Abstract

A 17-year-old man with mediastinal seminoma was treated with chemotherapy and mediastinal irradiation therapy. Then he received high-dose chemotherapy containing cyclophosphamide (CY) followed by autologous peripheral blood stem cell transplantation. He suffered from CY-induced cardiomyopathy beginning six days after the administration of high-dose CY. The predictable factors associated with the onset of CY-induced cardiomyopathy are not precisely known. It is suggested that the history of mediastinal irradiation was responsible for the onset of cardiomyopathy.

(Key words: cyclophosphamide, irradiation, cardiomyopathy)

Introduction

High-dose chemotherapy followed by hematopoietic stem cell transplantation has been used as salvage treatment for seminoma with non-pulmonary visceral metastases (1). Cyclophosphamide (CY) is a key drug in most pre-transplant conditioning regimens. Fatal cardiotoxicity induced by high-dose CY has been well recognized (2–4). However, only a few predictable factors associated with the onset of cardiomyopathy have been reported (5, 6). We describe a patient with mediastinal seminoma who suffered from CY-induced cardiomyopathy. He was treated with mediastinal irradiation prior to high-dose chemotherapy. We present the clinical course and discuss the predictable factors associated with the onset of CY-induced cardiomyopathy.

Case Report

A 17-year-old man presented to our hospital in October 1997 with a complaint of cough and shoulder pain. A chest X-ray and computed tomography (CT) of the chest demonstrated a large tumor in the superior mediastinum (Fig. 1). CT of the abdomen and pelvis revealed no evidence of metastatic tumor. The serum lactate dehydrogenase, β-human chorionic gonadotrophin, and α-fetoprotein level were all within normal limits. Open biopsy of the mediastinal tumor revealed abnormal findings pathologically compatible with seminoma. Resection of the mediastinal tumor, left upper lobectomy of the lung, and partial resection of the pericardium were performed due to direct tumor invasion into the lung and pericardium. Postoperative mediastinal irradiation (total: 40 Gy) was carried out. In September 1998, the patient complained of hip pain, and gadolinium-enhanced magnetic resonance imaging revealed a high intensity lesion in the right iliac bone on T1-weighted images. Needle biopsy of the iliac bone revealed evidence of seminoma. Because patients with non-pulmonary visceral metastases were predicted to have a poor prognosis (7), our patient was treated with cisplatin-based high-dose chemotherapy. After three cycles of chemotherapy that consisted of peplomycin 20 mg (days 1, 8, and 15), etoposide 100 mg/m² (days 1–5), and cisplatin 20 mg/m² (days 1–5), the high intensity lesion in the right iliac bone on T1-weighted images reached the same intensity level as that in the left normal side. Subsequent chemotherapy consisted of carboplatin 300 mg/m² (day 1) and etoposide 100 mg/m² (days 1–5), followed by granulocyte-colony stimulating factor (100 μg/day i.v.) for mobilization of peripheral blood stem cells (PBSC). PBSC containing
12.8×10^6 CD34-positive cells/kg were collected during hematological recovery and cryopreserved without purging. The patient then received high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (PBSCT) in July 1999. The conditioning regimen consisted of carboplatin (300 mg/m² i.v.) for 4 days, etoposide (500 mg/m² i.v.) for 3 days, and cyclophosphamide (50 mg/kg i.v.) for 2 days. The total dose of cyclophosphamide received by the patient was 5.4 g (100 mg/kg). On day 3 after autologous PBSCT, he complained of dyspnea at rest. EKG showed a sinus tachycardia and low voltage in the limb leads without significant ST-T changes, his body weight gained, the central venous pressure was elevated at 18 cmH₂O, and his systolic blood pressure decreased to below 60 mmHg. A chest X-ray revealed left pleural effusions and an increase in the cardiothoracic ratio (Fig. 2). Echocardiography showed a decrease in left ventricular ejection fraction (EF) and an increase in intraventricular septum thickness in diastole (IVSd) and a normal left ventricular diameter at end systole (LVDd) (Fig. 3). Serum creatine kinase was 1,553 IU/l (MB 99%; normal, 14–170 IU/l), serum cardiac troponin T 0.88 ng/ml (normal, <0.25 ng/ml), human atrial natriuretic peptide 460 pg/ml (normal, <40 pg/ml), and brain natriuretic peptide 3,310 pg/ml (normal, <20 pg/ml). These laboratory data indicated the severity of cardiomyopathy. Antibody titers for Coxsackie virus group B, ECHO virus, and Herpes simplex virus did not change. Oxygen was administered and continuous infusion of dopamine (5 μg/kg/min) and furosemide (100 mg/day) were started. In addition to this treatment, theophylline (5 mg/kg/day) as an adenosine antagonist and ascorbic acid (4 g/day) as an antioxidant were given. His condition gradually improved. On day 13, the clinical findings including echocardiography (Fig. 3) and chest X-ray (Fig. 2) returned to near normal levels. Aside from this cardiac episode, the regimen-related toxicity was well tolerated and hematological recovery was rapid. The patient is doing well without any clinical evidence of recurrence of seminoma at this time of reporting.

**Discussion**

Cardiotoxicity induced by high-dose cyclophosphamide (CY) has been recognized since the 1970s (8). The incidence of fatal cardiomyopathy varies between 2.0% and 17.0% (2–5), depending on different regimens and patient populations. In contrast to cardiomyopathy occurring months to years after high cumulative doses of anthracyclines (9), CY-induced cardiomyopathy occurs within the initial 2 or 3 weeks after treatment (10). Histopathological findings revealed microthrombi and multifocal myocardial necrosis caused by capillary endothelial damage (11, 12). Lee et al (10) reported the histological characteristics of CY-induced cardiomyopathy. Their autopsy findings revealed nondilated ventricles with focal subendocardial hemorrhage, prominent interstitial edema, extensive capillary congestion and few vacuoles in myocytes. Birchall et al (13) reported the echo-
The cardiographic characteristics of hemorrhagic myocarditis due to CY. An echocardiography of their patient showed thickening of the left ventricular wall and an increase in myocardial echogenicity, a decrease in left ventricular ejection fraction, and a normal chamber size. The present patient showed a restrictive cardiomyopathy with almost the same echocardiographic characteristics as that of their case. Myocarditis due to a viral infection should be considered in the differential diagnosis. Antibody titers for several viruses did not change during this episode and electrocardiography showed no significant ST-T changes. Thus, it is suggested that the cardiomyopathy of our case was due to high-dose CY.

Treatment for cardiomyopathy secondary to high-dose CY has not been established. Cellular mechanisms of cardiotoxicity are thought to be mediated by an increase in oxygen free radicals, through intracellular phosphoramidate mustard affecting endothelial and ion transport mechanisms (11, 12). Lee et al (10) treated patients suffering from CY-induced cardiomyopathy with ascorbic acid as an antioxidant and theophylline as an adenosine antagonist. We used both ascorbic acid and theophylline in addition to conventional therapy with diuretics and vasopressors. The effects of these drugs were not clear in our case. Additional follow-up of antioxidant therapy would be required before any firm conclusion can be made.

For successful management of chemotherapy, it is important to predict the onset of CY-induced cardiomyopathy prior to treatment of individual patients. The cumulative dose of anthracyclines and the reduced ejection fraction prior to high-dose chemotherapy containing CY may be associated with increased risk of cardiotoxicity due to CY (2, 3). On the other hand, our patient was not treated with anthracyclines and showed a preserved ejection fraction before high-dose chemotherapy. Moreover, subsequent studies have shown that both of these conventional markers are insufficient to independently predict the onset of cardiomyopathy (14, 15). In a recent report (5), prolongation of corrected QT interval before high-dose CY was strongly associated with the onset of cardiomyopathy. The corrected QT interval in our patient was not prolonged, and thus he would be classified in the lowest risk group in the report. Another predictive factor is mediastinal irradiation prior to high-dose CY. Nieto et al (6) reported that breast cancer patients with prior radiation therapy to the left chest wall or mediastinum had a significantly higher incidence of CY-induced cardiomyopathy (22.2%) than those without prior radiation to those areas (2.3%). Our case was treated with mediastinal irradiation (total: 40 Gy) before high-dose chemotherapy. Thus, it is suggested that the previous mediastinal irradiation might contribute to the induction of CY-induced cardiomyopathy.

To prevent patients from suffering from fatal cardiomyopathy, we must search for novel pretreatment characteristics indicating patients at increased risk of CY-induced cardiomyopathy. Furthermore, serial monitoring of clinical manifestations including electrocardiography, echocardiography, and serum markers associated with cardiomyopathy is necessary in clinical practice.

Figure 3. Time course of echocardiography. Parasternal long axis view (M-mode), EF: ejection fraction, LV: left ventricle, IVSd: intraventricular septum thickness in diastole, LVDd: left ventricular diameter at end systole.