Journal of Hainan Medical University

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The efficacy and safety of the targeted drug combined with adriamycin liposome solution for HER−2−positive breast cancer

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ARTICLE INFO

Article history:
Received 14 Apr 2017
Received in revised form 17 Apr 2017
Accepted 19 Apr 2017
Available online 24 May 2017

Keywords:
Breast cancer
Human epithelial growth factor receptor-2
Adriamycin liposome
Cardiotoxicity

ABSTRACT

Objective: To study the efficacy and safety of the targeted drug trastuzumab combined with adriamycin liposome solution for HER-2-positive breast cancer. **Methods:** A total of 112 patients with breast cancer who received chemotherapy in Department of Cardiothoracic Breast Surgery, Guangdong TongJiang Hospital between May 2014 and April 2016 were selected as the research subjects and divided into two groups by random number table, liposome group received trastuzumab + adriamycin liposome chemotherapy, and the control group received trastuzumab + adriamycin chemotherapy. Before chemotherapy as well as 4 weeks and 8 weeks after chemotherapy, serum levels of tumor markers, cytokines and myocardial injury indexes were detected, the electrocardiography was conducted and the degree of myocardial injury was determined. **Results:** 4 weeks and 8 weeks after chemotherapy, serum CEA, CA15-3, TPS, CTGF, TGF- β , TSGF, VEGF and MK levels of both groups were significantly lower than those before chemotherapy, serum CK-MB and cTnI levels were significantly higher than those before chemotherapy, limb leads QRS amplitudes and chest leads QRS amplitudes were significantly lower than those before chemotherapy, serum CEA, CA15-3, TPS, CTGF, TGF- β , TSGF, VEGF, MK, CK-MB and cTnI levels of liposome group were significantly lower than those of control group, and the limb leads QRS amplitudes and chest lead QRS amplitudes were significantly higher than those of control group. **Conclusion:** Targeted drug combined with adriamycin liposome therapy for HER-2-positive breast cancer can improve the curative effect and reduce the cardiotoxicity.

1. Introduction

Breast cancer is the most common female malignant tumor, the incidence is rising in recent years and the infected crowd is getting younger. In recent years, the study about the pathogenesis of breast cancer suggests that the high expression of human epidermal growth factor receptor-2 (HER-2) is an important pathological factor that leads to poor prognosis of breast cancer[1]. Trastuzumab is the targeted chemotherapy drug that targets and inhibits the biological functions of HER-2, and its combination with adriamycin is a standard chemotherapy regimen for HER-2-positive breast cancer[2,3]. But both trastuzumab and adriamycin are with strong cardiotoxicity, and combined chemotherapy can increase the risk of myocardial injury. Adriamycin liposome is a new kind of adriamycin preparation with targeting characteristics, and it can not only more effectively target the lesions and increase the drug concentration inside the lesions, but can also reduce drug toxicity to the myocardium[4]. In the following study, the efficacy and safety of the targeted drug trastuzumab combined with adriamycin liposome solution for HER-2-positive breast cancer were analyzed.

2. Subjects and methods

2.1 Research subjects

A total of 112 patients with breast cancer who received chemotherapy in Department of Cardiothoracic Breast Surgery,

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Fund Project: Medical Research Foundation Projects of Foshan No: 2015356.

Guangdong TongJiang Hospital between May 2014 and April 2016 were selected, all patients were clearly diagnosed with breast cancer by pathological examination, immunohistochemical staining showed that HER-2 expression intensity was ++ or +++, and the patients with cardiac function damage before chemotherapy were excluded. Random number table was used to divide the 112 patients with HER-2-positive breast cancer into the liposome group (who received trastuzumab + adriamycin liposome chemotherapy) and the control group (who received trastuzumab + adriamycin chemotherapy), liposome group were 43-65 years old and the BMI was (22.3±3.6) kg/m^2; the control group were 42-67 years old, and the BMI was (22.9±3.3) kg/m^2. The two groups of patients were not significantly different in general data (P>0.05).

2.2 Chemotherapy methods

Control group accepted trastuzumab combined with adriamycin solution, and the specific methods were as follows: trastuzumab, initial dose 4 mg/kg, by intravenous drip, and then 2 mg/kg each time, by intravenous drip, 1 time a week; adriamycin 50 mg/m2, by intravenous drip, 1 time/2 weeks; combined use for 8 weeks. Liposome group adopted trastuzumab combined with adriamycin liposome solution, and the specific methods were as follows: trastuzumab, initial dose 4 mg/kg, by intravenous drip, and then 2 mg/kg each time, by intravenous drip, 1 time a week; adriamycin liposome 20 mg/m^2, by intravenous drip, 1 time/2 weeks; combined use for 8 weeks.

2.3 Serum index detection methods

Before chemotherapy as well as 4 weeks and 8 weeks after chemotherapy, 5 ml fasting cubital venous blood was collected, let stand for coagulation and then centrifuged to separate serum, and enzyme-linked immunosorbent assay kits were used to determine carcinoembryonic antigen (CEA), carbohydrate antigen 15-3 (CA15-3), tissue polypeptide-specific antigen (TPS), connective tissue growth factor (CTGF), transforming growth factor-β 1 (TGF-β 1), tumor-specific growth factor (TSGF), vascular endothelial growth factor (VEGF), midkine (MK), creatine kinase isoenzyme (CK-MB) and troponin I (cTnI) levels.

2.4 Electrocardiography methods

Before treatment as well as 4 weeks and 8 weeks after treatment, 12-lead electrocardiography was conducted with electrocardiograph to measure R wave and S wave amplitudes, and the sum of R wave and S wave amplitudes was used as QRS amplitude to calculate all limb leads QRS amplitudes and all chest leads QRS amplitudes.

2.5 Statistical methods

SPSS 20.0 software was used to input the serum tumor markers, cytokines and myocardial injury indexes as well as electrocardiogram parameters, comparison of the above data between two groups was by t test and P<0.05 indicated statistical significance in differences.

3. Results

3.1 Serum tumor markers CEA, CA15-3 and TPS levels

Before chemotherapy as well as 4 weeks and 8 weeks after chemotherapy, analysis of serum tumor markers CEA (ng/mL), CA15-3 (U/mL) and TPS (U/L) between two groups of patients was as follows: (1) before chemotherapy, serum CEA, CA15-3 and TPS levels were not significantly different between two groups of patients (P>0.05); (2) 4 weeks and 8 weeks after chemotherapy, serum CEA, CA15-3 and TPS levels of both groups of patients were significantly lower than those before chemotherapy, and the differences in serum CEA, CA15-3 and TPS levels were statistically significant within group before and after treatment (P<0.05); (3) 4 weeks and 8 weeks after chemotherapy, above serum marker molecule levels of liposome group were significantly lower than those of control group, and differences in above serum marker molecules were statistically significant between groups 4 weeks and 8 weeks after chemotherapy (P<0.05).

3.2 Serum cytokines CTGF, TGF-β 1, TSGF, VEGF and MK levels

Before chemotherapy as well as 4 weeks and 8 weeks after chemotherapy, analysis of serum CTGF (ng/mL), TGF-β 1 (pg/mL), TSGF (U/L), VEGF (ng/mL) and MK (pg/mL) between two

Table 1.

Comparison of serum CEA, CA15-3 and TPS between two groups of patients before and after chemotherapy.

Groups	n	Time point	CEA	CA15-3	TPS
Liposome group	56	Before chemotherapy	32.51±5.62	69.76±9.24	102.54±15.64
		4 weeks after chemotherapy	12.19±1.85*&	23.31±3.64*&	45.76±7.51*&
		8 weeks after chemotherapy	8.97±1.14*&	17.65±2.94*&	32.15±5.64*&
Control group	56	Before chemotherapy	33.28±5.78	70.12±10.24	101.98±13.47
		4 weeks after chemotherapy	18.79±2.52*	45.51±6.72*	67.82±9.25*
		8 weeks after chemotherapy	13.12±1.82*	27.88±4.51*	45.41±6.85*

*: compared within group before and after treatment, P<0.05; &: comparison between groups after treatment, P<0.05.

Table 2.

Comparison of serum CTGF, TGF-β, TSGF, VEGF and MK between two groups of patients before and after chemotherapy.

Groups	*n*	Time point	CTGF	TGF-β1	TSGF	VEGF	MK
Liposome group	56	Before chemotherapy	9.38±1.03	113.54±15.68	98.34±11.34	62.52±9.62	526.53±72.35
		4 weeks after chemotherapy	4.24±0.67*&	48.79±7.24*&	45.65±7.61*&	26.72±4.14*&	237.87±41.25*&
		8 weeks after chemotherapy	3.09±0.52*&	34.21±5.41*&	32.14±5.64*&	19.33±2.94*&	157.65±20.14*&
Control group	56	Before chemotherapy	9.61±1.14	115.02±18.72	99.41±10.94	63.14±8.96	531.29±74.15
		4 weeks after chemotherapy	6.69±0.93*	79.76±9.35*	74.52±9.68*	40.21±5.62*	355.41±52.46*
		8 weeks after chemotherapy	5.24±0.78*	56.53±7.65*	62.58±8.79*	23.41±4.21*	231.24±34.59*

*: compared within group before and after treatment, $P<0.05$; &: comparison between groups after treatment, $P<0.05$.

Table 3.

Comparison of myocardial injury degree between two groups of patients before and after chemotherapy.

Groups	*n*	Time point	Serum indexes		QRS amplitudes	
			CK-MB	cTnI	Limb leads	Chest leads
Liposome group	56	Before chemotherapy	2.31±0.45	9.38±1.15	0.73±0.09	1.34±0.17
		4 weeks after chemotherapy	3.42±0.57*&	24.52±4.52*&	0.65±0.09*&	1.19±0.14*&
		8 weeks after chemotherapy	3.89±0.63*&	41.29±6.65*&	0.61±0.07*&	1.02±0.15*&
Control group	56	Before chemotherapy	2.36±0.42	9.61±1.09	0.75±0.10	1.36±0.19
		4 weeks after chemotherapy	5.61±0.84*	67.65±8.76*	0.55±0.70*	1.05±0.17*
		8 weeks after chemotherapy	8.52±1.16*	93.12±11.25*	0.51±0.06*	0.93±0.13*

*: compared within group before and after treatment, $P<0.05$; &: comparison between groups after treatment, $P<0.05$.

groups of patients was as follows: (1) before chemotherapy, serum CTGF, TGF-β, TSGF, VEGF and MK levels were not significantly different between the two groups ($P>0.05$); (2) 4 weeks and 8 weeks after chemotherapy, serum CTGF, TGF-β, TSGF, VEGF and MK levels of both groups were significantly lower than those before chemotherapy, and differences in serum CTGF, TGF-β, TSGF, VEGF and MK levels were statistically significant within group before and after treatment ($P<0.05$); (3) 4 weeks and 8 weeks after chemotherapy, above serum cytokine levels of liposome group were significantly lower than those of control group, and differences in above serum cytokines were statistically significant between groups 4 weeks and 8 weeks after chemotherapy ($P<0.05$).

3.3 Myocardial injury degree

Before chemotherapy as well as 4 weeks and 8 weeks after chemotherapy, analysis of serum myocardial injury indexes CK-MB (U/L) and cTnI (μg/L) as well as electrocardiogram QRS amplitudes (mV) between two groups of patients was as follows: (1) before chemotherapy, serum CK-MB and cTnI levels as well as limb leads QRS amplitudes and chest leads QRS amplitudes were not significantly different between two groups of patients ($P>0.05$); (2) 4 weeks and 8 weeks after chemotherapy, serum CK-MB and cTnI levels of both groups were significantly higher than those before chemotherapy, limb leads QRS amplitudes and chest leads QRS amplitudes were significantly lower than those before chemotherapy, and differences in serum CK-MB and cTnI levels as well as limb leads QRS amplitudes and chest leads QRS amplitudes were statistically significant within group before and after treatment ($P<0.05$); (3) 4 weeks and 8 weeks after chemotherapy, serum CK-MB and cTnI levels of liposome group were significantly lower than those of control group, the limb leads QRS amplitudes and chest lead QRS amplitudes were significantly higher than those of control group, and differences in serum CK-MB and cTnI levels as well as limb leads QRS amplitudes and chest leads QRS amplitudes were statistically significant between groups 4 weeks and 8 weeks after chemotherapy ($P<0.05$).

4. Discussion

Adriamycin liposome is a newly developed chemotherapy drug, and study has shown that trastuzumab combined with adriamycin liposome treatment of breast cancer with HER-2 over-expression has significantly better complete remission rate, partial remission rate and total effective rate than trastuzumab combined with conventional adriamycin therapy, and causes fewer adverse reactions[4]. Cancer cell proliferation activity is the important pathological factor influencing the breast cancer prognosis and chemotherapy effect, and the more active the cancer cell proliferation, the higher the levels of tumor markers synthesized from cancer cells and released into the blood circulation. In the study, in order to clarify the effect of trastuzumab combined with adriamycin liposome on the cancer cell proliferation activity, the serum markers that reflect cell viability were analyzed. CEA is a sensitive indicator for clinical assessment of tumor cell proliferation activity; CA15-3 is a glycoprotein on the cell membrane, and it is split during malignant tumor proliferation and enters into blood circulation[5,6]; TPS is a specific antigen that reflecting epithelial-derived malignant tumor cell proliferation activity[7]. The comparison of the markers between the two groups in the study showed that serum CEA, CA15-3 and TPS levels of liposome group were significantly lower than those of control group. This means that trastuzumab combined with adriamycin liposome has better killing effect on breast cancer cells than trastuzumab combined with conventional adriamycin therapy.

Cancer cell growth, invasion and angiogenesis are the important biological behaviors that cause breast cancer progression, and CTGF, TGF-β1, TSGF, VEGF, MK and various other cytokines are involved in the regulation of the malignant biological behavior of cancer cells. CTGF is from the cancer cells, fibroblasts and endothelial cells, and can promote angiogenesis and cell migration[8]; TGF-β1 is the TGF-β family member that regulates cell growth

and differentiation, and it can change the microenvironment outside of the tumor cells and promote the cell infiltration and angiogenesis[9]; TSGF is a vasoactive peptide synthesized and secreted by cancer cells, and it can expand the tumor lesion and its surrounding blood vessels to provide adequate blood flow for cancer cell growth[10]; VEGF is a cytokine with clear and strong pro-angiogenesis effect, which not only provides nutrients for the cancer cell proliferation, but also provides path for the cancer cell migration[11]; MK is a kind of heparin-binding growth factor that can promote the cancer cell proliferation[12]. In the study, analysis of malignant breast cancer biology-related cytokine levels proved that serum CTGF, TGF-β, TSGF, VEGF and MK levels of both groups after chemotherapy were significantly lower than those before chemotherapy, and above serum cytokine levels of liposome group were significantly lower than those of control group. This means that both adriamycin and adriamycin liposome combined with trastuzumab could inhibit the malignant biological behavior of breast cancer, and adriamycin liposome combined with trastuzumab has better inhibiting effect on malignant breast cancer biology-related cytokines than conventional adriamycin combined with trastuzumab.

Both trastuzumab and adriamycin have obvious cardiotoxicity, and combined application of the two drugs for breast cancer can increase the risk of myocardial injury[13]. Adriamycin liposome is an adriamycin preparation with targeting characteristics, and it can not only enhance the drug targeting to the tumor tissue and the killing effect on cancer cells, but can also reduce the drug accumulation in the normal organs, especically the heart, so as to reduce myocardial toxicity of the drugs[14,15]. Cardiotoxicity of chemotherapy drugs can lead to cell rupture, resulting in the release of CK-MB, cTnI and other molecules from the cytoplasm into the blood circulation[16]. In the study, analysis of serum CK-MB and cTnI before and after chemotherapy showed that after chemotherapy, serum CK-MB and cTnI levels of both groups of patients significantly increased, and serum CK-MB and cTnI levels of liposome group were lower than those of control group. This means that both types of chemotherapy regimens can lead to different degree of myocardial injury, and the toxic effect of adriamycin liposome combined with trastuzumab on myocardial cells is weaker than that of regular adriamycin combined with trastuzumab. The myocardial cell injury will not only cause molecule release from cytoplasm into the blood circulation, but will also cause cellular electrical activity changes, characterized by the reduced potential and the weakened amplitudes. In the study, comparison of the electrocardiogram QRS amplitudes between two groups of patients showed that the limb leads QRS amplitudes and chest lead QRS amplitudes of liposome group were significantly higher than those of control group. This means that the effect of adriamycin liposome combined with trastuzumab on the electrical activity of myocardial cells is weaker than that of conventional adriamycin combined with trastuzumab.

Based on above discussion, it can be preliminarily concluded in the study that trastuzumab combined with adriamycin liposome can more effectively kill breast cancer cells and reduce cardiotoxicity than trastuzumab combined with adriamycin. In future research, the effect and safety of different doses of adriamycin liposome for treatment of breast cancer can be further discussed so as to clarify the best adriamycin liposome dosage for breast cancer.

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