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Analysis of Cardiotoxicity from rh-Endostatin Therapy Combined with Chemotherapy

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OBJECTIVE To evaluate the cardotoxicity from recombinant human endostatin (rh-endostatin) combined with chemotherapy.
METHODS A total of 12 cancer patients treated with rh-endostatin combined with chemotherapy were selected, and their clinical data collected. Their symptoms, including cardiopalmus, chest distress, dyspnea and changes in their electrocardiogram (ECG), myocardium enzymogram and left ventricular ejection fraction (LVEF), were observed during the drug treatment. These indicators were used for early diagnosis of cardiotoxicity.
RESULTS Compared with a pre-therapeutic value, there was a significant increase in the CK-MB value at one week after starting the treatment as well as at the end of treatment ($P < 0.05$). There was a significant change in the ECG at the end of treatment, compared to a pre-therapeutic condition ($P < 0.05$), but there was no significant difference when comparing the pre- and post-therapeutic LVEF values.
CONCLUSION It was recognized that mild cardiac adverse reactions exist in the regimen of recombinant human endostatin combined with chemotherapy. This therapy caused definite injury to the cardiac muscle, but cardiac functions were not obviously changed. CK-MB and ECG may be used as indicators for early monitoring cardiac toxicity. Vigilance against cardiac adverse reactions should be heightened during a course of rh-endostatin combined with chemotherapy.

KEY WORS: re-endostatin, cardotoxicity, early diagnostic markers.

Introduction

Molecular targeted therapy has produced breakthroughs in tumor therapy, and has achieved remarkable results in treating various tumors. However long-term use of some drug targeted-treatment may result in cardiotoxicity, a problem of considerable concern[1]. rh-Endostatin, or endostar, as a new anti-angiogenic drug, has been shown to have a significant anti-tumor effect in clinical tests. However definite cardiotoxicity was also found in Stage I and III clinical trials[2,3]. The authors even found that, in early administration of endostar, on day 7, acute left heart failure occurred in a patient with advanced non-small cell lung cancer (NSCLC) who had been receiving the regimen of endostar plus Gemzar. His electrocardiogram examination showed a sinus tachycardia (ST), his heart rate ranged from 110 to 120 times/min, a ventricular premature beat sporadically occurred, and the pro-brain natriuretic peptide (pro-BNP) level increased up to 15,859 pg/ml, resulting in the patient's death. The patient had suffered from

hypertensive disease over the past 10-plus years, but his cardiac function was basically normal before administration of the drugs. This case indicates the importance of vigilance regarding cardiotoxicity during the course of endostar combined chemotherapy, especially for patients with a past medical history of angiocardiopathy. Therefore, during endostar combination chemotherapy, it is necessary to monitor related indices of myocardial damage, and to prevent congestive heart failure.

Our study involved 12 advanced-stage tumor patients who received a regimen of endostar combined with chemotherapy. The incidence of adverse reactions from the regimen and the early effective diagnostic criteria were investigated.

Materials and Methods

General data

A total of 12 advanced-stage tumor patients from the Tumor Department of the Nanfang Hospital, Guangzhou, China were selected, during a period from July 2006 to August 2007. Among these patients, a non-small cell lung cancer was found in 9, osteosarcoma in 2, and uterine cervix cancer in 1. Five patients were male and 7 female, with their ages ranging from 24 to 68 years, and a median age of 42. Karnofsky performance scores (KPSs) of the patients all were over 60 points. Past treatments, such as anthracyclines etc., or/and thoracic radiotherapy, which can cause severe cardiotoxicity, had not been conducted within half a year. Usually endostar has been chosen to be used in second-line or third-line treatments. In these treatments, an endostar + NP (NVB plus DDP) regimen was utilized in 9 cases, endostar + Gemzar in 2, and endostar + Alimta in 1. One of these 12 patients had suffered from hypertensive disease for 10 plus years, and was diagnosed before treatment with GradeⅡ hypertension. Other patients had no case history of cardiac or hypertensive disease.

Treatment methods

Intravenous administration: endostar was added to a 250 ml to 500 ml of sodium chloride solution, uniform i.v. drip for 3 to 4 h, once a day, with a dose of 7.5 mg/m^2 (1.2× 10^5 U/m^2), and a consecutive 14 day cycle. The next cycle of treatment continued following a week of rest. Endostar administration started together with chemotherapeutic agents at the same day, in accordance with the respective courses of treatment.

Cardiotoxicity monitoring

i) Blood pressure was measured twice a day, and pulse once a day; *ii*) cardiac muscle zymogram (CK-MB, CK, AST, LDH, HBDH) and ECG were conducted at d 0, d 8 and d 15 of each administrating cycle, respectively; *iii*) Color Doppler imaging of heart was conducted at both the beginning and the end of each cycle, and the left ventricular ejection fraction (LVEF) measured; *iv*)during the process of administration, the patient's uncomfortable symptoms, such as palpitation, chest distress, chest pain, dyspnea etc., and onset time of the symptoms, were observed.

Evaluation of cardiotoxicity

All blood and biochemical results of the cardiac muscle zymogram (CK-MB, CK, AST, LDH and HBDH) were compared to the range of normal values of the Clinical Laboratory Department, Nanfang Hospital, Guangzhou (Table 1). The values were considered to be abnormal if they went beyond the upper limit of the normal limit. The criteria for abnormal ECG results were as follow: *i*) ST; *ii*) a low limb-lead tension; *iii*) change of the *t* wave, i.e. low and flat, or inverted (over 3 leads); *iv*) the low ST segment pressure was over 0.3 mV; *v*) QT interval extension ($\geq$ 0.44 s). It was regarded as an abnormal ECG if one of the above occurred in a patient without a previous electrocardiographic abnormality, or it was considered significant if, after administration, aggravation occurred in the patient with a slightly abnormal ECG examination. LVEF: it would signify to be normal if the value was over 0.55. The value ranging from 0.40 to 0.50 meant a slight decrease of heart function, and from 0.30 to 0.40 signified a severe functional decrease in function.

Statistical analysis

SPSS 11.5 statistical software was used. The χ^2 test was employed for comparison of the numeration data, and *t* test for measurement data. The mean value ($\bar{x}$) ± standard deviation (s) were used to express the data, using the value of $P < 0.05$ for statistical significance.

Results

Symptoms and changes in the ECG

After a cycle of treatment, slight chest distress and palpitation were found in 4 (33.3%) of the 12 patients, most of which occurred one week following administration. A change in the ECG was seen in 6 (50%) of the 12 patients (4 with ST, 1 with a slight change of the S-T segment, and 1 with rare ventricular premature beats). Most of the symptoms and ECG changes reverted to normal after a 1-week rest following the drug treatment. During the course of medication, no obvious blood pressure changes were found. There was a statistically significant difference in the ECG comparing the results prior to with those following the treatment, see Table 2.

Changes in the cardiac muscle zymogram

A cardiac muscle zymogram was conducted on the 12 patients one week after staring the treatment. In 6 cases, the CK-MB abnormally increased at one week after initiating the treatment, and in 8 cases, it had increased

at the end of a treatment cycle. There was a statistical significance in the increase of the CK-MB, compared to that before the treatment, see Table 1. Slight increases occurred in the other values of the cardiac muscle zymogram, both at one week after starting the treatment and at the end of the treatment. Most of the values however were within the normal range, and there were no statistically significant differences in the comparison between the respective values and the pre-therapeutic baseline (Table 1).

Change in the LVEF

A contrast observation of the changes in the LVEF before and after the treatment was conducted in 8 of the 12 patients, showing a slight drop in LVEF in 3 of these 8 patients, with a decrease ranging from 5% to 15%. Basically there were no obvious changes in 5 of these 8 patients, and there was no statistically significant difference in comparing the 2 groups (Fig.1).

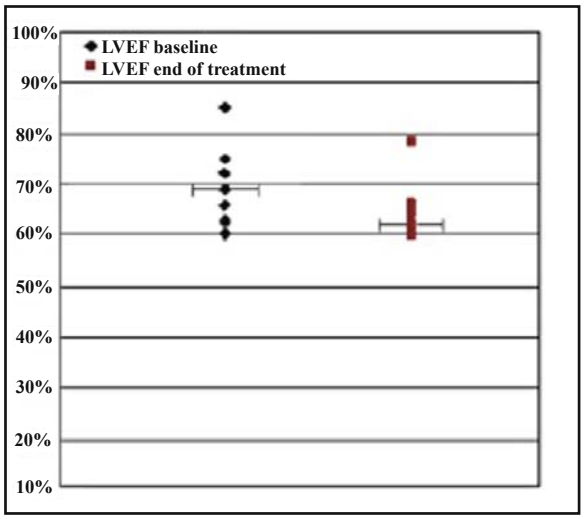

Fig.1. Values and median of LEVF at the baseline and at the end of treatment.

Discussion

In 1997, O'Reilly et al.[4] from Harvard Medical School, extracted endostatin from the supernatant of cultured endothelium from mouse angioma (EOMA). The endostatin had a strong inhibitory effect on tumor angiogenesis, and they achieved success in an in vivo murine experiment. A new-type of rh-endostar, independently developed in China, was the first endostatin anticancer drug of its kind in the world. The results from Stage I and III clinical trials showed that treatment with the endostar plus a NP regimen had a good therapeutic effect on advanced lung cancer. However, mild/moderate cardiologic adverse reactions occurred in 30 (6.38%) of the 470 advanced NSCLC patients, who were the subjects in the clinical trials. The major clinical abnormality, which did not endanger the patient's life, was myocardial ischemia within day 2~7 after treatment. Apparent symptoms, all of which were reversible, were found in 6.4‰ of these patients, but most did not influence the process of drug treatment. Alleviation of these effects was achieved in the patients, without any symptomatic treatment. In the patients with previous coronary heart disease and/or hypertension, rh-endostatin usually brought about the following commonly-encountered cardiologic adverse reactions: ST, slight ST-T change, AV conduction blocking, atrial premature beats and rare ventricular premature beats, etc.[2,3]

More studies on cardiotoxicity caused by anthracyclines and radiotherapy have been conducted over the past several years. Recently the cardiovascular adverse effects of some molecular-targeted drugs gradually have been discovered, resulting in increased interest in these effects. Detailed studies have been conducted on the mechanism of these effects and clinical observation made on the cardiotoxicity of both Herceptin and of Gleevec[5]. Previous reports showed that cardiac insufficiency, especially, congestive heart failure (CHF) and decrease in the LVEF, occurred in 4%~7% of the patients receiving only Herceptin[6-10]. In a 5-year clinical research, severe heart injury, or even CHF[11], was found in 10 chronic myelogenous leukemia patients several months following administration of Gleevec.

Cardiotoxicity was also found after using the regimen of endostar combined with chemotherapy. The main clinical abnormalities were palpitation, chest distress and ECG changes, as well as an increase in the CK-MB. All patients in our study were treated with chemotherapeutic agents, without previous reports of cardiotoxicity, such as the regimen of endostar plus NP, Gemzar or Alimta etc. The patients receiving anthracyclines associ-

Table 1. Values of the cardiac muscle enzymogram before and after treatment.

Biochem analysis of blood	Normal value	Before treatment (baseline)	One week after starting treatment	End of treatment	*P* value
CK-MB	0~20	15.8 ± 10.0	25.2 ± 15.7*	27.7 ± 16.2**	*P = 0.02, **P = 0.03
CK	26~174	67.7 ± 25.8	69.1 ± 19.8*	72.1 ± 28.9**	*P = 0.81, **P = 0.46
AST	0~45	19.7 ± 5.8	21.6 ± 9.0*	21.0 ± 9.7**	*P = 0.13, **P = 0.44
LDH	89~220	248.6 ± 176.4	276.9 ± 216.9*	299.6 ± 247.4**	*P = 0.11, **P = 0.06
HBDH	95~255	171.3 ± 147.3	212.3 ± 217.7*	229.2 ± 238.6**	*P = 0.09, **P = 0.07

The units of CK-MB, CK, AST, LDH and HBDH were U/L; * and ** respectively represent a comparison between the values before and after 1-week of treatment, and between the values before and at the end of treatment.

Table 2. ECG changes with the treatment.

	Normal cases	Abnormal cases	Abnormality rate (%)	*P* value
Before treatment	11	1	-	-
One week after starting treatment	8	4	33.3	0.132
End of treatment	6	6	50.0	0.025

ated with cardiotoxicity or thoracic radiotherapy, within about half a year since treatment started, were excluded. In our opinion, cardiotoxicity is mainly caused by endostar therapy. The gold standard for diagnosis of cardiotoxicity is pathological confirmation by a myocardial biopsy. However, myocardial biopsies are traumatic, and intolerable for patients, so few are feasible. Therefore, it is especially important to develop, effectual and sensitive markers, and other means to detect and estimate cardiotoxicity produced by endostar.

Our results showed that cardiotoxic symptoms and ECG changes, brought about by the regimen of endostar combined with chemotherapy, occurred respectively in 33.3% and about 50% of the patients. These rates were much higher compared to the report on the rate of cardiac adverse effects (6.38%) in the Stage-III clinical trials. We deem that there are two causative factors: *i*) a sample size that was relatively too small may have caused the discrepancy; *ii*) variation of the consistency of the regimen of combined chemotherapy and the difference in the general health of patients between the two studies may bring about various degrees of the cardiotoxicity.

Although the results have shown that the regimen of endostar combined with chemotherapy has a high risk of cardiotoxicity, most of these toxic manifestations will automatically vanish after treatment is discontinued, suggesting that the cardiotoxicity is temporary, mild and reversible. Examination of the cardiac muscle zymogram showed that the CK-MB value continually increased during the whole course of endostar treatment, but the increase was only slightly higher than the normal value. These results indicate on the one hand that the cardiotoxicity from endostar is not severe in the short term, and on the other hand that CK-MB displays a very high sensitivity to endostar cardiotoxicity, which can be considered to be a marker for early predicting and diagnosing cardiotoxicity.

Our study showed no apparent change in the LVEF before and after the treatment, suggesting again that in a short term mild cardiac damage, but not severe organic change, may be seen as a result of endostar administration. As long as clinicians lay stress on appraisement of the patient's cardiovascular condition before treatment, and are able to monitor cardiovascular functions during therapy, the regimen of endostar combined with chemotherapy should be considered safe.

Our preliminary investigation on the cardiotoxicity of the regimen of endostar combined with chemotherapy has produced significant findings. Nevertheless long-term cardiac adverse events, caused by the endostar cardiotoxicity, still need further observation and assessment.

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