Targeted Therapy Breakthrough: Apatinib Enhances Neoadjuvant Chemotherapy in Triple- Negative Breast Cancer

Yulai YIN (1972688583@qq.com)
Hebei Medical University
Xiaoyu ZHANG
Cangzhou Central Hospital

Research Article

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Abstract

Objective

To investigate the clinical efficacy, prognosis, and safety of apatinib combined with doxorubicin + cyclophosphamide (AC) followed by paclitaxel (T) neoadjuvant chemotherapy regimen in patients with triple-negative breast cancer (TNBC).

Methods

A retrospective analysis was conducted on 70 patients with TNBC treated at Cangzhou Central Hospital from July 2016 to January 2020. The patients were divided into a control group (n = 34) and an observation group (n = 36) based on the treatment regimen received. The control group received neoadjuvant chemotherapy with the AC-T sequential regimen, whereas the observation group received apatinib in addition to the control group's regimen. The occurrence of adverse reactions during chemotherapy was recorded. Fasting venous blood samples were collected from both groups of patients after neoadjuvant chemotherapy completion to measure the levels of vascular endothelial growth factor (VEGF), thymidine kinase 1 (TK1), carcinoembryonic antigen (CEA), and the objective response rate (ORR) was recorded. At 4 weeks after completing neoadjuvant chemotherapy, patients underwent breast-conserving surgery or modified radical mastectomy as decided by a treatment group physician in the Thyroid Breast and Thoracic Surgery Department of Cangzhou Central Hospital, with axillary lymph node dissection determined according to sentinel lymph node biopsy results. Surgical procedures and pathological complete response (pCR) were documented. Then, a 3-year follow-up was conducted from the start of treatment to record and analyze the 3-year disease-free survival rate and 3-year overall survival rate.

Results

After completing neoadjuvant chemotherapy, the observation group showed significantly higher pCR rate, breast-conserving rate, 3-year disease-free survival rate, and 3-year overall survival rate compared to the control group ($P < 0.05$). The observation group also demonstrated a significant decrease in VEGF and CEA levels compared to the control group ($P < 0.05$). No grade III or above adverse reactions were observed in both groups during chemotherapy, and adverse reactions such as nausea and vomiting, diarrhea, leukopenia, and proteinuria were mainly recorded. In the observation group, there were 3 cases of nausea and vomiting, 5 cases of diarrhea, 7 cases of leukopenia, and 9 cases of proteinuria. In the control group, there were 4 cases of nausea and vomiting, 4 cases of diarrhea, 5 cases of leukopenia, and 6 cases of proteinuria. There was no significant difference in the occurrence of adverse reactions between the two groups ($P > 0.05$).

Conclusion

Apatinib combined with the AC-T sequential neoadjuvant chemotherapy regimen shows good clinical efficacy, significant prognosis, and manageable safety in patients with TNBC.

Introduction

With the improvement in quality of life and increasing awareness of health, breast cancer has surpassed lung cancer as the most common malignancy among women[1, 2]. Most early-stage breast cancers have a favorable prognosis with timely intervention. However, triple-negative breast cancer (TNBC), characterized by the absence of hormone receptors (estrogen receptor and progesterone receptor) and human epidermal growth factor receptor 2 (HER2), is

associated with a higher risk of recurrence, metastasis, and a relatively limited range of treatment options[3–6]. Therefore, exploration of treatment strategies for TNBC with surgical opportunities has been conducted in the following areas: 1) neoadjuvant chemotherapy for improving pathological complete response rates[7–11]; 2) breast-conserving surgery (BCS) combined with neoadjuvant therapy[12, 13]; 3) the clinical efficacy of PD-1 inhibitors in combination with neoadjuvant chemotherapy. The results have shown that the anthracycline-taxane treatment regimen can maintain a pathological complete response rate of approximately 20%-40%; neoadjuvant chemotherapy significantly improves the rate of breast conservation; the addition of PD-1 inhibitors enhances the efficacy of neoadjuvant chemotherapy and is expected to further increase the probability of breast conservation.

Apatinib[14, 15] is a potent inhibitor of vascular endothelial growth factor receptor 2 (VEGFR2), which exerts anticancer effects by inhibiting the binding of vascular endothelial growth factor (VEGF) to its receptor (VEGFR), thereby inhibiting tumor angiogenesis and ultimately leading to tumor cell proliferation inhibition due to the resultant tumor hypoxia. Studies have shown that TNBC patients exhibit significant VEGF expression, confirming that VEGFR is an effective therapeutic target.

Therefore, in this study, we investigated the clinical efficacy and prognostic improvement of apatinib in combination with neoadjuvant chemotherapy in patients with TNBC, aiming to provide reference for clinical medication.

1. Materials and Methods

1.1 Study Population

A retrospective analysis was conducted on 70 patients diagnosed with triple-negative breast cancer who were treated at the Cangzhou Central Hospital from July 2016 to January 2020. The patients were divided into a control group and an observation group based on the treatment regimens. The control group consisted of 34 patients, while the observation group consisted of 36 patients. Inclusion criteria for the study were as follows: 1) histologically confirmed triple-negative breast cancer through core needle biopsy, 2) clinical stage II-III, 3) deemed suitable to tolerate the novel neoadjuvant chemotherapy regimen based on Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group (ECOG) Activity Score, 4) complete pathological results available, 5) complete clinical data retained, and 6) No prior treatment has been administered. Exclusion criteria were as follows: 1) patients with advanced-stage disease with distant metastasis, 2) patients with non-singular primary tumors, 3) pregnant or lactating women, 4) patients with severe organ dysfunction unable to tolerate chemotherapy, 5) patients who had previously received other chemotherapy regimens, and 6) patients with incomplete clinical data. This study was approved by the Hospital Ethics Committee [Ethics No.: 2021-134-02(z)], and informed consent was obtained from all patients.

1.2 Methods

1.2.1 Chemotherapy Regimen

The control group received preoperative sequential AC-T chemotherapy, while the observation group received sequential AC-T chemotherapy combined with the anti-angiogenesis agent apatinib.

Sequential AC-T chemotherapy regimen: AC: On day 1, intravenous infusion of liposomal doxorubicin hydrochloride at a dose of 35 mg/m^2 and cyclophosphamide at a dose of 600 mg/m^2; 1 cycle consists of 21 days of continuous treatment, with a total of 4 cycles. Following the completion of the first 4 cycles, sequential T treatment was

administered: On day 1, intravenous infusion of albumin-bound paclitaxel over 30 minutes, at a dose of 260 mg/m^2 every 3 weeks, with 1 cycle consisting of 21 days of continuous treatment, for a total of 4 cycles.

During the same period of AC-T sequential chemotherapy, patients in the observation group were administered apatinib tablets (manufacturer: Jiangsu Hengrui Medicine Co., Ltd.; approval number: National Medical Products Administration H20140103; specifications: 0.25g/tablet). Apatinib was taken orally at a dose of 250mg per day for 28 days, constituting one treatment cycle. The treatment was continued for 6 cycles. Any discomfort or adverse reactions experienced by patients were required to be promptly reported to the attending physician, who would take appropriate treatment measures.

1.2.2 Surgery

Four weeks after completion of neoadjuvant chemotherapy, the decision to perform breast-conserving surgery or modified radical mastectomy was made by the same group of doctors from the Thyroid and Breast Surgery Department at Cangzhou Central Hospital. Whether axillary lymph node dissection was performed was determined based on the results of sentinel lymph node biopsy. After surgery, all patients are given 4 cycles of adjuvant chemotherapy consisting of docetaxel (75mg/m^2) and cyclophosphamide (600mg/m^2), with a cycle duration of 21 days (d1, 21-day cycle). Patients who have undergone breast-conserving surgery will also receive conventional radiotherapy after surgery.

1.2.3 Outcome Measures

1.2.3.1 Efficacy Evaluation

The objective response rate (ORR) and pathological complete response rate (pCR) were observed and recorded for both groups of patients. The 3-year disease-free survival (DFS) rate and overall survival (OS) rate were also followed up, recorded, and analyzed to identify independent factors influencing pCR, 3-year DFS rate, and OS rate.

The response to treatment was evaluated according to the "Response Evaluation Criteria in Solid Tumors (RECIST)." Complete response (CR) was defined as the disappearance of all target lesions, no appearance of new lesions, normalization of tumor marker levels, and maintenance for 4 weeks. Partial response (PR) was defined as a decrease of 30% or more in the sum of the longest diameters of all target lesions, which was maintained for 4 weeks. Stable disease (SD) was defined as a decrease in the cumulative sum of the longest diameters of all target lesions that did not meet the criteria for partial response. Progressive disease (PD) was defined as an increase of 20% or more in the sum of the smallest target lesion long diameters already recorded or the appearance of new lesions.

1.2.3.2 Objective Response Rate (ORR)

ORR was calculated as the percentage of cases that achieved complete response (CR) or partial response (PR) out of the total number of cases, using the formula: (CR + PR) cases / total cases × 100%.

1.2.3.3 Pathological Complete Response (pCR)

pCR refers to the proportion of patients in each group whose primary breast tumor and regional lymph nodes achieved complete pathological response, compared to all patients in that group.

1.2.3.4 Disease-Free Survival (DFS)

DFS is defined as the time interval from the start of treatment to disease recurrence or metastasis.

1.2.3.5 3-Year Disease-Free Survival (DFS) Rate

The 3-year DFS rate is calculated as the percentage of patients who did not experience disease recurrence or metastasis at the 3-year follow-up, out of the total number of patients in that group, using the formula: number of patients without disease recurrence or metastasis at 3 years / total number of patients in the group × 100%.

1.2.3.6 Overall Survival (OS)

OS is defined as the time interval from the start of treatment to patient death or the last follow-up.

1.2.3.7 3-Year Overall Survival (OS) Rate

The 3-year OS rate is calculated as the percentage of surviving patients at the 3-year follow-up, out of the total number of patients in that group, using the formula: number of surviving patients at 3 years / total number of patients in the group × 100%.

1.2.4 Biomarker Measurement

Pre- and post-neoadjuvant chemotherapy, 4 mL of fasting venous blood samples were collected from the patients in the early morning. After appropriate processing, enzyme-linked immunosorbent assay (ELISA) kits (purchased from Shanghai Jianglai Biotechnology Co., Ltd.) were used to measure the levels of vascular endothelial growth factor (VEGF), thymidine kinase 1 (TK1), and carcinoembryonic antigen (CEA) and other biomarkers.

1.2.5 Follow-up

A 3-year follow-up was conducted using telephone and outpatient visits until February 6, 2023. The follow-up frequency was once every 3 months. During the follow-up period, one patient from the observation group was lost to follow-up due to failure to attend postoperative follow-up appointments and a change in contact information. As the data loss was less than 5%, the baseline data of the lost patients were retained according to research standards, but relevant clinical data was not imputed.

1.2.6 Safety Evaluation

Adverse reactions occurring during chemotherapy were observed and recorded. Chemotherapy-related adverse reactions were classified into grades 0 to IV according to the Common Terminology Criteria for Adverse Events (CTCAE) version 2.0, developed by the National Cancer Institute (NCI), USA.

1.2.4 Statistical Analysis

Statistical analysis was performed using SPSS 27.0 software and the Medsta statistical platform (https://www.medsta.cn/software). Categorical data were presented as rates and analyzed using the chi-square test and Fisher's exact test for different groups. For continuous data that followed a normal distribution, mean ± standard deviation (mean ± SD) was used for presentation, and the t-test was applied for group comparisons. Disease-free survival (DFS) and overall survival (OS) were calculated using the Kaplan-Meier method, and the log-rank test was used for comparing survival curves between the two groups. Univariate and multivariate logistic regression analysis were employed to identify independent factors influencing pathological complete response (pCR), 3-year DFS (%), and 3-year OS (%). Univariate and multivariate Cox regression analysis were utilized to

determine the independent prognostic factors affecting DFS and OS. A significant difference was defined as P < 0.05. Graphs were generated using R software (version 4.3.1) and the ChiPlot website (https://www.chiplot.online/).

2. Results

2.1 General Information

A total of 70 patients were included in this study, with 34 patients in the control group and 36 patients in the observation group. The baseline characteristics including age, tumor size, tumor location, histological type, menstrual status, Ki-67 expression level (high expression defined as Ki-67≥30%, low expression defined as Ki-67<30%), and clinical stage were compared between the two groups. There were no statistically significant differences observed in these general characteristics (P > 0.05), indicating comparability between the two groups. Please refer to Table 1 for detailed results.

Table 1. Comparison of baseline data (cases, %)

Variable	Total (n = 70)	Control Group (n = 34)	Observation Group (n = 36)	Statistic	P
Age, Mean ± SD	45.88 ± 6.45	45.80 ± 5.74	45.95 ± 7.13	t=-0.099	0.922
Size, Mean ± SD	33.94 ± 6.67	33.65 ± 6.90	34.21 ± 6.52	t=-0.345	0.731
Location, n (%)				-	0.537
Areola region	16 (22.86)	8 (23.53)	8 (22.22)		
Outer upper quadrant	34 (48.57)	17 (50.00)	17 (47.22)		
Outer lower quadrant	9 (12.86)	3 (8.82)	6 (16.67)		
Lower inner quadrant	5 (7.14)	4 (11.76)	1 (2.78)		
Upper inner quadrant	6 (8.57)	2 (5.88)	4 (11.11)		
Type, n (%)				χ^2=1.144	0.285
Invasive lobular carcinoma	25 (35.71)	10 (29.41)	15 (41.67)		
Invasive ductal carcinoma	45 (64.29)	24 (70.59)	21 (58.33)		
Status, n (%)				χ^2=0.051	0.822
Non-menopausal	11 (15.71)	5 (14.71)	6 (16.67)		
Post-menopausal	59 (84.29)	29 (85.29)	30 (83.33)		
Ki-67, n (%)				χ^2=2.313	0.128
Low level of expression	9 (12.86)	7 (20.59)	2 (5.56)		
High level of expression	61 (87.14)	27 (79.41)	34 (94.44)		
Stage, n (%)				χ^2=0.356	0.551
	47 (67.14)	24 (70.59)	23 (63.89)		
	23 (32.86)	10 (29.41)	13 (36.11)		

2.2 Efficacy Evaluation

After neoadjuvant chemotherapy, the observation group had complete response in 6 cases, partial response in 13 cases, stable disease in 14 cases, and disease progression in 3 cases, with an objective response rate of 52.8%. Postoperative pathological results revealed 18 cases of pathological complete response (pCR) in the observation group, with a pCR rate of 50%. In the control group, there were 4 cases of complete response, 8 cases of partial response, 16 cases of stable disease, and 6 cases of disease progression, yielding an objective response rate of 33.3%. Furthermore, 8 cases achieved pCR in the control group, resulting in a pCR rate of 23.5%. The results indicate a significant difference in pCR between the observation group and the control group (50% vs. 33.3%, $P < 0.05$), while there was no significant difference in objective response rate between the two groups.

Using pCR as the outcome variable, a univariate logistic regression analysis was conducted. Then, the factors with a significance level of P < 0.05 in the univariate analysis were included in a multivariate analysis using the backward stepwise logistic regression method. The results revealed that tumor size, neoadjuvant chemotherapy regimen, and pre-treatment Ki-67 level were independent influencing factors for achieving pathological complete response (P < 0.05). In other words, smaller tumor size, the selection of apatinib combined with AC-T regimen, and low expression of Ki-67 were more likely to be associated with achieving pCR. Please refer to Table 2 for detailed results.

Table 2. Logistic univariate and multivariate regression analyses with complete pathological remission as the outcome

Variables	Beta	S.E	Z	OR (95%CI)	P	aBeta	aS.E	aZ	aOR (95%CI)	aP
Size	-0.15	0.05	-3.10	0.86 (0.78 - 0.95)	0.002*	-0.16	0.05	-2.99	0.85 (0.77 - 0.95)	0.003*
Group										
AC-T				1.00 (Reference)					1.00 (Reference)	
Apatinib+AC-T	1.18	0.52	2.25	3.25 (1.16 - 9.08)	0.024*	2.40	0.78	3.06	11.00 (2.37 - 51.12)	0.002*
Low level of expression				1.00 (Reference)					1.00 (Reference)	
High level of expression	-2.05	0.85	-2.41	0.13 (0.02 - 0.68)	0.016*	-3.13	1.17	-2.67	0.04 (0.00 - 0.44)	0.008*

* Indicates P < 0.05

2.3 Levels of Related Biomarkers

After completion of neoadjuvant chemotherapy, the observation group showed a significant decrease in levels of vascular endothelial growth factor (VEGF) and carcinoembryonic antigen (CEA) compared to the control group (P < 0.05). However, there was no significant difference in thymidine kinase 1 (TK1) levels between the two groups (P > 0.05). Please refer to Table 3 for detailed results.

Table 3Comparison of marker levels

Group	TK1 pmol/L		VEGF pg/ml		CEA ng/ml	
	Before	After	Before	After	Before	After
AC-T	1.23 ± 0.16	1.18 ± 0.13	287.02 ± 28.69	279.08 ± 29.03	3.08 ± 0.37	2.20 ± 0.22
Apatinib+AC-T	1.20 ± 0.16	1.16 ± 0.18	278.84 ± 25.99	143.15 ± 15.730	3.00 ± 0.37	1.78 ± 0.23
t	0.840	0.420	1.250	24.16	0.840	7.840
P	0.404	0.676	0.215	<.001*	0.404	<.001*

* Indicates P < 0.05

2.4 Prognostic Evaluation

This study enrolled a total of 70 patients, comprising 34 in the control group and 36 in the observation group, of which one was lost to follow-up after receiving relevant treatment. By the end of the follow-up period, 9 patients in the control group experienced distant metastasis or recurrence, 25 achieved a 3-year disease-free survival, and 6 succumbed to death (all due to disease progression, including 2 with brain metastases, 3 with lung metastases, and 1 with bone metastasis). In the observation group, 2 patients experienced distant metastasis or recurrence, 1 was lost to follow-up, 33 reached a 3-year disease-free survival, and 1 died (due to disease progression, with brain metastasis). The 3-year disease-free survival rates for the observation and control groups were 91.67% and 73.53% respectively, while the overall survival rates were 94.44% and 82.35%. These differences were statistically significant ($P < 0.05$).

In this study, Kaplan-Meier survival curves were constructed based on pathological complete response (pCR), grouping, and clinical staging ($P < 0.05$), with results presented in Figure 1. Furthermore, the study conducted univariate Cox regression analyses based on disease-free survival (DFS) and overall survival (OS), incorporating variables with $P < 0.05$ into a multivariate Cox regression analysis using a backward stepwise method. The findings revealed that group, menstrual status, and clinical stage were independent prognostic factors for DFS ($P < 0.05$). Specifically, patients treated with Apatinib in combination with AC-T, those postmenopausal, and those with earlier clinical stages tended to have longer DFS. Clinical stage was identified as an independent prognostic factor for OS ($P < 0.05$), with earlier stages associated with longer OS benefits. The results are detailed in Tables 4 and 5. The study also carried out univariate and multivariate logistic regression analyses based on 3-year DFS and 3-year OS outcomes. Chemotherapy regimen, menstrual status, and clinical stage were independent factors impacting 3-year DFS ($P < 0.05$), indicating that patients on the Apatinib combined with AC-T neoadjuvant chemotherapy regimen, those postmenopausal, and those in earlier clinical stages were more likely to achieve 3-year disease-free survival. For 3-year overall survival, the only independent influencing factor was clinical stage, with earlier stages more likely to achieve this outcome. These findings are shown in Tables 6 and 7.

Table 4 Univariate and Multivariate Cox Regression Analysis with Disease-Free Survival (DFS) as the Outcome

Variables	Beta	S.E	Z	P	HR (95%CI)	m_Beta	m_S.E	m_Z	aP	aHR (95%CI)
Group										
AC-T					Ref					Ref
Apatinib+AC-T	-1.66	0.78	-2.12	0.034*	0.19 (0.04 - 0.88)	-2.42	0.85	-2.85	0.004*	0.09 (0.02 - 0.47)
Status										
Non-menopausal					Ref					Ref
Post-menopausal	2.24	0.61	3.68	<.001*	9.40 (2.85 - 31.01)	2.19	0.71	3.10	0.002*	8.94 (2.23 - 35.80)
Stage										
					Ref					Ref
	2.37	0.78	3.02	0.002*	10.66 (2.30 - 49.40)	2.32	0.82	2.82	0.005*	10.17 (2.03 - 50.92)

* Indicates P < 0.05

Table 5 Univariate and Multivariate Cox Regression Analysis with Overall Survival (OS) as the Outcome

Variables	Beta	S.E	Z	P	HR (95%CI)	m_Beta	m_S.E	m_Z	aP	aHR (95%CI)
Stage										
					Ref					Ref
	1.69	0.84	2.02	0.043*	5.42 (1.05 - 27.98)	1.69	0.84	2.02	0.043*	5.42 (1.05 - 27.98)

* Indicates P < 0.05

Table 6 Logistic one-way and multifactorial regression analyses with 3-year DFS as the outcome

Variables	Beta	S.E	Z	OR (95%CI)	P	aBeta	aS.E	aZ	aOR (95%CI)	aP
Group										
AC-T				1.00 (Reference)					1.00 (Reference)	
Apatinib+AC-T	1.81	0.82	2.20	6.12 (1.21 - 30.83)	0.028*	3.06	1.20	2.56	21.39 (2.05 - 223.46)	0.010*
Status										
Non-menopausal				1.00 (Reference)					1.00 (Reference)	
Post-menopausal	2.56	0.76	3.35	12.96 (2.89 - 58.04)	<.001*	2.62	1.09	2.41	13.72 (1.64 - 115.17)	0.016*
Stage										
				1.00 (Reference)					1.00 (Reference)	
	-2.67	0.84	-3.18	0.07 (0.01 - 0.36)	0.001*	-3.20	1.07	-2.98	0.04 (0.00 - 0.33)	0.003*

* Indicates P < 0.05

Table 7 Logistic univariate and multivariate regression analyses with 3-year OS as the outcome

Variables	Beta	S.E	Z	OR (95%CI)	P	aBeta	aS.E	aZ	aOR (95%CI)	aP
Stage										
				1.00 (Reference)					1.00 (Reference)	
	-1.83	0.88	-2.08	0.16 (0.03 - 0.90)	0.038*	-1.83	0.88	-2.08	0.16 (0.03 - 0.90)	0.038*

* Indicates P < 0.05

2.5 Surgical Benefits

After receiving different neoadjuvant chemotherapy regimens, doctors selected breast-conserving surgery or modified radical mastectomy based on individual differences and indications. The decision to perform axillary lymph node dissection was made based on intraoperative sentinel lymph node biopsy results. The results showed that in the observation group, 16 patients underwent breast-conserving surgery, 20 patients underwent modified radical mastectomy, and a total of 12 patients were exempt from axillary lymph node dissection. In the control group, 7 patients underwent breast-conserving surgery, 27 patients underwent modified radical mastectomy, and a total of 11 patients were exempt from axillary lymph node dissection. The breast-conserving rate was significantly higher in the observation group compared to the control group (20.6% vs. 44.4%, P < 0.05), while the exemption rate from axillary lymph node dissection showed no significant difference (P > 0.05).

2.6 Safety Evaluation

During the process of receiving different neoadjuvant chemotherapy regimens, adverse reactions related to chemotherapy were assessed according to the National Cancer Institute Common Toxicity Criteria (NCICTC version 2.0). Adverse reactions were graded from 0 to IV, and no grade III or higher adverse reactions were observed. There were also no patients who had to discontinue chemotherapy due to intolerable adverse reactions. The overall analysis showed no significant differences in the occurrence of adverse reactions between the control group and the observation group (P > 0.05), indicating relatively manageable drug compatibility safety. Please refer to Table 6 for detailed results.

Table 8. Comparison of the occurrence of adverse reactions

Adverse Reaction	Grade	Observation Group n=36	Control Group n=34	c^2	P
Nausea & Vomiting	0	33(91.7)	30(88.2)	0.229	0.632
		2(5.5)	3(8.9)		
		1(2.8)	1(2.9)		
		0	0		
		0	0		
Diarrhea	0	31(86.1)	30(88.2)	0.070	0.791
		4(11.1)	2(5.9)		
		1(2.8)	2(5.9)		
		0	0		
		0	0		
Leucopenia	0	29(80.6)	29(85.3)	0.276	0.599
		5(13.9)	4(11.8)		
		2(5.5)	1(2.9)		
		0	0		
		0	0		
Proteinuria	0	27(75.0)	28(82.4)	0.561	0.454
		6(16.7)	5(14.7)		
		3(8.3)	1(2.9)		
		0	0		
		0	0		

3. Discussion

3.1 Triple-negative breast cancer

Triple-negative breast cancer (TNBC) is a subtype of breast cancer that is particularly challenging to treat due to its aggressive growth, high recurrence and metastasis rates, and resistance to treatment. TNBC is characterized by significant expression of molecular markers such as PD-1, PD-L1, VEGF, and AR, providing reliable targets for targeted therapy. Inhibition of PD-1/PD-L1 targets with drugs like pembrolizumab and atezolizumab has been used for neoadjuvant and salvage therapy in TNBC[1, 16–19], achieving satisfactory pathological complete response rates and prognoses. Studies have also indicated that PD-1 inhibitors can significantly enhance the antitumor efficacy of anthracycline drugs and reduce the risk of TNBC recurrence. Furthermore, the use of androgen receptor (AR) inhibitors[20] has partially improved the poor response to neoadjuvant chemotherapy, low pathological complete response rates, and unfavorable outcomes in AR-positive TNBC patients.

3.2 Apatinib

Apatinib is an anti-angiogenic drug that exerts its antitumor effects by targeting VEGFR2. In recent years, many researchers worldwide have explored its advantages in salvage therapy for advanced TNBC, especially when combined with PD-1 inhibitors. The combination of apatinib and PD-1 inhibitors for salvage therapy in advanced TNBC significantly improves objective response rates and progression-free survival, with an overall good safety profile. To investigate the clinical benefits of apatinib in neoadjuvant chemotherapy for TNBC, this study determined the combination scheme and dosage based on the following considerations: 1. A low dose of apatinib was used for neoadjuvant chemotherapy[21–23], as previous studies have shown that blindly increasing the dosage of apatinib does not lead to more significant antitumor effects or clinical benefits. This is because the unique angiogenesis-inhibiting effect of apatinib also hinders the direct delivery of other chemotherapy drugs to the tumors. Therefore, a low dose of apatinib achieves a dual effect of inducing tumor cell hypoxia and allowing the transport of other chemotherapy drugs without interference. 2. Apatinib increases the sensitivity of TNBC cells to doxorubicin by inducing inactivation of NF-κB[24]. Apatinib also synergistically promotes the production of reactive oxygen species (ROS) with doxorubicin, leading to caspase-dependent apoptotic cell death. Additionally, apatinib can reverse resistance to anthracycline drugs by inducing cancer cell apoptosis. This provides theoretical support for the

combination of apatinib with doxorubicin in TNBC treatment. 3. Apatinib enhances the antitumor effect of paclitaxel on TNBC cells through the PI3K/p65/Bcl-xl molecular pathway[25]. The combination of apatinib and paclitaxel reduces the motility and migration capabilities of cells, impacting their repair capacity after damage and decreasing their invasive ability. The combination of these two drugs exhibits strong inhibitory effects on tumor cell growth. This strongly supports the combination of apatinib with albumin-bound paclitaxel. Therefore, the observation group in this study adopted a neoadjuvant chemotherapy regimen combining apatinib with sequential AC-T to investigate its impact on clinical efficacy and prognosis in TNBC.

3.3 Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is an important approach to improve clinical efficacy and prognosis in triple-negative breast cancer (TNBC). It not only increases the objective response rate and pathological complete response rate but also provides an opportunity for breast conservation in patients. Professor Zhimin Shao's team has found that neoadjuvant chemotherapy regimens containing platinum (such as TP) significantly improve the pathological complete response rate in TNBC, especially in patients with BRCA mutations. In recent years, the addition of PD-1 inhibitors has brought new breakthroughs to neoadjuvant chemotherapy regimens for TNBC, and to some extent, reduced the risk of TNBC recurrence and metastasis, which has significant implications for improving long-term prognosis. The use of apatinib in neoadjuvant chemotherapy for TNBC is a new exploration based on anti-angiogenic therapy, providing potential references for clinical treatment.

3.4 Results Analysis

The incorporation of low-dose Apatinib with the neoadjuvant chemotherapy regimen AC-T significantly enhances the pathological complete response rate, notably improving the 3-year disease-free survival rate and the 3-year overall survival rate. This regimen also demonstrates an advantage in breast conservation, but does not effectively reflect the benefit of sparing axillary lymph node dissection. The potential reason is that the combination of Apatinib with AC-T primarily inhibits tumor cell growth, mainly manifesting as a reduction in tumor burden, but has limited effect on controlling cancer cell migration. Univariate and multivariate logistic regression analyses identified tumor size, the neoadjuvant chemotherapy regimen, and pre-treatment Ki-67 levels as independent influencing factors for pathological complete response; chemotherapy regimen, menstrual status, and clinical staging as independent prognostic factors for disease-free survival (DFS); and clinical staging as an independent prognostic factor for overall survival. Therefore, focusing on regular check-ups, early detection, and early treatment, along with choosing a scientific chemotherapy regimen, are key to improving the prognosis of patients with triple-negative breast cancer.

4. Conclusion

The combination of apatinib with AC-T sequential neoadjuvant chemotherapy regimen shows good clinical efficacy, promising prognosis, and controllable safety in TNBC. However, this study is a retrospective cohort study with a small sample size from a single center, and the follow-up time is relatively short. Cox regression analysis was not conducted, so the results may be biased. Further research by relevant scholars is expected to reveal the clinical advantages of apatinib in neoadjuvant chemotherapy for TNBC.

Declarations

Ethical Approval

The study was approved by the Ethics Committee of Cangzhou Central Hospital, and all subjects signed an informed consent form.

Consent for publication

Not applicable

Availability of data and materials

All study data were obtained with informed consent from patients.

Competing interests

The author(s) declare that they have no competing interests.

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Authors' contributions

Y.Y. and X.Z. wrote the main manuscript text, Y.Y. prepared Figures,X.Z.prepared Tables. All authors reviewed the manuscript.

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Figures

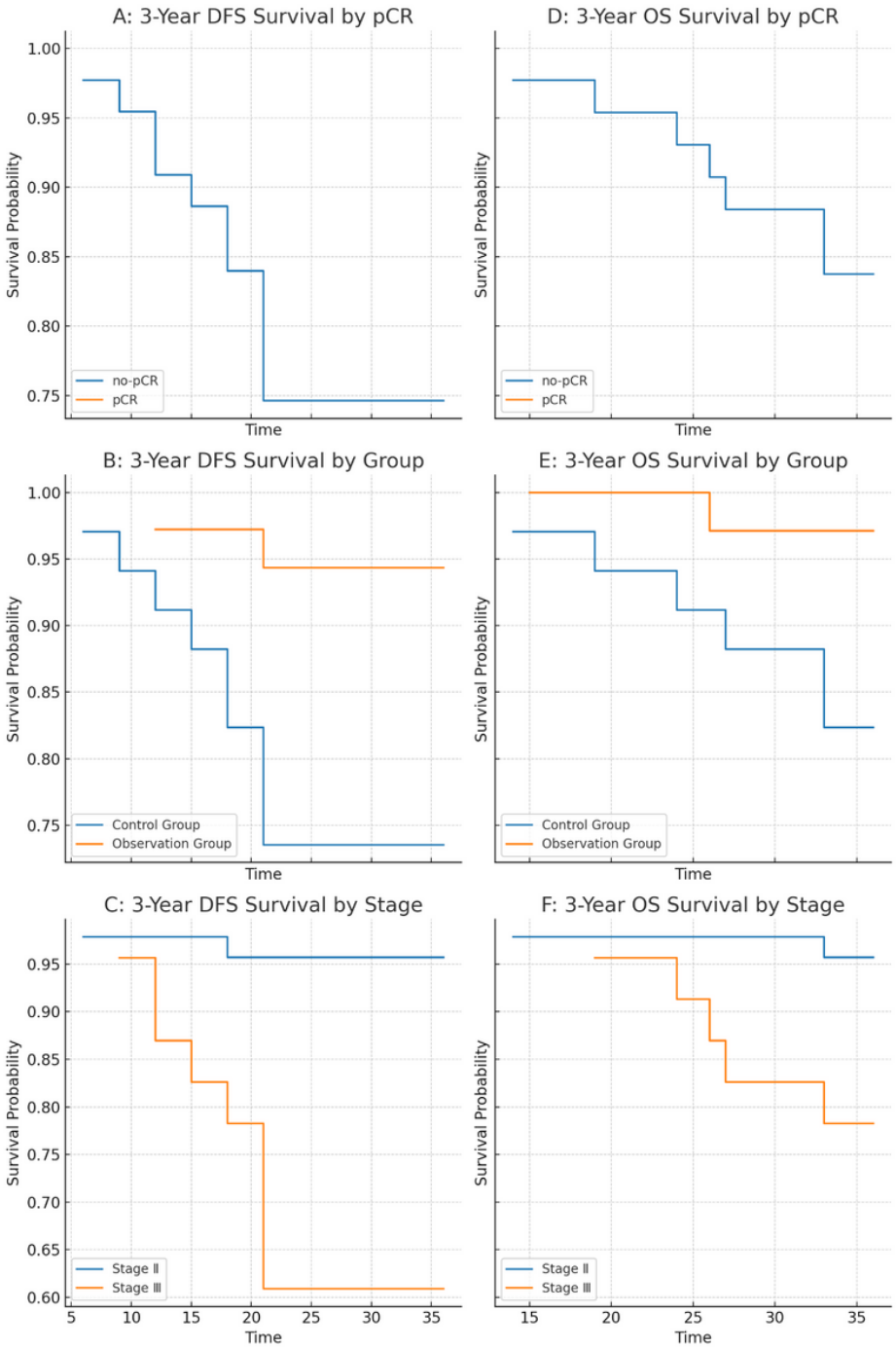

Figure 1

Survival Curves