a statistically significant difference of $p < 0.05$.

3. Results

3.1 Clinical efficacy

Efficacy at 6 months post-treatment is summarized in Table 1. The combination therapy group had significantly higher ORR (67.00% *vs.* 46.00%, $\chi^2 = 4.058$, $p = 0.044$) and CBR (86.00% *vs.* 68.00%, $\chi^2 = 4.574$, $p = 0.032$) than the conventional chemotherapy group.

3.2 Dose modification in combination therapy group

During treatment, anlotinib dose remained unmodified at 12 mg/capsule for 17 of 50 patients. It was reduced to 10 mg/capsule for 19 patients, to 8 mg/capsule for 14 patients in the combination therapy group. Neither patient had to discontinue treatment due to intolerance.

3.3 Serum marker levels

Before treatment, serum BSP, PRL, IGF-1 and Ang-2 levels were similar between the two groups ($t = 0.040$, 1.688, 1.055 and 0.063, $p = 0.968$, 0.095, 0.294 and 0.950, respectively). There was a significant reduction in these 4 serum markers after treatment in both groups with the combination therapy group significantly lower than the conventional chemotherapy group ($p < 0.05$) (Table 2).

3.4 Adverse reactions

Adverse reactions of varying severity were observed during treatment (Table 3). Neither group experienced any serious adverse events or treatment-related deaths during the first 6 months of treatment, and the incidence of adverse reactions was similar between the two groups. All adverse reactions resolved after symptomatic interventions.

3.5 Survival

All patients were tracked until June 2023, with a follow-up time of 8 to 36 months. As of the follow-up cutoff date, 21 deaths (58.00% survival) occurred in the conventional chemotherapy group and 13 deaths (74.00% survival) in the combination therapy group. Conventional chemotherapy had a median PFS of 29.38 months (95% CI: 26.918–31.842) and combination therapy had a median PFS of 33.72 months (95% CI: 2.417–5.023). There was a significant difference in survival between the two groups (log rank = 4.072, $p = 0.044$) (Fig. 1).

4. Discussion

National coverage for breast cancer screening is continuously expanding under the Healthy China strategy, reinforcing the concept of "early screening, early prevention, and early treatment" for BC [14]. As of now, China's early detection rate of BC is under 20%, and <5% BC cases are detected through screening [15]. For patients over 40 years of age without breast disease, breast-related genetic factors or a family history of breast conditions, regular physical screenings are recommended [16]. China has slightly lower prevalence and mortality rate of BC than the global average, but its prevalence is increasing every year as lifestyle, dietary habits, and environmental factors change [17, 18]. Chemotherapy, radiation therapy, endocrine therapy and targeted therapy are traditional treatments that aim to suppress tumor cell proliferation. However, due to abnormal angiogenesis, traditional drugs and immune cells cannot penetrate abnormal tumor blood

TABLE 1. Comparison of clinical efficacy (n (%)).

Group	Number of patients	CR	PR	SD	PD
Conventional chemotherapy	50	3 (6.00)	20 (40.00)	11 (22.00)	16 (32.00)
Combination therapy	50	6 (12.00)	27 (54.00)	10 (20.00)	7 (14.00)

CR: complete remission; PR: partial response; PD: progressive disease; SD: Stable disease.

TABLE 2. Comparison of serum markers.

Group	Number of patients	Time	BSP (μg/L)	PRL (μg/L)	IGF-1 (μg/mL)	Ang-2 (pg/mL)
Conventional chemotherapy	50	Pre-treatment	54.05 $\pm$ 7.73	27.45 $\pm$ 3.62	260.77 $\pm$ 33.45	94.53 $\pm$ 19.38
		Post-treatment	27.00 $\pm$ 6.83	19.33 $\pm$ 3.87	219.55 $\pm$ 31.35	50.88 $\pm$ 8.90
Combination therapy	50	Pre-treatment	54.11 $\pm$ 7.23	26.11 $\pm$ 4.28	253.08 $\pm$ 39.15	94.79 $\pm$ 22.00
		Post-treatment	21.47 $\pm$ 4.22	12.18 $\pm$ 2.72	152.55 $\pm$ 21.36	37.63 $\pm$ 9.33
t			4.868	10.693	12.488	7.265
p			<0.001	<0.001	<0.001	<0.001

BSP: bone sialoprotein; PRL: prolactin; IGF-1: insulin like growth factor-1; Ang-2: angiopoietin-2.

TABLE 3. Comparison of adverse reactions (n (%)).

Adverse reaction	Conventional chemotherapy group (n = 50)				Combination therapy (n = 50)				χ^2	p
	I	II	III–IV	Total	I	II	III–IV	Total		
Skin itching	14	15	7	36 (72.00)	12	10	5	27 (54.00)	3.475	0.062
Hand-foot syndrome	13	7	8	28 (56.00)	10	7	6	23 (46.00)	1.000	0.317
Granulocytopenia	9	7	3	19 (38.00)	7	7	4	18 (36.00)	0.043	0.836
Thrombocytopenia	18	9	6	33 (66.00)	16	8	4	28 (56.00)	1.051	0.305
Abnormal liver function	11	4	6	21 (42.00)	8	5	5	18 (36.00)	0.378	0.539
Gastrointestinal reaction	14	10	5	29 (58.00)	12	8	6	26 (52.00)	0.364	0.546
Fatigue	20	12	11	43 (86.00)	19	13	8	40 (80.00)	0.638	0.424
Anorexia	14	10	6	30 (60.00)	10	8	4	22 (33.00)	2.564	0.109
Diarrhea	24	15	7	46 (92.00)	22	11	8	41 (82.00)	2.210	0.137
Stomatitis	8	3	1	12 (24.00)	5	4	1	10 (20.00)	0.233	0.629
Proteinuria	23	10	2	35 (70.00)	18	7	3	28 (56.00)	2.102	0.147

vessels and mediate their effects inside the tumor, leading to drug resistance [19]. Vascular regeneration plays a crucial role in tumor angiogenesis [20]. Tyrosine kinase inhibitors (TKIs) are antiangiogenic agents with antitumor properties that inhibit tumor angiogenesis through specific blockade of vascular endothelial growth factor receptor signaling [21, 22]. TKIs commonly used in clinical settings include apatinib and anlotinib.

TNBC is increasingly treated with platinum agents, with platinum-based chemotherapy regimens and antiangiogenic therapy showing satisfactory effects [23]. During the growth, invasion and metastasis of various tumors, angiogenesis transports key substances required for growth to the tumors. Higher permeability of newly formed blood vessels is more conducive to tumor cell invasion and metastasis [24]. In other tumor treatment processes, anlotinib has been shown to reduce tumor metastases, prolong survival, and inhibit tumor angiogenesis. Anlotinib has therapeutic effects on t tumors, but also adverse reactions. An adverse reaction requires a doctor's intervention to adjust the dosage or stop the medication [25]. As a result,
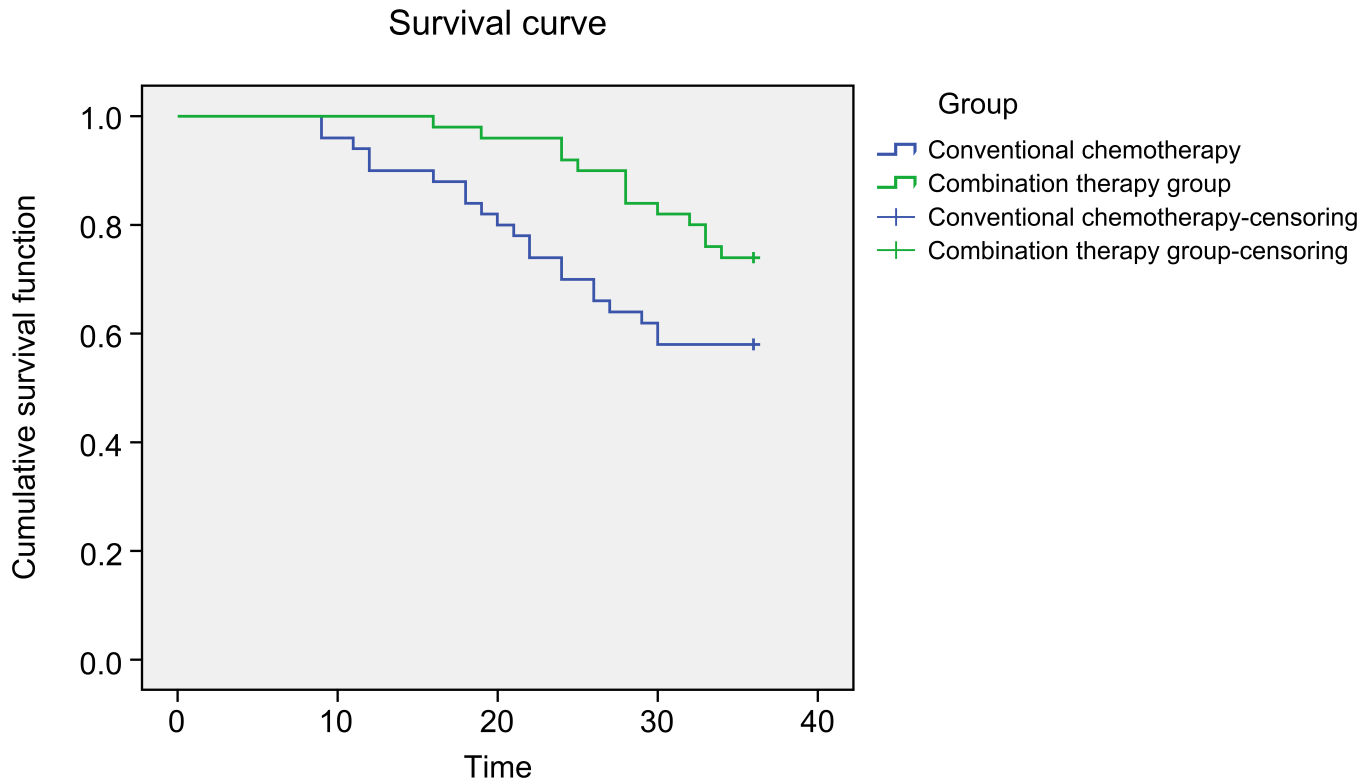
Survival curve

F I G U R E 1. Survival curve.

we added anlotinib to cisplatin plus albumin-bound paclitaxel combination chemotherapy to validate its efficacy.

Objective response rate (ORR) refers to the proportion of patients whose tumors have shrunk to a certain amount and remained stable for a defined period of time. Clinical benefit rate (CBR) is an important measure of patients' overall efficacy during tumor treatment. In this study, the combination therapy group showed a significantly higher ORR and CBR than the conventional chemotherapy group, suggesting the combination therapy with anlotinib can markedly improve treatment response in TNBC. Comparing the levels of several representative serum cytokines between the two groups provided further insight into the mechanism of action of this drug. BSP is an acidic glycoprotein in the extracellular matrix that is associated with angiogenesis [26]. Among primary BC patients, Dehdari *et al*. [27] demonstrated that elevated serum BSP is a sign of early bone metastasis and is closely related to poor prognosis. PRL plays a key role in breast growth and development. Carrasco-Ceballos *et al*. [28] showed that PRL receptor expression is associated with various cell signaling pathways in BC development. A cytokine synthesized by the liver, IGF-1 has been shown to promote tumor cell growth, invasion and metastasis. BC patients have high levels of IGF-1 expression, which is negatively correlated with prognosis [29]. Ang-2 is a pro-angiogenic factor that enhances endothelial cell sensitivity to mitotic signaling and promotes angiogenesis [30]. Our findings demonstrated that the serum levels of these cytokines were significantly decreased after 6 treatment cycles in both groups and were markedly lower in the combination therapy group. Arotinib reduces BSP, PRL, IGF-1 and Ang-2 expression in TNBC. It is related to angio-

genesis, tumor cell invasion and metastasis. All indicators were downregulated, suggesting that it inhibited BC migration and invasion. This study compared the incidence of adverse reactions during treatment between two groups to verify the safety of the combination therapy. More adverse reactions occurred during the treatment process, including fatigue, diarrhea, thrombocytopenia, proteinuria, and hand-foot syndrome. Also, the combination chemotherapy group experienced fewer adverse reactions than the conventional chemotherapy group. Combination chemotherapy decreased fatigue by 3 patients, diarrhea by 5 and thrombocytopenia by 5. Among them, anorexia decreased the most in 8 cases, and the levels of various adverse reactions were reduced to varying degrees. These adverse reactions were within the expected range of the treatment plan, and no serious adverse events occurred during the treatment period. Through timely intervention or adjusting the medication dosage, they improved. Based on these findings, anlotinib combined with chemotherapy is a safe treatment option without significantly increasing adverse reactions. Furthermore, analysis of survival during the follow-up period also revealed that combination therapy resulted in prolonged PFS and OS in TNBC patients.

5. Conclusions

In summary, anlotinib in combination with chemotherapy is an effective and safe treatment approach that improves treatment response, downregulates serum BSP, PRL, IGF-1 and Ang-2 expression, and prolongs survival in TNBC patients. However, adverse reactions should be closely monitored during treatment and treated as soon as possible by appropriate dose modifications. This study is limited by a 3-year follow-up period. Our

next step will be to expand the sample size, delve deeper into the research content, and extend the follow-up period to 5 years to further verify its efficacy and safety.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

YQQ—designed the study and carried them out. YQQ, HFW and LG—supervised the data collection, analyzed the data, interpreted the data. YQQ and LG—prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Zongyang County People's Hospital (Approval no. 2019011). Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

ACKNOWLEDGMENT

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Katsura C, Ogunmwonyi I, Kankam HK, Saha S. Breast cancer: presentation, investigation and management. British Journal of Hospital Medicine. 2022; 83: 1–7.

[2] Xia C, Dong X, Li H, Cao M, Sun D, He S, *et al*. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. Chinese Medical Journal. 2022; 135: 584–590.

[3] Lei S, Zheng R, Zhang S, Wang S, Chen R, Sun K, *et al*. Global patterns of breast cancer incidence and mortality: a population-based cancer registry data analysis from 2000 to 2020. Cancer Communications. 2021; 41: 1183–1194.

[4] Tsang JYS, Tse GM. Molecular classification of breast cancer. Advances in Anatomic Pathology. 2020; 27: 27–35.

[5] Sukumar J, Gast K, Quiroga D, Lustberg M, Williams N. Triple-negative breast cancer: promising prognostic biomarkers currently in development. Expert Review of Anticancer Therapy. 2021; 21: 135–148.

[6] Yang F, Xiao Y, Ding JH, Jin X, Ma D, Li DQ, *et al*. Ferroptosis heterogeneity in triple-negative breast cancer reveals an innovative immunotherapy combination strategy. Cell Metabolism. 2023; 35: 84–100.e108.

[7] Popovic LS, Matovina-Brko G, Popovic M, Punie K, Cvetanovic A, Lambertini M. Targeting triple-negative breast cancer: a clinical perspective. Oncology Research. 2023; 31: 221–238.

[8] Latif F, Bint Abdul Jabbar H, Malik H, Sadaf H, Sarfraz A, Sarfraz Z, *et al*. Atezolizumab and pembrolizumab in triple-negative breast cancer: a meta-analysis. Expert Review of Anticancer Therapy. 2022; 22: 229–235.

[9] Baranova A, Krasnoselskyi M, Starikov V, Kartashov S, Zhulkevych I, Vlasenko V, *et al*. Triple-negative breast cancer: current treatment strategies and factors of negative prognosis. Journal of Medicine and Life. 2022; 15: 153–161.

[10] Lv B, Chen J, Liu XL. Anlotinib-induced hypertension: current concepts and future prospects. Current Pharmaceutical Design. 2022; 28: 216–224.

[11] Su Y, Luo B, Lu Y, Wang D, Yan J, Zheng J, *et al*. Anlotinib induces a T cell-inflamed tumor microenvironment by facilitating vessel normalization and enhances the efficacy of PD-1 checkpoint blockade in neuroblastoma. Clinical Cancer Research. 2022; 28: 793–809.

[12] Li Q, Liu J, Jiang Z, Liu Q. CSCO breast cancer guideline: precise, economical and oriental. Science China Life Sciences. 2020; 63: 1410–1412.

[13] Marazzi F, Orlandi A, Manfrida S, Masiello V, Di Leone A, Massacesi M, *et al*. Diagnosis and treatment of bone metastases in breast cancer: radiotherapy, local approach and systemic therapy in a guide for clinicians. Cancers. 2020; 12: 2390.

[14] Jiang J, Jiang S, Ahumada-Canale A, Chen Z, Si L, Jiang Y, *et al*. Breast cancer screening should embrace precision medicine: evidence by reviewing economic evaluations in China. Advances in Therapy. 2023; 40: 1393–1417.

[15] Jiang H, Zhang R, Liu X, Ran R, Zhang J, Liu Y, *et al*. Bilateral breast cancer in China: a 10-year single-center retrospective study (2006–2016). Cancer Medicine. 2021; 10: 6089–6098.

[16] Jokar N, Velikyan I, Ahmadzadehfar H, Rekabpour SJ, Jafari E, Ting HH, *et al*. Theranostic approach in breast cancer: a treasured tailor for future oncology. Clinical Nuclear Medicine. 2021; 46: e410–e420.

[17] Su H, Li X, Lv Y, Qiu X. Breast cancer epidemiology and survival analysis of Shenyang in Northeast China: a population-based study from 2008 to 2017. The Breast Journal. 2022; 2022: 6168832.

[18] Tao X, Li T, Gandomkar Z, Brennan PC, Reed WM. Incidence, mortality, survival, and disease burden of breast cancer in China compared to other developed countries. Asia-Pacific Journal of Clinical Oncology. 2023; 19: 645–654.

[19] Bianchini G, De Angelis C, Licata L, Gianni L. Treatment landscape of triple-negative breast cancer—expanded options, evolving needs. Nature reviews. Clinical Oncology. 2022; 19: 91–113.

[20] Zhao S, Wang P, Yin F, Wu J, Wang Y, Li P, *et al*. Cardiovascular toxicity associated with the multitargeted tyrosine kinase inhibitor anlotinib. Tumori Journal. 2023; 109: 186–196.

[21] Lasica M, Tam CS. Bruton tyrosine kinase inhibitors in chronic lymphocytic leukemia. Hematology/Oncology Clinics of North America. 2021; 35: 761–773.

[22] Dybowski S, Torke S, Weber MS. Targeting B cells and microglia in multiple sclerosis with Bruton tyrosine kinase inhibitors: a review. JAMA Neurology. 2023; 80: 404–414.

[23] Marra A, Curigliano G. Adjuvant and neoadjuvant treatment of triple-negative breast cancer with chemotherapy. The Cancer Journal. 2021; 27: 41–49.

[24] Zou G, Zhang X, Wang L, Li X, Xie T, Zhao J, *et al*. Herb-sourced emodin inhibits angiogenesis of breast cancer by targeting VEGFA transcription. Theranostics. 2020; 10: 6839–6853.

[25] Xu Q, Wang J, Sun Y, Lin Y, Liu J, Zhuo Y, *et al*. Efficacy and safety of sintilimab plus anlotinib for PD-L1-positive recurrent or metastatic cervical cancer: a multicenter, single-arm, prospective phase II trial. Journal of Clinical Oncology. 2022; 40: 1795–1805.

[26] Kriegel A, Langendorf E, Kottmann V, Kammerer PW, Armbruster FP, Wiesmann-Imilowski N, *et al*. Bone sialoprotein immobilized in collagen type I enhances angiogenesis *in vitro* and *in ovo*. Polymers. 2023; 15: 1007.

[27] Dehdari H, Moradian F, Barzegar A, Ebrahimzadeh MA. CYP1A1 contiguous hypermethylation within a putative CpG block is associated with breast cancer progression: feasibility to define boundary motives. Experimental Cell Research. 2022; 413: 113062.

[28] Carrasco-Ceballos JM, Barrera-Hernandez D, Locia-Espinosa J, Sampieri CL, Lara-Reyes JA, Hernandez-Aguilar ME, *et al*. Involvement of the PRL-PAK1 pathway in cancer cell migration. Cancer Diagnosis & Prognosis. 2023; 3: 17–25.

[29] Sair AT, Liu RH. Molecular regulation of phenolic compounds on IGF-1 signaling cascade in breast cancer. Food & Function. 2022; 13: 3170–3184.

[30] Yan Y SQ, Yao L, Zhao L, Cai H. YAP overexpression in breast cancer cells promotes angiogenesis through activating YAP signaling in vascular endothelial cells. Analytical Cellular Pathology. 2022; 2022: 5942379.