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Abstract

Cyclophosphamide is one of the most widely used antineoplastic drugs. It is also a potent immunosuppressive agent administered to patients undergoing bone marrow transplantation (BMT). Here we report two cases of aplastic anemia in which severe cardiac dysfunction followed the serial administration of cyclophosphamide (50 mg/m² for 4 days). Both patients gradually developed dyspnea and showed oliguria 3–4 days after BMT. Cardiomegaly was seen on chest X-ray. Echocardiography showed reduced left ventricular contraction, pericardial effusion, and myocardial thickening. Cyclophosphamide-induced cardiotoxicity was suspected and the patients were treated accordingly but were refractory to pharmacotherapy. They were transferred to the intensive care unit where they received mechanical cardiopulmonary support, which improved left ventricular cardiac performance and led to a regression of myocardial thickening. Although both patients died because of severe pulmonary and renal complications, the rapid initiation of mechanical cardiopulmonary support may be a useful strategy in patients with a deteriorating condition, by allowing cardiac recuperation and therefore gaining time for further, potentially life-saving treatment.

Key words: cyclophosphamide, bone marrow transplantation (BMT), cardiotoxicity, percutaneous cardiopulmonary support (PCPS), intra-aortic balloon pump (IABP)

Introduction

Cyclophosphamide (CPA) is widely used as a chemotherapeutic agent and in conditioning regimens for patients undergoing bone marrow transplantation (BMT).[1)] However, CPA-induced cardiotoxicity is a dose-limiting toxic effect and a well-known complication. The cardiac manifestations that result from high-dose CPA are heterogeneous and range from innocuous to fatal, but there is little risk of cumulative toxicity.[1)] Here we report the cases of two patients with aplastic anemia who developed severe cardiac dysfunction following the serial administration of cyclophosphamide (50 mg/m² for 4 days) prior to BMT. Post-transplantation, both suffered profound cardiopulmonary failure and in both cases the clinical course was deemed inevitably fatal without definitive hemodynamic support. Mechanical circulatory support was provided in the form of percutaneous cardiopulmonary support (PCPS) and the use of an intra-aortic balloon pump (IABP). The enormous advances in mechanical circulatory support have provided additional options for achieving hemodynamic stability in patients suffering profound cardiopulmonary failure, cardiogenic shock, or cardiac arrest. The use of these procedures in a wide variety of clinical settings[2)] can be expanded to include the acute life-threatening situations described herein.

Case Presentation

Case1

A previously healthy 15-year-old girl developed purpura on her lower extremities and facial pallor. A peripheral blood examination indicated pancytopenia, with white blood cell counts (WBC) of 2,900/μl, a hemoglobin concentration (Hb) of 5.5 g/dl, and a platelet count (Plt) of 2.4×10^4 /μl. She was therefore referred to our hospital, where she underwent bone marrow aspiration, which revealed a hypocellular marrow (nucleated cell count (NCC) 1.5×10^4 /μl, no megakaryocytes) but no chromosomal abnormalities. Flow cytometry showed a CD55 deficiency, based on a detection rate of 5.2%, 9.3%, and 16.8% of her red blood cells (RBCs), neutrophils, and monocytes. A CD59 deficiency was also detected (5.1%, 10.8%, and 53.1%, respectively). She was diagnosed as having aplastic anemia with paroxysmal nocturnal hemoglobinuria (PNH). She was admitted to our hospital for BMT. Her body weight, height, and body surface area were 55.5 kg, 149.8 cm, and 1.52 /m², respectively. Laboratory findings were as follows: WBCs, 1,680/μl; neutrophils, 479/μl; Hb, 5.0 g/dl; Plt, 2.6×10^4/μl; and reticulocyte counts, 41,850/μl. She was administered 30 mg/m² of fludarabine, 2.5 mg /kg of rabbit anti-human thymocyte immunoglobulin (ATG), and 50 mg/m² of CPA for 4 days prior to BMT (days −5 to −2). She was transplanted with a graft from her HLA-matched brother. On day 4, she complained of chest pain and dyspnea, with concomitant systemic involvement as evidenced by a decrease in urine output (<1,000 ml/day) and an increase in her body weight. Echocardiography showed pericardial effusion with diastolic collapse of the right atrium (RA), a moderate free echo space of 17.0 mm behind the posterior wall of the left ventricle (LV) and of 10.0 mm ahead of the anterior right ventricular (RV) wall in diastole. Severe myocardial thickening based on an intraventricular septal thickness at diastole (IVSd) of 15.0 mm, a LV posterior wall thickness at dimensions (LVPWd) of 17.0 mm, and a reduced left ventricular ejection fraction (LVEF) of 50.0% (Fig. 1A). She was transferred to the intensive care unit (ICU) on the same day. Despite an intermittent infusion of diuretics and a continuous infusion of human atrial natriuretic peptide (hANP), olprinone, and dobutamine hydrochloride, her pulse and blood pressure gradually dropped. On day 5, she developed low-output syndrome (cardiac index below 2.0 ml/kg/m² or less) and oliguria (<500 ml/day) with reduced LV contraction (LVEF 30.0%) as determined on echocardiography. Shortly thereafter, she went into cardiac arrest. Return of spontaneous circulation after resuscitation, a 21-French sheath of PCPS drainage cannula (CX-EB21VLX: Terumo, Tokyo, Japan) was withdrawn from the right femoral vein and a 16.5-French sheath of blood supply cannula (CX-EB16ALX: Terumo, Tokyo, Japan) was inserted into the right femoral artery. Subsequently PCPS was initiated as an additional treatment with an initial blood flow was 1.8 L/min and a rotation rate of the biopump was 1,800 rpm using a Capiox SP Pump Controller Sp-100 plus (Terumo, Tokyo, Japan) to support the state of low cardiac output. These measures resulted in an improvement of LV contraction and the regression of myocardial thickening. On day 11, the use of an IABP was added to obtain a synergistic effect. On day 19, echocardiography showed improved LV contraction (LVEF 55.0%) and reductions of myocardial thickening (IVSd 15.0→12.0 mm, LVPWd 17.0→11.0 mm) and pericardial effusion (posterior wall of the left ventricle 17.0→5.0 mm) (Fig. 1B). PCPS flow was gradually decreased when PCPS flow was 1.0 L/min and hemodynamics were stable as systolic blood pressure was more than 80 mmHg, central venous pressure was less than 15 mmHg, and pulse pressure was more

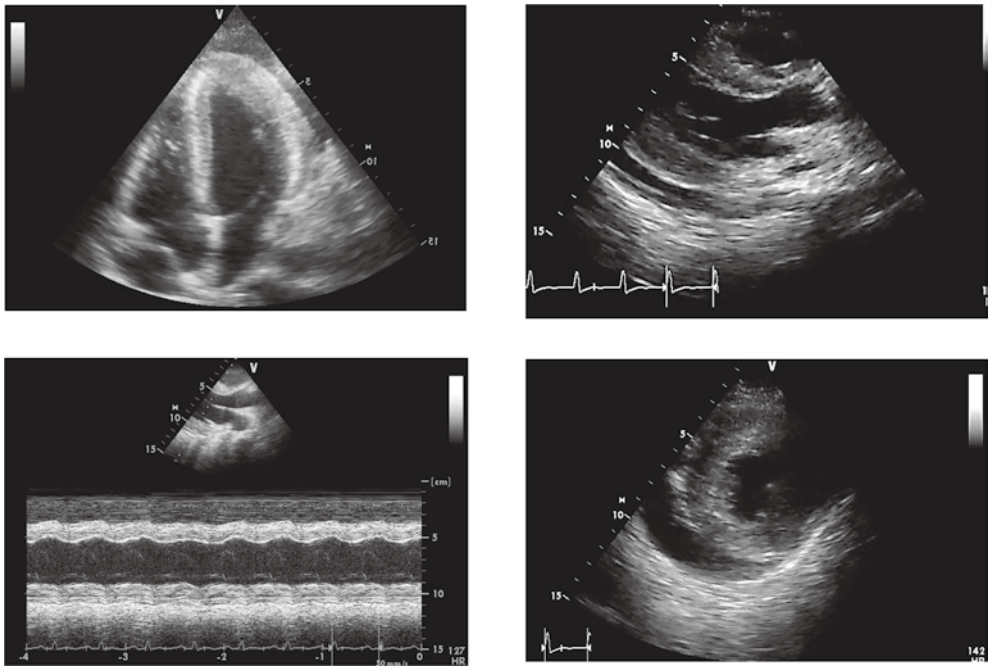

Fig 1A. Echocardiography showed pericardial effusion with diastolic collapse of the right atrium, reduced left ventricular contraction and severe myocardial thickening on day 4 after BMT.

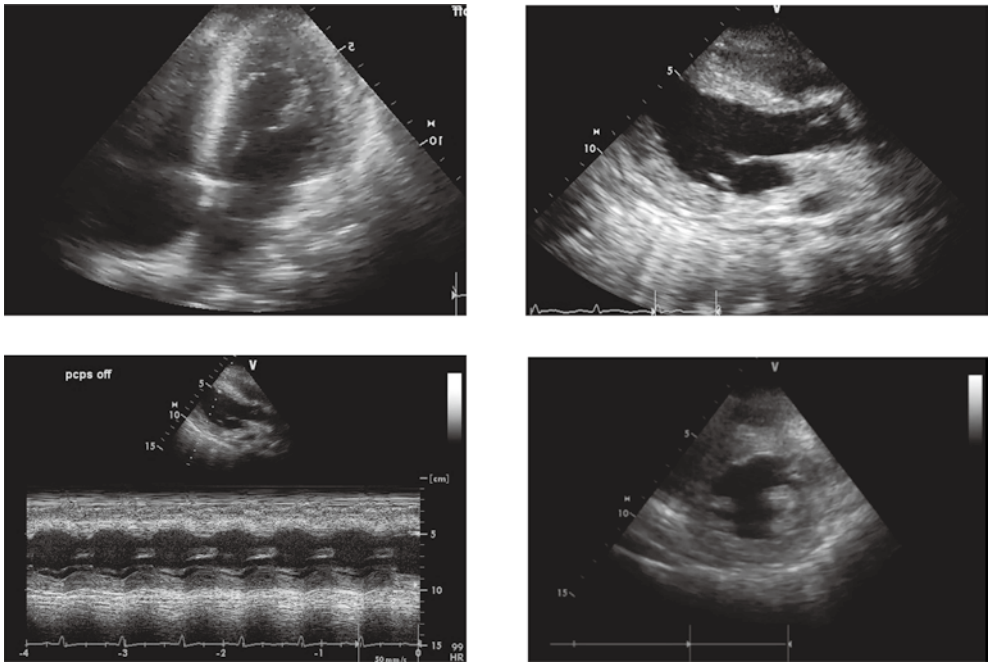

Fig 1B. Echocardiography showed improved left ventricular contraction and reductions of myocardial thickening and pericardial effusion on day 22 after BMT.

than 40 mmHg with sufficient preload and requisite dose of catecholamine. On day 22, she was successfully weaned from PCPS and shifted to extracorporeal membrane oxygenation (ECMO). However, she could not be weaned off mechanical ventilation support and ECMO. On day 55, she died from a severe disturbance of oxygenation with lung injury and sepsis due to *Stenotrophomonas maltophilia* (Fig. 2).

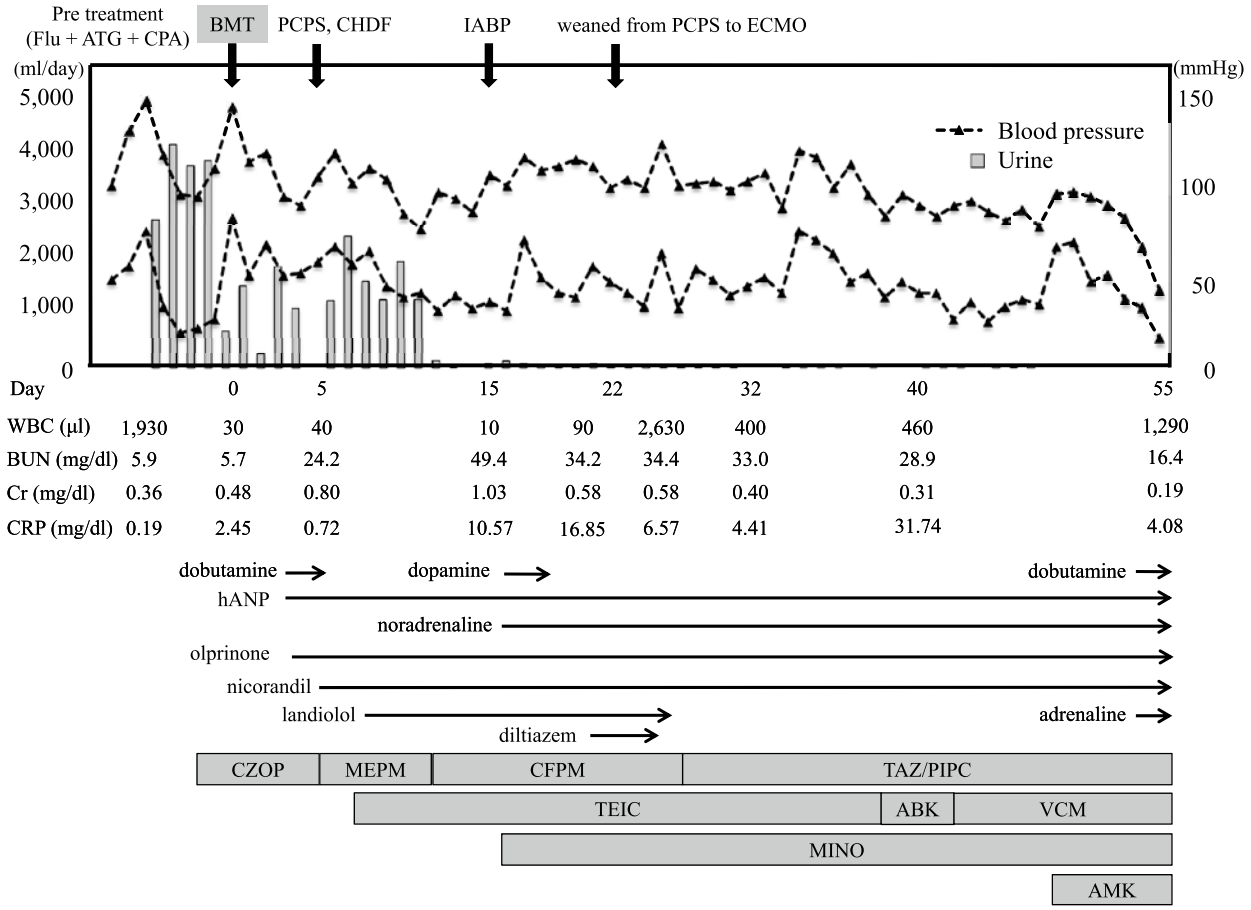

Fig 2. Case1; Patient's clinical course and laboratory data
Patient developed dyspnea and showed oliguria after BMT, and was transferred to the intensive care unit where they received mechanical circulatory support, which improved left ventricular cardiac performance. However, she died from a moderate disturbance of oxygenation with lung injury and sepsis due to Stenotrophomonas maltophila.

Case 2

A previously healthy 8-year-old girl developed purpura and recurrent epistaxis. She went to nearby hospital and her laboratory findings showed pancytopenia. She had been on close observation due to her pancytopenia that was considered to be induced by viral infection. At the age of 10 years, a bone marrow aspiration revealed a hypocellular marrow (NCC 1.3×10^4 /μl, no megakaryocytes) but no chromosomal abnormalities. Her laboratory findings were as follows: WBC, 3,930/μl; neutrophil counts, 1,460/μl; Hb, 10.2 g/dl; Plt, 4.2×10^4 /μl; reticulocyte counts, 52,972/μl. She was diagnosed with moderate aplastic anemia and followed without specific therapy. At the age of 14 years, her laboratory findings showed decreased neutrophil counts (439/μl), reticulocytes (61,800/μl), and Plt (1.6×10^4/μl). She was therefore diagnosed with severe aplastic anemia and admitted to our hospital for therapeutic BMT. As a conditioning regimen, she was administered 5 mg/kg of rabbit ATG and 50 mg/kg of CPA for 4 days. She received a graft from her HLA-matched younger sister, which was nonetheless rejected. When she was 15 years

old, she was admitted to our hospital for a second BMT. Her body weight, height, and body surface area were 40.7 kg, 156.3 cm, and 1.33 /m², respectively. She was administered 20 mg/m² of fludarabine, 2.5 mg/kg of ATG, and 50 mg/m² of CPA for 4 days (days −5 to −2) and 2 Gy of total body irradiation (days −2 to −1). Following transplantation with bone marrow from her HLA-mismatched mother, her volume status was carefully monitored and included the administration of diuretics to increase urine output and relieve fluid tension. However, her renal function deteriorated and she gradually complained of dyspnea. On day 3, she developed low-output syndrome and oliguria (<500 ml/day). Cardiomegaly was seen on chest X-ray. Echocardiography showed mildly reduced LV contraction (LVEF 50.0%) with myocardial thickening (IVSd, 10.0 mm; LVPWd, 15.0 mm) and pericardial effusion both behind the posterior wall of the LV (6.0 mm) and ahead of the anterior RV wall (14.0 mm) in diastole (Fig. 3A). Despite the continuous infusion of dopamine hydrochloride and hANP, her condition deteriorated further. On day 5, she was transferred to the ICU, where she was managed with a continuous infusion of olprinone hydrochloride, nicorandil, and randiorol hydrochloride, but their effects were limited. Soon thereafter, she lost consciousness because of a dramatic fall in blood pressure and went into cardiac arrest. Return of spontaneous circulation after resuscitation, a 21-French sheath of PCPS drainage cannula (CX-EB21VLX: Terumo, Tokyo, Japan) was withdrawn from the right femoral vein and a 16.5-French sheath of blood supply cannula (CX-EB16ALX: Terumo, Tokyo, Japan) was inserted into the right femoral artery. Subsequently PCPS was initiated as an additional treatment with an initial blood flow was 2.2 L/min and a rotation rate of the biopump was 2,800 rpm using a Capiox SP Pump Controller Sp-100 plus (Terumo, Tokyo, Japan) to support the state of low cardiac output. IABP and CHDF were also initiated for the treatment of severe cardiopulmonary failure. Under close supervision, those treatments resulted in improved myocardial thickening (IVSd 10.0→6.0 mm, LVPWd 15.0→8.0 mm) and LV contraction (LVEF 70%) as well as the disappearance of the pericardial effusion. PCPS flow was gradually decreased when PCPS flow was 1.0 L/min and hemodynamics were stable as systolic blood pressure was more than 90 mmHg, central venous pressure was less than 13 mmHg, and pulse pressure was more than 50 mmHg with sufficient preload and requisite dose of catecholamine. On day 18, she was successfully weaned from PCPS and IABP (Fig. 3B). However, she could not be weaned off mechanical support (CHDF and ECMO). On day 57, she died from a moderate disturbance of oxygenation with lung injury, progressive renal impairment, and sepsis due to fungal infection (Fig. 4).

Discussion

In patients with severe aplastic anemia, ATG and high-dose CPA have been used as combination chemotherapy and to enhance engraftment after BMT.[3] However, CPA is associated with life-threatening toxic adverse effects such as heart failure, myocarditis, and pericarditis. Thus, cardiotoxicity is the dose-limiting toxic effect of CPA.[1, 4-7] It occurs abruptly within days of drug infusion and is fatal, but there is little risk of cumulative toxicity.[1] A total dose >170–180 mg/kg per course or 1.55 g/m2/day are correlated well with the incidence of CPA-induced cardiotoxicity.[6, 7]

The pathophysiology of high-dose CPA-induced cardiotoxicity may involve endothelial damage followed by extravasation of toxic metabolites, resulting in damage to the myocardium, interstitial hemorrhage, and edema.[8] In addition, CPA may cause ischemia-related damage via the development of capillary microemboli or coronary angiospasm.[9] The histological findings of CPA-induced cardiotoxicity include multiple areas of myocardial hemorrhage, extravasation of blood, interstitial edema, and multifocal myocardial necrosis with fibrin microthrombi. A loss of myofilaments and damage to mitochondrial cristae has been observed in electron micrographs obtained from animal models of CPA-induced cardiotoxicity.[10] The early recognition of CPA-induced cardiotoxicity and the prompt initiation of treatment of these patients may have potent beneficial therapeutic effects, given that CPA-induced toxicity seems to be transient and the end-organ toxicity is reversible.[1, 11]

In mild or moderate cases of CPA-induced cardiotoxicity, elevated ventricular filling pressure should be treated with diuretics, vasodilators, and β-blockers unless contraindicated.[12] In patients suffering severe cardiopulmonary failure and with a worsening clinical course that seems to be inevitably fatal, mechanical circulatory support may be therapeutically promising. Early diagnosis and intervention are important in preventing hypoperfusion-related injury and death. Mechanical circulatory support may improve LV contraction via reducing in LV volume and restoring of a more elliptical cardiac chamber, which suggests that the remodeling process is reversible.[13] Moreover, these support was shown to reverse structural and molecular remodeling and to improve both baseline contractility and contractile

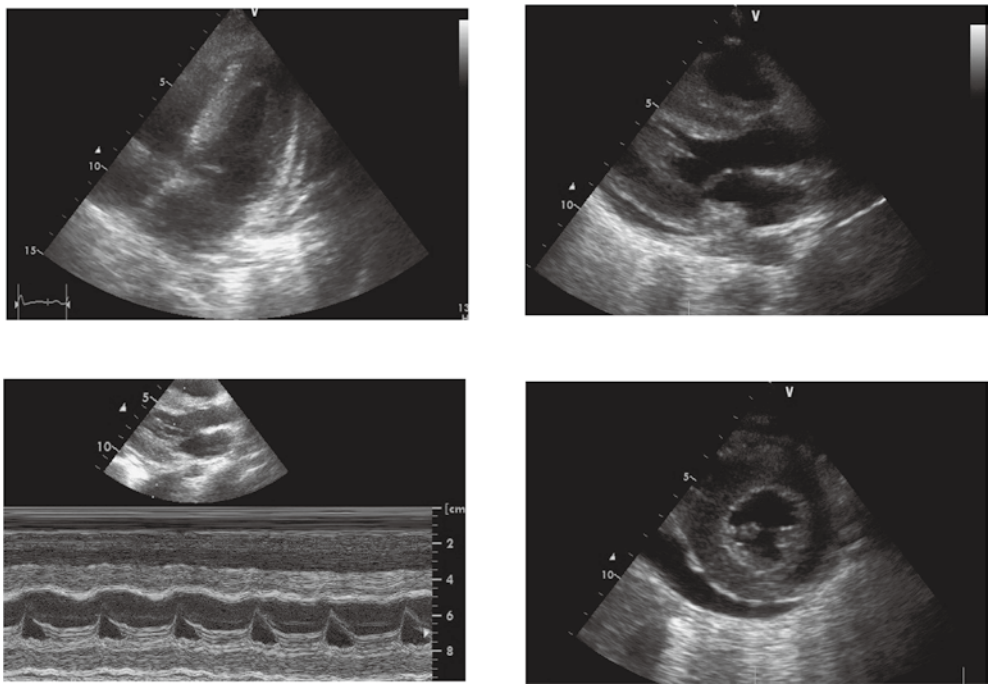

Fig 3A. Echocardiography showed pericardial effusion both behind the posterior wall of the left ventricle and ahead of the anterior right ventricle wall in diastole, reduced left ventricular ejection fraction with myocardial thickening on day 5 after BMT.

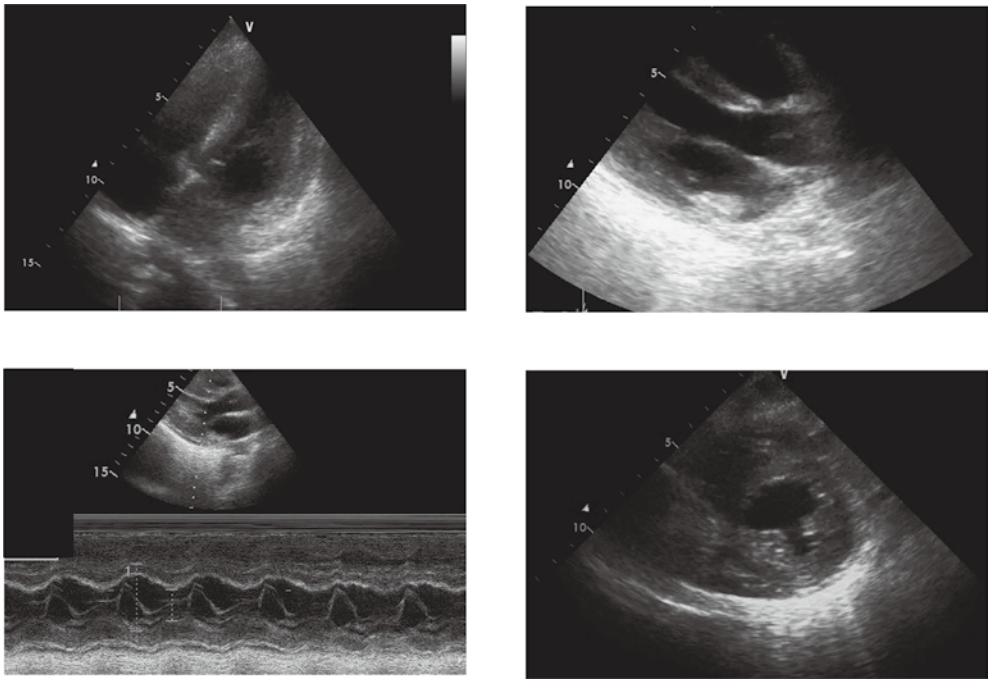

Fig 3B. Echocardiography showed improved left ventricular contraction and reductions of myocardial thickening and pericardial effusion on day 18.

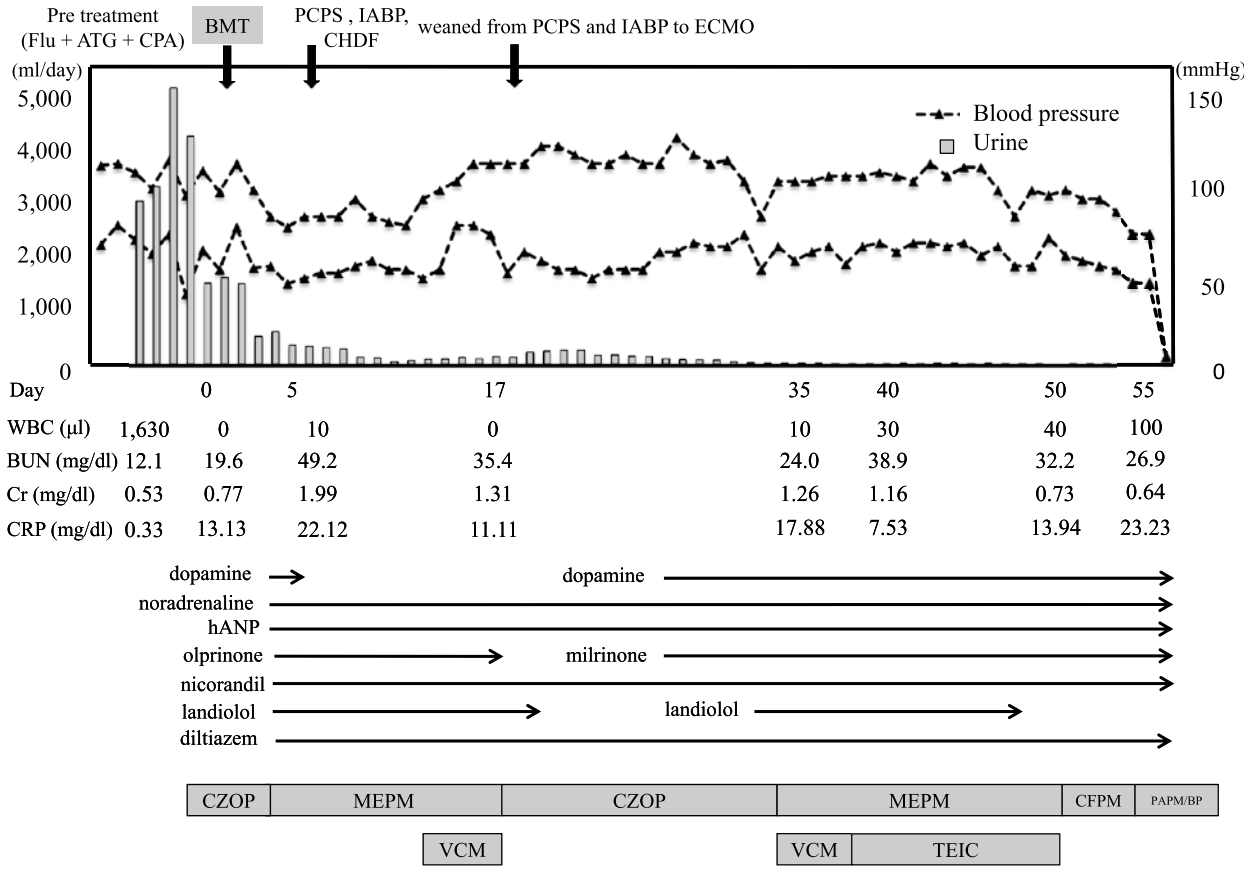

Fig 4. Case2; Patient's clinical course and laboratory data
Patient developed dyspnea and showed oliguria after BMT, and was transferred to the intensive care unit where they received mechanical circulatory support, which improved left ventricular cardiac performance. However, she died from a moderate disturbance of oxygenation with lung injury, progressive renal impairment, and sepsis due to fungal infection.

Flu, fludarabine; ATG, rabbit anti-human thymocyte immunoglobulin; CPA, cyclophosphamide; BMT, bone marrow transplantation; PCPS, percutaneous cardiopulmonary support; IABP, intra-aortic balloon pump; CHDF, continuous hemodiafiltration; ECMO, extracorporeal membrane oxygenation; WBC, white blood cell counts; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; hANP, human atrial natriuretic peptide; CZOP, cefozopran; MEPM, meropenem; CFPM, cefepime; TAZ/PIPC, tazobactam/piperacillin; TEIC, teicoplanin; ABK, arbekacin; VCM, vancomycin; MINO, minomycin; AMK, amikacin; PAPM/BP, panipenem/betmipron

response, thereby increasing the heart rate and the response to β-agonist stimulation.[14] Combined PCPS and IABP were introduced in our patients with severe CPA-induced cardiotoxicity, neither of whom responded to conventional medical treatment, and those were useful to maintain total circulation by quick application.[15] In our patients, there were no clear indications for the use of PCPS, but PCPS need to be initiated because deteriorating of systolic pressure after using inotropic agents, hypoxia and acidosis. The experiences with the presented two patients, both of whom had oliguria, cardiomegaly, a decrease in cardiac contraction, and pericardial effusion in spite of appropriate medical treatment, suggest that the rapid administration of mechanical circulatory support is an effective and valuable approach to achieve clinical improvement. Although, our patients could be successfully weaned off PCPS over time, long-term

support with ventricular associated device (VAD) should be considered as a bridge to myocardial recovery to resuscitate impaired organ function.[16] Because, PCPS cannot augment coronary blood flow which could be one of the contributors to a lower rate of left ventricle recovery and may gradually increase left ventricular afterload.[15] There was few report and no established therapy for patients with CPA-induced cardiotoxicity suffering severe cardiopulmonary failure, these mechanical circulatory support could be an useful therapeutic effect and could extend a life prognosis.

Our patients could be successfully weaned off PCPS and their cardiac function improved, they eventually died because of severe pulmonary and renal complications in the presence of sepsis. Pulmonary complications may have arisen from the cardiogenic pulmonary edema resulting from the increased capillary hydrostatic pressure secondary to elevated pulmonary venous pressure or from the sepsis-related multiple organ failure, driven in part by graft failure. Oxidative stress or using CPA as conditioning agents prior to BMT also could be a risk factor for CPA-induced lung toxicity.[17, 18] Early-onset pneumonitis due to CPA is generally reversible process following discontinuation of CPA.[19] The role of glucocorticoids in the treatment in CPA-induced lung toxicity remains unclear, but most successfully treated patients have received glucocorticoids though magnitude of benefit due to glucocorticoid use remains unknown.[20] Moreover, genetic susceptibility was reported to be associated with the development of lung toxicity in humans.[21] Further intensive-care management and more effective hematologic treatment may lead to a better prognosis for patients with pulmonary, renal, and cardiac complications of CPA-induced toxicity.

This report described two cases in which pediatric patients with aplastic anemia developed severe heart failure following the serial administration of high-dose CPA before BMT. Our experience showed that mechanical circulatory support for patients with CPA-induced cardiotoxicity could allow the recovery of cardiac function such that the other clinical manifestations can be adequately addressed. Therefore, the early recognition and initiation of mechanical circulatory support may be life-saving in patients with CPA-induced cardiotoxicity.

Disclosure of potential conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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シクロフォスファミドに伴う重症心筋障害を合併した患者に対する補助循環装置の有用性について

中江広治[1)]、上野健太郎[1)]、川村順平[1)]、柳元孝介[2)]、江口太助[1)]、野村裕一[1)]、垣花泰之[2)]、河野嘉文[1)]

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シクロフォスファミドは抗腫瘍薬として、また骨髄移植の前処置時に免疫抑制薬としても広く使用されている。われわれは、シクロフォスファミド投与後（50mg/m^2 4 日間）に重症心筋障害をきたした再生不良性貧血の２症例を経験した。両患者ともに移植後 3-4 日で呼吸困難、乏尿がみられ、胸部エックス線で心拡大、心エコー検査で左室収縮能の低下、心嚢液貯留および心筋肥厚所見を認めた。シクロフォスファミドによる重症心筋障害から循環不全をきたしたと考え、循環作動薬で加療したが改善せず、集中治療室で経皮的心肺補助装置、大動脈内バルーンパンピングを用いた補助循環装置を導入した。補助循環装置での治療開始後、心収縮力は改善し、心筋肥厚も軽快した。両患者ともに補助循環装置から離脱することができたが、重篤な移植後合併症で死亡した。シクロフォスファミドによる重症心筋障害はまれに発生するが、早期の診断ならびに補助循環装置を用いた集中治療管理を行うことで心筋の回復が得られ、予後の改善に繋がる可能性がある。