CASE REPORT

Fulminant fatal cardiotoxicity following cyclophosphamide therapy

Minako Katayama (MD)a,∗, Yukihiro Imai (MD)b, Hisako Hashimoto (MD)c, Masayuki Kurata (MD)d, Kenichi Nagai (MD)c, Koichi Tamita (MD)e, Shigefumi Morioka (MD, FJCC)e, Yutaka Furukawa (MD)e

a Department of Cardiology, Institute of Biomedical Research and Innovation, 2-2 Minatojima Minamimachi Chuoku, Kobe 650-0047, Japan
b Department of Pathology, Kobe City Medical Center General Hospital, Kobe, Japan
c Department of Cell Therapy, Institute of Biomedical Research and Innovation, Kobe, Japan
d Department of Hematology, Kobe City Medical Center General Hospital, Kobe, Japan
e Department of Cardiology, Kobe City Medical Center General Hospital, Kobe, Japan

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Summary A 59-year-old male with an abdominal mass that showed a diffuse large B cell lymphoma underwent extirpation of the tumor and chemotherapy. He subsequently received high-dose chemotherapy containing cyclophosphamide (1.5 g/m²/day × 2 days), followed by autologous peripheral blood stem cell transplantation. He developed congestive heart failure 5 days after administration of cyclophosphamide. His electrocardiogram showed extremely low voltage with ST segment change and echocardiogram showed diffusely increased left ventricular wall thickness, an increase in myocardial echogenicity, pericardial effusion, and generally decreased systolic function. Congestive heart failure progressed rapidly and he died the following day. Post-mortem examination of the heart revealed myocardial hemorrhage, yellowish brown pericardial effusion, and fibrinous pericarditis. His liver was atrophic and focal necrosis was observed histologically. Cyclophosphamide-induced cardiotoxicity occurred, even though the patient had both shown normal cardiac function before high-dose chemotherapy and had received a lower dose of cyclophosphamide. Concomitant administration of cytarabine might have affected his liver function and there might have been interaction between the drugs.

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Introduction

Cyclophosphamide-induced fatal cardiotoxicity is a rare complication, occurring within 10 days of receiving cyclophosphamide [1]. Although cardiotoxicity is related to dosage, previous anthracycline treatment, previous radiation, age over 50, and the presence of left ventricular (LV) dysfunction, no definitive risk factors have yet been identified [1,2]. We came across a case whose clinical course was rapidly progressive and fatal, even though he had presented with normal cardiac function before high-dose chemotherapy and subsequent peripheral blood stem cell transplantation (PBSCT).

Case history

A 59-year-old male presented with an abdominal mass, which showed a diffuse large B cell lymphoma. He underwent extirpation of the tumor and chemotherapy.

Chemotherapy was performed with two courses of cyclophosphamide, doxorubicin, vincristine and prednisolone, and 8 weeks’ treatment with cyclophosphamide, doxorubicin, methotrexate, bleomycin, vincristine, etoposide, ifosfamide, and prednisolone. As complete remission was obtained, high-dose chemotherapy with PBSCT was initiated. Peripheral blood stem cell harvest was performed using high-dose etoposide.

The total treatment dose of cyclophosphamide and doxorubicin received by the patient was 2700 mg/m², and 400 mg/m², respectively. Electrocardiogram was normal, and echocardiogram indicated normal LV systolic and diastolic function; LV ejection fraction (LVEF) was 58%, E/A = 0.96, and the deceleration time of E wave was 245 ms.

Fig. 1 Electrocardiograms. (a) An electrocardiogram on admission. (b) An electrocardiogram on the day the patient developed congestive heart failure. Extremely low voltage in limb leads and ST elevation in I, II, V3-6 were observed.
An echocardiogram showed a diffuse increase in left ventricular wall thickness and in myocardial echogenicity, and pericardial effusion. The patient developed general fatigue after the initiation of cytarabine, with significant elevation of serum liver enzymes. Creatine phosphokinase was elevated (220 IU/L) on Day 7, the second day of high-dose cyclophosphamide therapy. Stem cells were reinfused on Day 9. His urine volume decreased on Day 10, and paroxysmal atrial fibrillation was observed on Day 11.

Physical examination on Day 11 revealed a blood pressure of 110/80 mmHg, an irregular heart rate of 110 beats/min, and a body temperature of 36.3°C. No cardiac murmur was present and inspiratory crackles were detected by chest auscultation. The jugular vein was dilated and peripheral edema was observed. An electrocardiogram on that day showed extremely low voltage in limb leads and ST elevation in I, II, V3-6 (Fig. 1). An echocardiogram showed diffusely increased LV wall thickness, and myocardial echogenicity, pericardial effusion, and generally impaired systolic function with a LVEF 35%. The diastolic thickness of interventricular septum and posterior LV wall was 1.4 cm and 1.5 cm, respectively (Fig. 2).

The serum asparate aminotransferase concentration was 350 IU/L (normal 3—40 IU/L), serum alanine aminotransferase concentration was 106 IU/L (normal 8—40 IU/L), serum lactate dehydrogenase was 5260 IU/L (normal 200—450 IU/L), serum creatine phosphokinase (CK) was 938 IU/L (normal 15—130 IU/L) (MB 3%), and cardiac troponin T was positive.

A diagnosis of drug-induced myocarditis was suspected and the patient was transferred to the intensive care unit. In spite of intensive supportive treatment with diuretics and catecholamines, low cardiac output aggravated renal function and continuous hemodiafiltration was started. Percutaneous cardiopulmonary support was not applied to the patient because of critical thrombocytopenia and neutropenia following high-dose chemotherapy. The patient deteriorated and irreversible cardiac arrest occurred the following day (Day 12).

Post-mortem examination showed a fibrinous pericarditis with spotty pericardial hemorrhage and a yellowish brown pericardial effusion (120 ml). The heart weighed 430 g. The coronary arteries were patent. Cut surface of the myocardium showed
Fulminant fatal cardiotoxicity

Fig. 3 Post-mortem examination showed fibrinous pericarditis with spotty pericardial hemorrhage (a). The heart weighed 430 g. Cut surface of the myocardium showed diffusely hemorrhagic muscle and bulging appearance of myocardial tissue (b). Histologically, there were interstitial edema and extravasation of erythrocytes without infiltration of inflammatory cells nor lymphoma cells (c, d). Although foci of contraction band necrosis were observed (e), most of the cardiac myocytes were histologically preserved.

diffusely hemorrhagic muscle and bulging appearance of myocardial tissue. Histologically, there were interstitial edema and extravasation of erythrocytes without infiltration of inflammatory cells nor lymphoma cells. Although foci of contraction band necrosis were observed, most of the cardiac myocytes were histologically preserved. There was no myocyte hypertrophy or interstitial fibrosis (Fig. 3). The liver was atrophic and weighed 870 g. Focal necrosis was observed histologically, and there were no residual lymphoma cells.

Discussion

The number of therapeutic modalities available for the treatment of neoplastic disease has increased and tremendous progress has been made in improving the morbidity and mortality from neoplastic disease. However, life-threatening toxicities of such treatment remain a problem. It is therefore crucial to optimally manage comorbid illnesses and associated toxicities, especially critical cardiotoxicity.

Drug-related cardiac toxicity in patients treated with high-dose chemotherapy is an uncommon but potentially serious complication, and has been associated mostly with cyclophosphamide-containing regimens [1–3]. In the pathogenesis of high-dose cyclophosphamide-associated cardiac toxicity, toxic endothelial damage by cyclophosphamide causes extravasation of toxic metabolites and results in myocyte damage, interstitial hemorrhage, and edema [1,2]. The incidence of fulminant congestive heart failure is reported to be 5–19% [1,4,5].

This patient’s clinical course and the post-mortem pathological findings of his heart were typical of cyclophosphamide-induced cardiotoxicity. Although he was elderly and had received previous anthracycline 400 mg/m², which is the maximum dosage for the heart, LVEF and dias-
tolic function of the heart were preserved before high-dose chemotherapy for PBSCT. Single-agent high-dose cyclophosphamide-associated cardiotoxicity is dose dependent; however, the dose in the present patient was 1.5 g/m²/day (46.5 mg/kg) for 2 days, a level at which severe cardiotoxicity is not common. On the other hand, cytarabine is associated with cardiac arrhythmia and pericarditis. The highest incidence and severity of cardiac toxicity have been reported when the two drugs were coadministered [2]. In the present case, liver dysfunction, as a side effect of cytarabine, might have affected the metabolism of cyclophosphamide, or there might have been some interaction between the drugs.

The occurrence of acute heart failure after high-dose cyclophosphamide is difficult to predict. Cardiac monitoring including electrocardiography and echocardiography are important in the detection of clinical signs of cardiotoxicity. Diffuse voltage loss as shown by electrocardiogram, increased LV wall thickness and generalized increase in echogenicity by echocardiogram are findings that indicate myocardial hemorrhage [1,6]. Echocardiographic figures of myocardial thickening of the LV wall are also observed in myocarditis of any cause, infiltrative cardiomyopathy, hypertrophic cardiomyopathy, and also in cases of cardiac invasion of malignant lymphoma [1,6,7]. Drug-induced cardiotoxicity should therefore be taken into consideration when using cyclophosphamide therapy. Close communication between oncologists and cardiologists is required because differential diagnosis is difficult in some situations.

Recent studies have elucidated that cardiac troponin I can be considered a sensitive and reliable marker of acute minor myocardial damage in patients undergoing high-dose chemotherapy [8]. It might be helpful to apply a rapid and high-sensitive troponin test to cardiac monitoring for the early detection of drug-induced cardiotoxicity.

References