Clin. Cardiol. 21, 777–779 (1998)

Doxorubicin-Induced Cardiomyopathy Treated with Carvedilol

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Summary: Even today, heart failure due to doxorubicin-induced dilated cardiomyopathy seems to have a poor prognosis, as it is often irreversible and relatively unresponsive to standard medical treatment. This paper describes the first case of a patient complaining of severe symptoms of congestive heart failure due to doxorubicin-induced dilated cardiomyopathy unresponsive to standard medical treatment (digoxin, diuretics, and angiotensin-converting enzyme inhibitor), who showed complete clinical recovery and significant improvement of left ventricular dysfunction after carvedilol treatment. It also illustrates the possibility that carvedilol may be a first-choice drug for the treatment of this disease.

Key words: doxorubicin, cardiomyopathy, carvedilol

Introduction

The anthracycline drug doxorubicin (adriamicin) is an effective chemotherapeutic agent for the treatment of several malignancies, but its use is often associated with cardiotoxicity. Doxorubicin may cause acute or, more commonly, chronic cardiotoxicity. Acute cardiotoxicity is associated with arrhythmias, electrocardiographic (ECG) abnormalities, a pericarditis-myocarditis syndrome, and occasionally myocardial infarction and sudden death. Chronic cardiotoxicity is due to the development of biventricular dilated cardiomyopathy, the incidence of which is proportional to the cumulative dose administered.[1] Until today, heart failure due to doxorubicin-induced cardiomyopathy has been thought to be irreversible, relatively unresponsive to standard medical treatment (digoxin, furosemide, and captopril), and fatal in up to 60% of patients.[2] However, some reports suggest that improvement in left ventricular function may occur in selected patients, and four cases have shown a well-documented reversibility of severe, chronic cardiotoxicity.[3,4]

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Received: December 12, 1997
Accepted with revision: May 21, 1998

Case Report

A 35-year-old woman with infiltrating ductal carcinoma of the left breast (T_3 N_1 M_0), without any anamnestic or clinical evidence of cardiovascular or pulmonary diseases, received three courses of fluorouracil, cyclophosphamide, and doxorubicin, followed by modified radical mastectomy. Subsequently, she received additional four courses of doxorubicin, followed by two courses of cyclophosphamide, fluorouracil, and methotrexate. The total cumulative dose of doxorubicin was 500 mg/m^2. One week after completion of chemotherapy, the patient was hospitalized with cough, constrictive chest pain, and progressive dyspnea, orthopnea, oliguria, and peripheral venous congestion and edema. Her pulse rate was 120/min, blood pressure 100/60 mmHg, and the ECG showed sinus tachycardia with low voltage and diffuse T-wave abnormalities. Chest x-ray showed cardiomegaly with pulmonary venous congestion and pleural effusion. Echocardiographic data showed a global dilated cardiomyopathy (left ventricular end-diastolic dimension 60 mm), with severe diffuse hypokinesis (ejection fraction 14%), moderate mitral and tricuspidal regurgitation, and small pericardial effusion. Digoxin, furosemide, and enalapril were administered at the dosages of 0.250 mg/day, 25 mg/day, and 5 mg/day, respectively. One month later, as symptoms were persisting, the patient came to our attention and was hospitalized in our department. Her pulse rate was 110/min, blood pressure 110/70 mmHg, and the ECG showed sinus tachycardia with low voltage and diffuse T-wave abnormalities. A chest x-ray (Fig. 1A) and the echocardiogram confirmed cardiomegaly with a pattern of dilated cardiomyopathy, with no evidence of pleural and pericardial effusion. Furosemide dosage was increased to 50 mg/day, and the patient was followed up monthly. No significant improvement

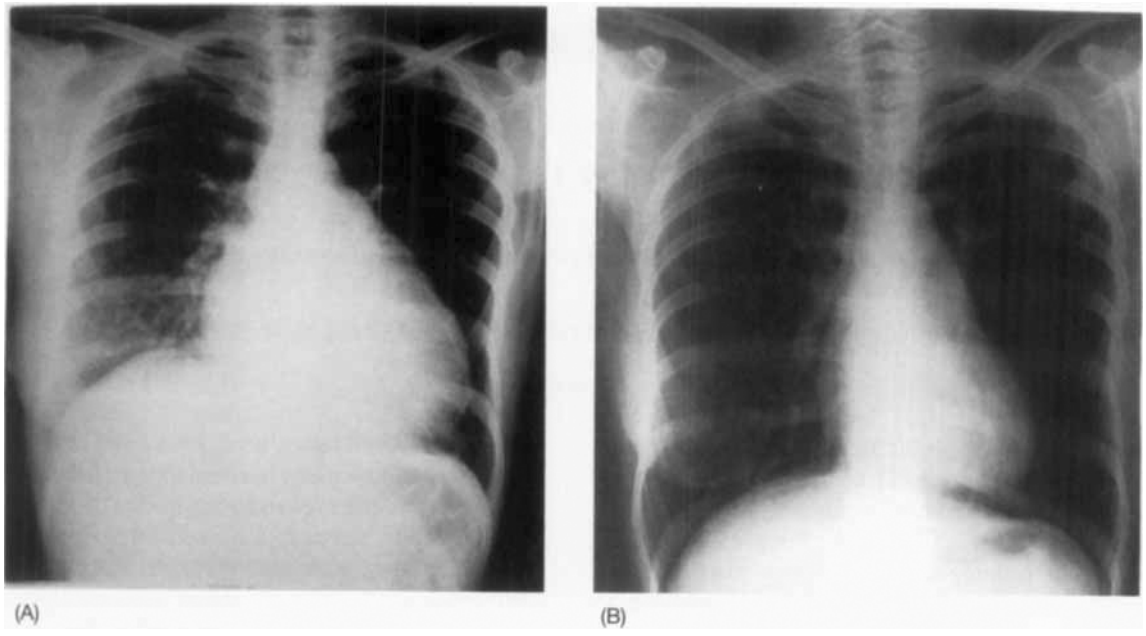

FIG. 1 Chest x-ray images before (A) and after carvedilol therapy (B).

was observed in the subsequent 4 months; rather, the patient developed marked hypotension. Therapy was therefore modified by suspending enalapril and adding carvedilol at the initial dosage of 6.25 mg twice daily, subsequently raised to 12.5 mg twice daily. At the successive monthly controls, we observed progressive clinical improvement, and furosemide was progressively reduced. At 6 months follow-up, the patient was free of symptoms and furosemide was administered at the dosage of 25 mg every second day. Therefore, the patient was examined for cardiac dysfunction. Her pulse was 80/min, blood pressure 120/80 mmHg, and the ECG showed an improvement in voltage and the diffuse T-wave abnormality. A chest x-ray was completely negative, with absence of signs of cardiomegaly and of pulmonary congestion (Fig. 1 B). Echocardiographic data showed a significant improvement in global kinesis (ejection fraction 45%), with reduction of left ventricular dimension (left ventricular end-diastolic dimension 56 mm). Digoxin, carvedilol, and furosemide (every second day) were continued. In the subsequent year, the patient reports a progressive improvement in her quality of life.

Discussion

Doxorubicin-induced cardiotoxicity is the result of a series of repeated injuries to the myocardium that gradually overcome cellular defenses and result in cell damage with decreased contractility and eventually cell death. The common mechanism for doxorubicin-induced cardiomyopathy appears to be free of radical damage in either iron-dependent or iron-independent fashion.[5] In myocytes, the injury to the cell membrane and the damage to the sarcoplasmic reticulum causes increased intracellular calcium concentration with a decrease in calcium binding.[6] This, in turn, leads directly to decreased contractility through action on the actin-myosin complex. Free Ca^{++} may also activate proteases within the heart, causing myofibrillar damage and turning on the apoptotic cell program.

In our patient, the mechanism for recovery of cardiac function during carvedilol therapy is speculative. Carvedilol is a nonselective β_1/β_2-receptor antagonist that also blocks α_1-receptor, reduces cardiac norepinephrine levels, and does non elicit upregulation of cardiac β-receptors. Previous studies have shown that carvedilol reduces the symptoms of heart failure, improves functional capacity, enhances exercise tolerance, and reduces the risk of death as well as the risk of hospitalization for cardiovascular causes in patients with heart failure.[7] Furthermore, unlike other beta blockers, carvedilol has a potent antioxidant effect,[8] which may protect against the continuing loss of cardiac myocytes that characterizes the progression of heart failure.[9] The α_1/β_2-blockade and the antioxidant properties of carvedilol may account for its different effects on survival compared with other beta blockers. In this respect, according to the free radical damage theory for the doxorubicin-induced cardiotoxicity, we speculate that the antioxidant effects of carvedilol could have contributed largely to the recovery of cardiac function observed in our patient. Furthermore, we cannot exclude the possibility that, in our patient, spontaneous recovery may represent the natural history of doxorubicin-induced cardiotoxicity, even though the short time between the administration of carvedilol and the improvement of cardiac function seems to show a strict cause–effect relationship. On the other hand, since this is only a case report, it is uncertain whether the dramatic beneficial effect

shown in this patient may represent the result of the action of carvedilol on congestive heart failure in general or a specific action of the drug in doxorubicin-induced cardiomyopathy.

Conclusion

This report confirms that heart failure due to doxorubicin-induced dilated cardiomyopathy may be reversible and suggests that carvedilol may be a first-choice drug in the treatment of this disease. This preliminary finding should encourage the planning of larger controlled clinical trials to assess the specific beneficial action of carvedilol in doxorubicin-induced dilated cardiomyopathy.

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