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ORIGINAL ARTICLE

Retrospective Study

Efficacy and prognostic factors of neoadjuvant chemotherapy for triple-negative breast cancer

Feng Ding, Ru-Yue Chen, Jun Hou, Jing Guo, Tian-Yi Dong

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Abstract

BACKGROUND

Breast cancer mainly occurs in young and premenopausal women; its incidence is increasing annually. Patients with triple-negative breast cancer (TNBC) have relatively high recurrence and transfer rates during the operation and 3 years after postoperative adjuvant chemotherapy. Currently, the treatment for patients with TNBC is mainly based on a comprehensive combination of surgery and chemotherapy. Therefore, identifying additional effective treatments to improve patient prognosis is important.

AIM

To explore and discuss the effects and prognostic factors of neoadjuvant chemotherapy in TNBC.

METHODS

In total, 118 patients diagnosed with TNBC from January 2016 to January 2020 in our hospital were selected and divided into the observation (n = 60) and control (n = 58) groups according to the rapeutic regimen. The control group received routine chemotherapy, and the observation group received neoadjuvant chemotherapy. The therapeutic effects of the two groups were observed, and the survival of patients was followed up.

RESULTS



The karyopherin A2 (KPNA2)-positive and SRY-related HMG box-2 (SOX2)-positive expression rates of patients with TNBC with intravascular tumor thrombus and tumor-node-metastasis (TNM) stage IV were 92.00% and 91.67% and 96.00% and 95.83%, respectively, which were significantly higher than those of patients with no intravascular tumor thrombus and TNM stage III (P < 0.05). KPNA2 was positively associated with SOX2 expression ($r_s = 0.514$, P < 0.50). The short-term curative effect of the observation group was better than that of the control group (*P* < 0.05), and the total effective rate was 58.33%. After treatment, carcinoembryonic antigen, cancer antigen (CA) 19-9, and CA125 Levels in the observation group were 11.40 ± 2.32 mg/L, 19.92 ± 3.42 kU/L, and 54.30 ± 12.28 kU/L, respectively, which were significantly lower than those in the control group (P < 0.05). The median survival time of the observation group was 33 mo (95%CI: 31.21-34.79), which was significantly longer than that of the control group (P < 0.05). TNM stage, degree of differentiation, lymph node metastasis, KPNA2 and SOX2 expressions, and treatment plan were prognostic factors of TNBC (relative risk = 1.575, 1.380, 1.366, 1.433, 1.411, and 0.581, respectively, P < 0.05).

CONCLUSION

Neoadjuvant chemotherapy for TNBC treatment can achieve good curative effects. TNM stage, differentiation degree, lymph node metastasis, KPNA2 and SOX2 expressions, and treatment plan are prognostic factors of TNBC.

Key Words: Neoadjuvant chemotherapy; Triple-negative breast cancer; Clinical effect; Prognosis; Influencing factor

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Core Tip: Neoadjuvant chemotherapy for triple-negative breast cancer (TNBC) treatment can achieve good curative effects. Moreover, tumor-node-metastasis stage, differentiation degree, lymph node metastasis, karyopherin A2 and SRY-related HMG box-2 expressions, and treatment plan are prognostic factors of patients with TNBC.

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INTRODUCTION

Breast cancer has several types, and each subtype has different biological behaviors and clinicopathological and molecular characteristics. The corresponding treatment methods and prognoses of breast cancer are also different[1]. Triple-negative breast cancer (TNBC) is a type of breast cancer with no expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2, and its incidence accounts for approximately one-fifth of the incidence of breast cancer[2]. TNBC has high morbidity and shows an upward trend annually. However, due to the lack of effective targeted endocrine therapy, only conventional treatment can be provided in clinical practice. However, the curative effect of conventional treatment is poor, and its local recurrence rate is high, which has become one of the areas of interest in breast cancer studies in recent years[3]. For the past few years, drugs (anthracyclines, taxanes) are often used for TNBC treatment in clinical settings, although the therapeutic regimen for TNBC remains unclear. Some patients are drug-resistant, which can influence the treatment effect[4]. Currently, neoadjuvant chemotherapy is one of the most ideal treatments for locally advanced breast cancer, which can effectively improve the overall efficacy for breast cancer[5]. According to a previous study[6], tumor markers are consistent with the biological characteristics of breast cancer, and cytokines can predict the occurrence and development of tumors and the prognosis of patients. Patients with TNBC in our hospital were selected to explore and discuss the effects and prognostic factors of neoadjuvant chemotherapy in TNBC.

MATERIALS AND METHODS

Baseline data

A total of 118 patients with TNBC from January 2016 to January 2020 in our hospital were selected. The inclusion criteria were as follows: (1) Patients who were pathologically diagnosed with TNBC; (2) patients with tumor-node-metastasis (TNM) stages III-IV; (3) patients who were all first-treated; (4) female patients; and (5) patients or their family members who provided an informed consent. The exclusion criteria were as follows: (1) Patients with an estimated survival period of < 3 mo; (2) patients complicated with other systemic malignant tumors; (3) patients complicated with liver, kidney, and other important organ diseases and immune system diseases; (4) patients with mental illness; and (5) patients with incomplete clinical follow-up data. Patients were divided into the observation group (n =60) and the control group (n = 58) according to the rapeutic regimen.

Treatment and follow-up methods

Recent therapeutic efficacy[7]: Complete response (CR) was defined as complete disappearance of the lesion, partial response (PR) was defined as tumor shrinkage ≥ 50% compared with that before treatment, stable disease was defined as tumor shrinkage < 50% or increase < 20% compared with that before treatment, and progressive disease was defined as tumor enlargement ≥ 20%. Total effectiveness was achieved using the following formula: CR + PR.

Inspection method

Patients in the two groups received chemotherapy on the first day after the admission. The control group received routine chemotherapy: on the first day of chemotherapy, intravenous cyclophosphamide (Baxter Oncology GmbH, batch no. 20151211) (500 mg/m²), intravenous fluorouracil (on day 1 and day 8) (Shanghai Xudong Haipu Pharmaceutical Co., Ltd., 20151022) (700 mg/m²), and methotrexate [Pfizer (Perth) Pty Limited, 20151103] (35 mg/m²) were administered. All patients received granulocyte colonystimulating factor support therapy on the second day after chemotherapy in a 21-d cycle. After four consecutive cycles of chemotherapy, surgery could be performed if the effect of chemotherapy was significant.

The observation group received neoadjuvant chemotherapy for the epirubicin-paclitaxel (ET) regimen. Epirubicin [Pfizer (Wuxi) Co., Ltd., 20150724] (75 mg/m²) and paclitaxel (Hainan Haiyao Co., Ltd., 20151202) (75 mg/m²) were administered intravenously for 21 d. After four consecutive cycles of chemotherapy, surgery could be performed if the effect of chemotherapy was significant.

Cancer antigen (CA) 125, CA19-9, and carcinoembryonic antigen (CEA) levels were detected using a Roche Cobas E601 automatic electrochemiluminescence immunoanalyzer, which was purchased from Roche. The next day before and after treatment, 5 mL of the patient's fasting venous blood was collected and centrifuged at 3000 r/min for 5 min, and the serum was separated. Electrochemical luminescence automatic immunoanalyzer and corresponding reagents were used for detection. All operations were performed in strict accordance with the instructions to avoid hemolysis and contamination.

The monoclonal antibodies karyopherin A2 (KPNA2), protein 53, and KI-67 were purchased from Roche, and BenchMark ULTRA was used for immunohistochemical staining. The experimental procedures were performed according to the provided instructions. Known positive tissue was used as the positive control, and phosphate buffered saline was used instead of a primary antibody as the negative control. Organization immunohistochemical staining results were provided by two senior pathologists using the semi-quantitative method, according to the density of dyeing (negative = 0, weakly positive = 1, moderately positive = 2, strongly positive = 3) and the positive cell percentage (0: negative, 1: < 25%, 2: 25%-50%, 3: 51%-75%, 4: > 75%), and five high-power electric field immune response scores (IRSs) were calculated. The final results were as follows: negative (IRS = 0) (-); weakly positive (IRS = 1-4) (+); moderately positive (IRS = 5-8) (++); and strongly positive (IRS = 9-12) (+++).

Statistical analysis

The Statistical Package for the Social Sciences version 22.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Normally distributed data are expressed as mean ± SD, and t-tests were used for comparisons between groups. Counting data are expressed as n (%), and the χ^2 test was used for comparisons between groups. Survival curves were analyzed using the Kaplan-Meier method. Cox proportional risk regression analysis was used for multiple factors. Spearman rank correlation analysis was used to assess correlation. Inspection level was set at an α level of 0.05.

RESULTS

Association between karyopherin A2 and SRY-related HMG box-2 expression and clinicopathology of patients with triple-negative breast cancer

The KPNA2-positive expression rates of patients with TNBC with intravascular tumor thrombus and TNM stage IV were significantly higher than those of patients with no intravascular tumor thrombus and TNM stage III (P < 0.05) (Table 1). The SRY-related HMG box-2 (SOX2)-positive expression rates of patients with TNBC with intravascular tumor thrombus and TNM stage IV were significantly higher than those of patients with no intravascular tumor thrombus and TNM stage III (P < 0.05) (Table 2).

Correlation between the expressions of KPNA2 and SOX2

The expression of KPNA2 was positively correlated with the expression of SOX2 ($r_s = 0.514$, P < 0.50) (Table $\bar{3}$).

Comparison of clinical data between the two groups

The clinical data of the two groups were compared (Table 4).

Comparison of short-term therapeutic effects between the two groups

The short-term therapeutic effects of the observation group were better than those of the control group (P < 0.05), and the total effective rate was 58.33% (Table 5).

Comparison of tumor markers before and after chemotherapy between the two groups

There were no significant differences in CEA, CA19-9, and CA125 Levels between the observation and control groups before treatment (P > 0.05). CEA, CA19-9, and CA125 Levels in the observation and control groups were lower after treatment than those before treatment (P < 0.05). CEA, CA19-9, and CA125 Levels in the observation group were significantly lower than those in the control group (P <0.05) (Table 6).

Comparison of survival curves between the two groups

The median survival time of the observation group was 33 mo (95%CI: 31.21-34.79), which was significantly longer than that of the control group (22 mo, 95%CI: 20.69-23.31), and the difference was statistically significant ($\chi^2 = 15.994$, P = 0.000 < 0.05) (Figure 1).

Cox proportional risk regression analysis

Cox proportional risk regression analysis showed that TNM stage, differentiation degree, lymph node metastasis, KPNA2 and SOX2 expressions, and treatment plan were prognostic factors of TNBC (relative risk = 1.575, 1.380, 1.366, 1.433, 1.411, and 0.581, respectively, P < 0.05) (Table 7) (Figure 2).

DISCUSSION

The ET regimen uses neoadjuvant chemotherapy before surgery, and its main target population is patients with locally advanced breast cancer [8-10]. The paclitaxel used in the regimen was a taxane antitumor drug, which can bind to free tubulin, accelerate the assembly speed of microtubules, inhibit the aggregation of microtubules, and effectively inhibit the growth of tumor cells[11]. The chemical composition of epirubicin, an anthracycline antitumor drug, is similar to that of adriacin, which plays an anticancer role mainly by inhibiting nucleic acid synthesis. The drug is inserted directly into the double strand of DNA, stopping the process of cell division and killing tumor cells. When used in combination, the two drugs have significant antitumor effects with few side effects[12].

According to the study results, the short-term curative effect of the observation group was significantly better than that of the control group, and the median survival time of the observation group was significantly longer than that of the control group (P < 0.05), indicating that the two chemotherapy regimens can all achieve good treatment effects, and the efficacy of the neoadjuvant chemotherapy regimen is relatively significant. The mechanisms of action of the two regimens are different. Cyclophosphamide mainly inhibits the proliferation of breast cancer cells by inhibiting the expression of the key protein pKAT in the PBK pathway. Neoadjuvant chemotherapy can control micrometastases in the body and effectively reduce the clinical stage of breast cancer. Paclitaxel binds specifically to specific parts of tubulin in cancer cells, preventing it from depolymerization, so that the division of cancer cells will always stay in the G2 and M phases, leading to the inability of the cancer cells to replicate and ultimately to the death of the cancer cells. Epirubicin can inhibit DNA replication and RNA synthesis, inhibit the division of cancer cells, and can affect the DNA superhelical DNA replication and transcription process by inhibiting topoisomerase II. It also chelates iron ions, producing free radicals that damage DNA, proteins, and cell membrane structures. KPNA2 is a member of the nuclear transport signal superfamily, transporting mRNA, DNA, and RNA polymerase and

Table 1 The association between the expressions of karyopherin A2 and clinicopathology of patients with triple-negative breast cancer, n (%)

Clinical data	Cases	KPNA2 positive expression rate	X ²	P value
Age (yr)			2.868	0.090
< 50	55	33 (60.00)		
≥ 50	63	47 (74.60)		
BMI (kg/m^2)			0.271	0.602
< 22	60	42 (70.00)		
≥ 22	58	38 (65.52)		
Karnofsky score (points)			0.088	0.767
< 70	52	36 (69.23)		
≥70	66	44 (66.67)		
Differentiation degree			0.393	0.531
High differentiation	51	33 (64.71)		
Medium low differentiation	67	47 (70.15)		
Intravascular tumor thrombus			8.511	0.004
Yes	25	23 (92.00)		
No	93	57 (61.29)		
Tumor size			0.136	0.712
> 5 cm	53	35 (66.04)		
≤5 cm	65	45 (69.23)		
TNM stages			7.863	0.005
III	94	58 (61.70)		
IV	24	22 (91.67)		
Pathological type			0.301	0.583
Invasive ductal carcinoma	96	64 (66.67)		
Other	22	16 (72.73)		
Ki-67			2.764	0.096
≤14%	37	29 (78.38)		
> 14%	81	51 (62.96)		
P53			0.034	0.854
Positive	79	54 (68.35)		
Negative	39	26 (66.67)		

KPNA2: Karyopherin A2; BMI: Body mass index; TNM: Tumor-node-metastasis.

transcription factors into and out of the nucleus, thereby promoting cell proliferation and differentiation, and participating in cell development, apoptosis, migration, and DNA damage response.

Studies have shown that [13,14] tumor markers are closely related to the biological behavior of tumors, among which CEA, CA19-9, and CA125 are common. As a common type of hormone in humans, CA125 is a marker for ovarian cancer and can be highly expressed in breast cancer. CEA is elevated in advanced breast cancer, and CA19-9 can indicate the nature of the tumor. The combined detection of three tumor markers can improve the diagnosis rate of tumor, with high prognostic value, and the change level of cytokines after treatment is also of high value in predicting the prognosis of breast cancer [15-17]. In our study, CEA, CA19-9, and CA125 Levels in the observation and control groups after treatment were lower than those before treatment (P < 0.05). CEA, CA19-9, and CA125 Levels in the observation group after treatment were lower than those of the control group (P < 0.05), suggesting that neoadjuvant chemotherapy with the ET regimen can significantly reduce the levels of

Table 2 The association between the expression of SRY-related HMG box-2 and clinicopathology of patients with triple-negative breast cancer, n (%)

Clinical data	Cases	SOX2 positive expression rate	χ²	P value
Age (yr)			0.000	0.994
< 50	55	41 (74.55)		
≥ 50	63	47 (74.60)		
BMI (kg/m^2)			0.545	0.460
< 22	60	43 (71.67)		
≥ 22	58	45 (77.59)		
Karnofsky score (points)			0.574	0.449
< 70	52	37 (71.15)		
≥70	66	51 (77.27)		
Differentiation degree			0.000	0.988
High differentiation	51	38 (74.51)		
Medium low differentiation	67	50 (74.63)		
Intravascular tumor thrombus			7.689	0.006
Yes	25	24 (96.00)		
No	93	64 (68.82)		
Tumor size			0.420	0.517
> 5 cm	53	38 (71.70)		
≤5 cm	65	50 (76.92)		
TNM stages			7.180	0.007
III	94	65 (69.15)		
IV	24	23 (95.83)		
Pathological type			0.049	0.825
Invasive ductal carcinoma	96	72 (75.00)		
Other	22	16 (72.73)		
Ki-67			0.073	0.787
≤14%	37	27 (72.97)		
> 14%	81	61 (75.31)		
P53			0.741	0.389
Positive	79	57 (72.15)		
Negative	39	31 (79.49)		

SOX2: SRY-related HMG box-2; BMI: Body mass index; TNM: Tumor-node-metastasis.

tumor markers and cytokines in patients with good therapeutic effect. According to the literature [18], patients with TNBC have the worst prognosis and a short survival time and are at risk of developing distant metastasis. Cox proportional risk regression analysis in this study showed that TNM stage, differentiation degree, lymph node metastasis, KPNA2 and SOX2 expressions, and treatment plan were prognostic factors of TNBC, which could be used as important indicators for clinical observation of efficacy and prognosis and may be related to the reduced sensitivity of tumor cells to chemotherapy drugs.

In the comprehensive treatment of breast cancer, neoadjuvant chemotherapy is no longer limited to breast preservation, staging surgery, and other advantages. It can evaluate the sensitivity of chemotherapy, realize personalized treatment, and develop targeted drugs[18-20]. There are many studies on the side effects of chemotherapy drugs, but few studies on the factors that affect the prognosis of patients after chemotherapy have been conducted. This study had certain reference value

Table 3 Correlation analysis SOX2 expression **KPNA2** expression P value r_s **Positive** Negative Positive 72 8 0.514 0.000 22 Negative 16

KPNA2: Karyopherin A2; SOX2: SRY-related HMG box-2.

Clinical data	Observation group ($n = 60$)	Control group $(n = 58)$	t/χ²	P value
Age (yr)	54.49 ± 4.29	55.70 ± 5.10	-1.396	0.165
BMI (kg/m²)	22.02 ± 2.05	22.10 ± 2.54	-0.189	0.851
Karnofsky score (points)	74.40 ± 5.12	75.52 ± 6.02	-1.090	0.278
Differentiation degree			1.188	0.276
High differentiation	23 (38.33)	28 (48.28)		
Medium low differentiation	37 (61.67)	30 (51.72)		
ntravascular tumor thrombus			0.337	0.562
es/es	14 (23.33)	11 (18.97)		
No	46 (78.33)	47 (81.03)		
Eumor size			0.576	0.448
• 5 cm	29 (48.33)	24 (41.38)		
55 cm	31 (51.67)	34 (58.62)		
TNM stages			0.009	0.926
II	48 (80.00)	46 (79.31)		
V	12 (20.00)	12 (20.69)		
Pathological type			0.735	0.391
nvasive ductal carcinoma	47 (78.33)	49 (84.48)		
Other	13 (21.67)	9 (15.52)		
TPNA2 expression			0.016	0.899
ositive	41 (68.33)	39 (67.24)		
Negative	19 (31.67)	19 (32.76)		
OX2 expression			0.012	0.914
ositive	45 (75.00)	43 (74.14)		
Negative	15 (25.00)	15 (25.86)		
(i-67			0.518	0.472
14%	17 (28.33)	20 (34.48)		
14%	43 (71.67)	38 (65.52)		
53			0.210	0.647
ositive	39 (65.00)	40 (68.97)		
Vegative	21 (35.00)	18 (31.03)		

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 $KPNA2: Karyopherin\ A2; SOX2: SRY-related\ HMG\ box-2; BMI:\ Body\ mass\ index; TNM:\ Tumor-node-metastasis.$

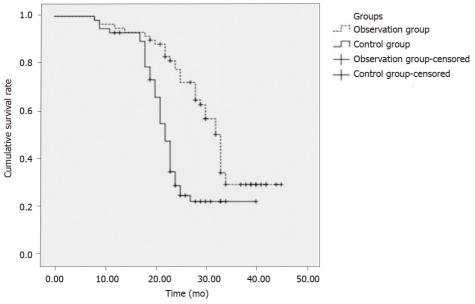
Table 5 Comparison of short-term therapeutic effects between the two groups, n (%)							
Group	Cases	CR	PR	SD	PD	Z	P value
Observation group	60	0 (0.00)	35 (58.33)	19 (31.67)	6 (10.00)	-2.183	0.029
Control group	58	0 (0.00)	23 (39.66)	23 (39.66)	12 (20.69)		

CR: Complete response; PR: Partial response.

Table 6 Comparison of tumor markers before and after chemotherapy between the two groups (mean ± SD)							
Crown	Canan	CEA (mg/L)		CA19-9 (kU/L)		CA125 (kU/L)	
Group	Cases	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	60	38.49 ± 6.12	11.40 ± 2.32^{a}	50.30 ± 12.21	19.92 ± 3.42 ^a	163.30 ± 34.43	54.30 ± 12.28 ^a
control group	58	40.02 ± 7.05	20.24 ± 2.50^{a}	52.29 ± 11.73	28.38 ± 2.95^{a}	168.29 ± 37.71	79.10 ± 14.42 ^a
t		-1.260	-19.919	-0.902	-14.368	-0.751	-10.070
P value		0.210	0.000	0.369	0.000	0.454	0.000

 $^{^{}a}P < 0.05 \ vs$ before treatment.

CA: Cancer antigen; CEA: carcinoembryonic antigen.



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Figure 1 The survival curves.

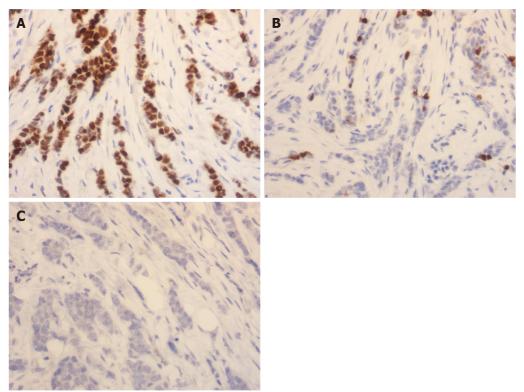
for clinical treatment. However, due to the short follow-up duration of this study and considering that influencing factors were not assessed in this study, larger multicenter study sample sizes to explore the clinicopathological characteristics and prognosis of elderly patients with TNBC are required in the future to develop a standard treatment plan for better prognosis.

CONCLUSION

In conclusion, neoadjuvant chemotherapy for TNBC treatment can achieve good curative effects. Moreover, TNM stage, differentiation degree, lymph node metastasis, KPNA2 and SOX2 expressions, and treatment plan are prognostic factors of patients with TNBC.

Table 7 Multivariate analysis of the prognosis of triple-negative breast cancer								
Factors		SE	Walds	P value	RR (95%CI)			
TNM staging	0.454	0.102	19.811	0.000	1.575 (1.289-1.923)			
Degree of differentiation	0.322	0.104	9.586	0.000	1.380 (1.125-1.692)			
Lymph node metastasis	0.312	0.112	7.760	0.000	1.366 (1.097-1.702)			
KPNA2	0.360	0.121	8.852	0.000	1.433 (1.131-1.817)			
SOX2	0.344	0.132	6.792	0.000	1.411 (1.089-1.827)			
Chemotherapy regimens	-0.543	0.142	14.623	0.000	0.581 (0.440-0.767)			

KPNA2: Karyopherin A2; SOX2: SRY-related HMG box-2; TNM: Tumor-node-metastasis; RR: Relative risk.



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Figure 2 Karyopherin A2 expression. Immunohistochemical staining (×400). A: High expression of Karyopherin A2 (KPNA2) in triple-negative breast cancer tissue; B: KPNA2 positive and low expression in non-triple-negative breast cancer tissue; C: Negative expression of KPNA2 in normal breast tissue.

ARTICLE HIGHLIGHTS

Research background

Patients with triple-negative breast cancer (TNBC) have relatively high recurrence and transfer rates during the operation and 3 years after postoperative adjuvant chemotherapy.

Research motivation

This study identified the additional effective treatments to improve patient prognosis.

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Research objectives

This study aimed to explore and discuss the effects and prognostic factors of neoadjuvant chemotherapy in TNBC.

Research methods

Total 118 patients diagnosed with TNBC from January 2016 to January 2020 in our hospital were selected and divided into the observation (n = 60) and control (n = 58) groups according to the apeutic



regimen. The control group received routine chemotherapy, and the observation group received neoadjuvant chemotherapy.

Research results

The short-term curative effect of the observation group was significantly better than that of the control group, and the median survival time of the observation group was significantly longer than that of the control group (P < 0.05). The epirubicin-paclitaxel regimen can significantly reduce the levels of tumor markers and cytokines in patients with good therapeutic effect.

Research conclusions

Neoadjuvant chemotherapy for TNBC treatment can achieve good curative effects. Moreover, tumornode-metastasis stage, differentiation degree, lymph node metastasis, karyopherin A2 and SRY-related HMG box-2 expressions, and treatment plan are prognostic factors of patients with TNBC.

Research perspectives

Next, we will investigate the mechanism of neoadjuvant chemotherapy for TNBC.

FOOTNOTES

Author contributions: Dong TY and Ding F designed this retrospective study; Dong TY and Chen RY wrote this paper; Dong TY, Chen RY, Hou J, Guo J and Ding F were responsible for sorting the data.

Institutional review board statement: The study was approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University (SWYX: No.2021-223).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: No conflict of interest.

Data sharing statement: No additional data are available.

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