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Changes in ischemia-modified albumin in myocardial toxicity induced by anthracycline and docetaxel chemotherapy

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Abstract

This study aims to evaluate differences in myocardial toxicity induced by different chemotherapy regimens. Patients were divided into 2 groups: epirubicin (EPI) combined with cyclophosphamide (EC) group and docetaxel combined with cyclophosphamide (TC) group. Changes in electrocardiograph (ECG) and ischemia-modified albumin (IMA) were determined pre- and 1, 3, and 6 courses of postchemotherapy. After the first course of chemotherapy, there was no significant difference in ECG and abnormal IMA incidence rates between the TC groups and EC groups ($P > .05$). After the third course and at the end of the sixth course, ECG and abnormal IMA incidence rates in the EC group were significantly higher than in the TC group ($P < .05$). Besides, IMA values significantly increased with the increase in chemotherapy courses in the EC group; and the value of the postsixth course was significantly higher than in the pre- and postfirst and -third courses of chemotherapy. IMA value in the postsixth course in the TC group was significantly higher than that in the pre- and postfirst and -third courses of chemotherapy. In addition, IMA values at the postfirst and -third courses of chemotherapy in the EC group were significantly higher than in the TC group. Both EC and TC chemotherapy regimens were harmful to the myocardium, and the incidence rate of myocardial damage increased with the increase of cumulative dose. Besides, the degree of myocardial damage in EC group was significantly higher than in the TC group.

Abbreviations: CTX = cytoxan, EC = epirubicin combined with cyclophosphamide, ECG = electrocardiograph, EPI = epirubicin, HSA = human serum albumin, IMA = ischemia-modified albumin, TC = docetaxel combined with cyclophosphamide.

Keywords: anthracycline, docetaxel, ischemia-modified albumin, myocardial damage

1. Introduction

At present, the anthracycline represented by epirubicin (EPI) and the taxanes represented by docetaxel are the bases of breast cancer chemotherapy regimens, which are characterized with strong antitumor activity.[1] However, potential myocardial injuries induced by these 2 types of drugs not only affect the prognosis of patients, but also limit their applications in clinic.[2,3] Myocardial damages caused by chemotherapy drugs are divided into acute, subacute, tachycardias or bradycardias, pericardial effusion, and heart failure. Once it developed into congestive heart failure, mortality can reach as high as 48%.[4,5] Therefore, it is of great significance to timely screening and early drug intervention for patients with reversible myocardial injury. Current diagnostic methods of myocardial damage used in clinic include electrocardiograph (ECG), Doppler echocardiography, brain natriuretic peptide, cardiac troponin-T, and creatine kinase-MB fraction levels.[6,7] Among these, ECG has the best cost performance and is most commonly used. For patients with acute or subacute myocardial damage which usually caused by edema of myocardial cells and myocardial cell vacuolar degeneration, the ECG manifested with nonspecific ST-T (ST segment-T wave) alternations, lowing and flatting of QRS wave (QRS complex), and prolongation of QT interval. However, for patients with chronic myocardial damage, the changes in ECG signs are transient and not easy to be captured.[8–10] A simple ECG detection cannot instantly reflect the degree of myocardial damage in patients after chemotherapy, and commonly used clinical cardiac markers are lack of enough sensitivity and specificity for detection.[6,8]

Ischemia-modified albumin (IMA) is produced by human serum albumin (HSA) which local structure changed when it flows through ischemic tissues. Local tissues can produce oxidative stress reaction when myocardial ischemia occurred, and the N-terminal amino acid sequence of albumin was oxidatively modified, which result in IMA formation. IMA concentration rapidly increased in 5 to 10 minutes postmyocardial ischemia in peripheral blood, and sustained increase during the course of ischemia, it would lasted for 2 to 4 hours, and returned to baseline level in 6 to 10 hours.[11,12] Since it can be detected in the reversible phase of myocardial injury, and possesses the advantages of high sensitivity, high negative predictive value and early appearing,[13] it has become a hot topic in clinical research.

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Therefore, we attempted to determine the relationship between the IMA—changes and ECG alternations—caused by EPI and docetaxel, and to assess the value of IMA combined with ECG as the diagnosis of the degree of drug-induced myocardial damage.

2. Materials and methods

2.1. General data

Patients who diagnosed with breast cancer by pathology and received postoperative adjuvant chemotherapy from the Breast Surgery Department of Qingdao Center Hospital and treated from January 1, 2014 to January 1, 2015 were enrolled into this study. All patients were female, and the age of these patients ranged from 24 to 59 years old. All patients were initially diagnosed with breast cancer and pathologically confirmed as invasive ductal carcinoma. Besides, in these patients, tumor node metastasis staging was I to II, physical status scored $\leq$2 points, expected survival period was 1 year, and routine blood and liver and kidney function tests were normal. In addition, other malignant tumors were excluded, there were no previous histories of coronary heart disease, angina, myocardial infarction, heart failure, and other serious heart diseases, there were no previous histories of radiotherapy and chemotherapy, no postoperative radiotherapy were performed in patients during the gestation and suckling period. According to the principle of informed consent, and approved by the local ethics committee, a total of 101 patients were randomly divided into 2 groups: EPI combined with cyclophosphamide (EC) group ($n=55$) and docetaxel combined with cyclophosphamide (TC) group ($n=56$). There were no statistical differences in age distribution, tumor size, lymph node metastasis, and other general information between the 2 groups ($P>.05$) (Table 1).

2.2. Treatment method

Regimen in the EC group: An intravenous drip of 100 mg/m^2 of EPI (Pfizer Pharmaceutical Wuxi Co., Ltd., Wuxi City, Zhejiang Province China, Pfizer, batch number: H20000496) was administered at the first day; an intravenous drip of 600 mg/m^2 of cytoxan (CTX, manufactured by Jiangsu Hengrui Medicine Co., Ltd., Lianyugang City, Jiangsu Province China, batch number: 131012) was administered at the first day, every 21 days as an course, and sustained treatment for 6 courses. Regimen in the TC group: An intravenous drip of 75 mg/m^2 of docetaxel (Taxotere; Aventis Pharma, Hangzhou City, Zhejiang Province China, batch number: H20030540) was administered at the first day; an intravenous drip of 600 mg/m^2 of CTX (manufactured by Jiangsu Hengrui Medicine Co., Ltd., batch number: 131012) was administered at the first day, every 21 days as an course, and sustained treatment for 6 courses.

Table 1

The general data of EC group and TC group.

Number	EC 56	TC 55	t/χ^2	P
Age, y	50.2±10.2	51.5±9.7	0.476	>.05
Tumor size, cm	2.5±0.6	2.3±0.5	1.91	>.05
Lynphnode metastasis (+) (n), %	32 (57.1)	29 (52.7)	0.219	>.05
ER (+) (n), %	39 (69.6)	36 (65.4)	0.222	>.05
HER-2 (+) (n), %	23 (41.0)	19 (34.5)	0.502	>.05

EC = epirubicin combined with cyclophosphamide, ER = esotrogen receptor, HER-2 = human epidermal growth factor receptor-2, TC = docetaxel combined with cyclophosphamide.

2.3. Observation

ECG examinations were performed on these 2 groups of patients before and at the end of the first, third, and sixth courses of chemotherapy. Besides, the conditions of nodal tachycardia, ventricular arrhythmia, atrial fibrillation, atrial tachycardia ST-T changes, and limb lead QRS low voltage were observed.

IMA test: combination of albumin and cobalt ions is used to measure and Roche COBAS8000 is used to detect and reagent whose manual shows that IMA < 85kU/L is normal reference value. A unit of 2 mL of peripheral venous blood was collected at pre- and postchemotherapy, anticoagulated with heparin, and IMA level was detected by enzyme-linked immunosorbent assay. If IMA value was $\geq$85 kU/L, the result was considered as positive.

2.4. Statistical methods

SPSS 18.0 software (SPSS Inc, Chicago, IL) was used for statistical analysis, count data were expressed with the number of cases (constituent ratio), and χ^2-test was used for comparison between groups. $P<.05$ was considered statistically significant. Measurement data were expressed as mean ± standard deviation ($\overline{x}\pm s$), and t test was used for comparisons between groups. analysis of variance was used in above 3 groups. $P<.05$ was considered statistically significant.

3. Results

3.1. Comparison of the abnormal occurrence rates of ECG and IMA at the end of the different courses

No difference in abnormal occurrence rates of ECG and IMA were found in patients who received EC and TC chemotherapy at the end of the first course of chemotherapy ($\chi^2=2.03$, $\chi^2=1.01$; $P>.05$). Besides, at the end of the third course, the abnormal occurrence rates of ECG and IMA in the EC group were higher than in the TC group ($\chi^2=3.95$, $\chi^2=2.04$; $P<.05$); and at the end of the sixth course, the abnormal occurrence rates of ECG and IMA in the EC group were significantly higher than in the TC group ($\chi^2=7.15$, $\chi^2=7.15$; $P<.05$) (Table 2 and Fig. 1).

Table 2

Comparison of the abnormal occurrence rates of ECG and IMA at the end of the different courses.

Groups periods	IMA				ECG			
	Epirubicin	Docetaxel	P	χ^2	Epirubicin	Docetaxel	P	χ^2
At the end of the first course	1	0	>.05	1.01	2	0	>.05	2.03
At the end of the third course	4	2	<.05	2.036*	8	2	<.05	3.95*
At the end of the sixth course	13	5	<.05	7.15*	13	5	<.05	7.15*

Compared with docetaxel. ECG = electrocardiograph, IMA = ischemia-modified albumin.
* $P<.05$.

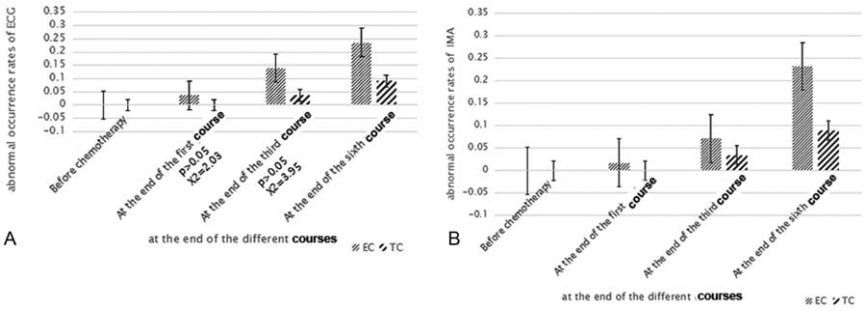

Figure 1. Comparison of the abnormal occurrence rates of electrocardiograph (ECG) and ischemia-modified albumin (IMA) at the end of the different courses. (A) The abnormal occurrence rates of ECG at the end of the different courses. (B) The abnormal occurrence rates of IMA at the end of the different courses.

Table 3

Changes of IMA (kU/L) at the end of the different courses in the EC group and TC group $(\overline{x} \pm s)$.

Times	EC group (56 cases)	TC group (55 cases)	*t*	*P*
Before chemotherapy	80.5±68.2	81.5±68.0	0.0774	>.05
At the end of the first course	86.5±60.3	83.5±67.9	0.2462	>.05
At the end of the third course	134.5±78.0*,†	90.5±65.2	3.214	<.05
At the end of the sixth course	195.6±81.3*,†,‡	145.0±82.2*,†,‡		
F	30.41	9.89	3.228	<.05

EC = epirubicin combined with cyclophosphamide, TC = docetaxel combined with cyclophosphamide.
* Compares with before chemotherapy ($P < .05$).
† Compared with at the end of the first period ($P < .05$).
‡ Compared with at the end of the third period ($P < .05$).

3.2. Changes of IMA (kU/L) at the end of the different courses in the EC group and TC group

There was no difference in IMA values between the EC and TC groups before chemotherapy. In the EC group, IMA value significantly increased at the end of the third and sixth courses of chemotherapy, as compared with before chemotherapy (q = 5.584, $P < .05$; q = 11.90, $P < .05$; respectively); and this value significantly increased at the end of the third and sixth courses of chemotherapy, compared with the end of the first course of chemotherapy (q = 4.96, $P < .05$; q = 11.28, $P < .05$; respectively). In addition, this value significantly increased at the end of the sixth course, compared with the end of the third course of chemotherapy (q = 6.31, $P < .05$). In the TC group, IMA value at the end of the sixth course of chemotherapy significantly increased, compared with before and at the end of the first and third courses of chemotherapy (q = 6.62, 6.41, and 5.68, respectively; $P < .05$). There were no differences between the postthird course of chemotherapy versus the pre- and postfirst course of chemotherapy (q = 0.93, 0.73; $P > .05$). Besides, there was no significant difference in IMA values between the EC and TC group at the first course of chemotherapy ($t = 0.077$, $P > .05$). However, this difference was significant at the third course ($t = 3.214$, $P < .05$). At the end of the sixth course, the difference was statistically significant ($t = 3.23$, $P < .05$) (Table 3 and Fig. 2).

4. Discussion

Chemotherapy regimens containing anthracycline and docetaxel have been widely used in patients with breast cancer. These 2 kinds of chemotherapeutic drugs are characterized with a wide antitumor spectrum and strong anticancer activity. However, their toxic effects on heart are significant; various arrhythmias could be found in the early stage of damage, and heart failure would occur if the damage is severe.

The mechanism research of myocardial injury induced by anthracycline is mainly focused on the aspects of free radical, mitochondrial damage, and calcium overloading. Most researchers have accepted the theory of free radicals, in which the formation of free radicals could be induced. However, free radicals have anticancer activity and can also cause oxidative stress in heart and aggravate the damage of myocardial tissue.[8,14]

Taxanes are natural products isolated from taxus plants. They can terminate mitosis and trigger apoptosis of tumor cells by inhibiting microtubule depolymerization. These drugs can also cause cardiac toxicity with manifestations of ECG alternations,

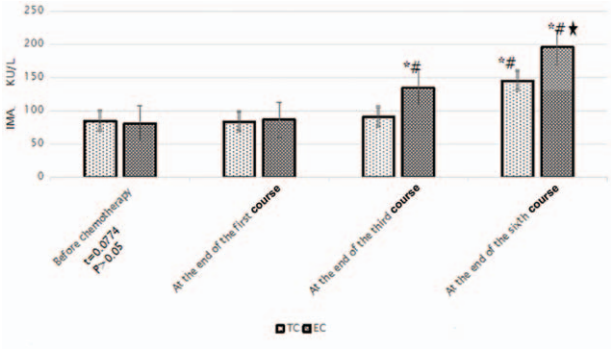

Figure 2. Changes of ischemia-modified albumin (kU/L) at the end of the different courses in the epirubicin combined with cyclophosphamide group and docetaxel combined with cyclophosphamide group. *Compared with before chemotherapy, $P < .05$; #compared with at the end of the first course, $P < .05$; compared with at the end of the third course, $P < .05$.

which may be related to the oxidative stress of free radicals in myocardial cells.[9,10,15,16]

As a marker of myocardial injury, IMA is a substance produced by HSA, local structure of which changed when it flew through the ischemic tissue. Albumin is the most abundant protein in human plasma. When the myocardium was locally oxidatively stressed, local hydroxyl radical increased. Albumin was damaged by the hydroxyl radical, which resulted in the formation of IMA. Roy et al[17] pointed out for the first time that the formation of IMA is directly related to the formation of active oxidation products and confirmed that hydroxyl radicals play an important role in the formation of IMA. Once these free radicals in local myocardium increased, an increase in IMA would be subsequently induced.[13,18–22]

Nowadays, IMA is often used in testing ischemic disease, and especially for acute myocardial ischemia, has high sensitiveness. In 2003, Food and Drug Administration of the United States of America approve IMA as biochemical marker of early myocardial ischemia. Through analysis of IMA for the emergency patients with suspected chest pain, Peacock et al[23] found that sensitiveness to IMA is 80% and positive predictive value is 91%. Oxygen free-radical increases in the ischemic disease. So far, IMA has been applied to diagnose stroke, lower limb ischemia, and pulmonary embolism in the early state.[24–26]

These above theories indicate that myocardial damage would occur in the applications of anthracycline and docetaxel drugs; and when damage occurs, it would cause IMA changes. Therefore, the sensitivity of IMA is very high. Combined with the changes in ECG, IMA can be used as an indicator to determine early myocardial damage induced by these 2 kinds of chemotherapeutic agents. From these experimental results, we could find that the incidence rate of myocardial damage induced by taxanes was lower than that induced by anthracycline; Abnormities in ECG and the positive rates of IMA in different courses of chemotherapy in the TC group were significantly lower than those in the EC group ($P > .05$), and myocardial damage occurred in a dose-dependent manner, as dosage increased, the occurrence of myocardial damage also increased. So was the circumstance in the EC group, the occurrence of myocardial damage increased as the dosage increased.

Our research does have limitations. On the one hand, the limitation is the chemotherapy here specifically talking about anthracycline and docetaxel chemotherapy, rather than a more general chemotherapy. On the other hand, there is the lack of follow-up studies data about the degree of myocardial ischemia recover between anthracycline and docetaxel chemotherapy. Therefore, the credibility could be affected. We have since established a standard to ensure that future studies do not encounter this difficulty.

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