



Cyclophosphamide-Induced Cardiotoxicity in a Child with Severe Aplastic Anemia After Allogeneic Hematopoietic Stem Cell Transplantation: Case Report and Literature Review

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Abstract

Background: Severe Aplastic Anemia (SAA) is a life-threatening bone marrow failure disorder. Hematopoietic Stem Cell Transplantation (HSCT) represents a potentially curative treatment for SAA, with Cyclophosphamide (CY) being a key component of conditioning protocols. CY-induced cardiotoxicity is a rare but lethal complication. high-dose CY (200 mg/kg daily) has been identified as an independent risk factor for cardiotoxicity, whereas standard doses (50 mg/kg daily) are rarely associated with cardiotoxicity.

Case Presentation: We presented an 11-year-old child with SAA who underwent allogeneic HSCT. Following the completion of standard-dose Cy administration (50 mg/kg/day for 4 days), the patient developed severe Cy-induced cardiotoxicity 120 hours after the final dose, accompanied by severe Cytokine Release Syndrome (CRS)-related multi-organ dysfunction. She was urgently transferred to the Hematology Intensive Care Unit (HCU). Management included glucocorticoids and anti-IL-6 receptor therapy (tocilizumab) to mitigate CRS, alongside Continuous Renal Replacement Therapy (CRRT) for volume control, pulmonary edema management and cytokine adsorption. Despite initial clinical deterioration during the first three days of HCU admission, the patient demonstrated progressive improvement with this therapeutic regimen.

Conclusion: This case underscores the critical need for vigilant monitoring of severe complications in the immediate post-HSCT period, particularly given the risk of Cy-induced cardiotoxicity. Improved outcomes may be attributed to early diagnosis and timely management in the HCU.

Keywords: Severe aplastic anemia; Cyclophosphamide, Cardiotoxicity; Hematopoietic stem cell transplantation

Introduction

Severe Aplastic Anemia (SAA) is a serious bone marrow failure disorder characterized by pancytopenia and hypocellular bone marrow. Hematopoietic Stem Cell Transplantation (HSCT) represents a potentially curative therapeutic option for SAA. The majority of conditioning regimens for allogeneic HSCT (allo-HSCT) incorporate high-dose cyclophosphamide (CY) as a foundational element. CY-induced cardiotoxicity is a rare but potentially life-threatening complication, typically manifesting within 2 to 10 days following the initial dosage. Previous studies have identified several risk factors associated with CY-induced cardiotoxicity, including high-dose CY, age >50 years, prior anthracycline use, and pre-existing left ventricular dysfunction [1-3]. A CY dosage \geq 200 mg/kg was identified as an independent risk factor for cardiotoxicity, and the mortality rate of CY-induced Acute Heart Failure (AHF) was extremely high (91.6%) [3]. Cardiotoxicity has also been reported at a CY dose of 120 mg/kg.⁴ To our knowledge, only one case report has documented standard-dose (50 mg/kg daily) CY-induced cardiotoxicity in a 4-year-old HSCT patient.⁵ Herein, we present the case of an 11-year-old child with SAA who developed grade 4 Cytokine Release Syndrome (CRS) and standard-dose Cy-induced cardiotoxicity, culminating in AHF following allo-HSCT. We described the application of Continuous Renal Replacement Therapy (CRRT) as an effective therapeutic approach for CY-induced AHF in the Hematology Intensive Care Unit (HCU), combined with prompt administration of glucocorticoids and tocilizumab to suppress severe CRS.

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Case Presentation

A 11-year-old girl diagnosed with SAA, measuring 150 cm in height and 40 kg in body weight, was admitted to our hospital to undergo allo-HSCT, after one month of clinical cyclosporine and hematopoietic-stimulating therapy. Pre-transplant evaluation, including echocardiography and ECG, showed normal findings. The patient underwent allo-HSCT from her sister following a conditioning regimen consisting of busulfan (Bu, 3.2 mg/kg/day on days -7 and -6), Cy, (50 mg/kg/day on days -5 through -2, total 200 mg/kg), and antithymocyte globulin (ATG, 2.5 mg/kg/day on days -5 through -2, total 10 mg/kg). On Day +3 (approximately 120 hours after the final Cy dose), the patient developed hypotension, cool extremities and shortness of breath. Despite initial management with oxygen treatment via nasal cannula, resuscitative fluid, and vasopressor therapy, her condition rapidly deteriorated, manifesting as tachycardia, fever, syncope, and bilateral lower lung wet rales. The patient was urgently transferred to the Hematological Intensive Care Unit (HCU) to receive aggressive vital support. Subsequently, she gradually regained consciousness. However, her condition remained critical with unstable vital signs, manifesting as lethargy, a body temperature of 38.2°C, hypotension ranging from 64/36 mmHg, tachycardia with heart rate between 140 and 150 bpm, tachypnea with respiratory rate between 30 and 35 bpm, and a peripheral oxygen saturation (SpO₂) of 98%. The severity of the myocardial injury was noteworthy: echocardiography revealed the left ventricular dysfunction, with an Ejection Fraction (LVEF) of 40% and a small pericardial effusion. cardiac troponin I (cTn-I) was 3489pg/mL, serum N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) 35000pg/ml. ST-segment depression was found in leads II and V3-V6 on electrocardiography (Figure 1). The patient demonstrated a significant elevation of inflammatory markers, with IL-6 5000 pg/ml, alongside evidence of organ dysfunction, including elevated alanine Aminotransferase (ALT) at 91.8 U/L and Total Bilirubin (TBIL) at 122 μmol/L. The complete blood count revealed pancytopenia with profound neutropenia. The serum Procalcitonin (PCT) level was 0.61 ng/mL. Considering the patient presented with severe neutropenic fever, empirical intravenous anti-infective therapy was administered. For anti-shock treatment, the patient received resuscitative fluid and vasopressor therapy via a central venous line. Nitroglycerin was given to mitigate myocardial injury, while methylprednisolone (MP, 1 mg/kg daily) was concurrently initiated to suppress the Systemic Inflammatory Response Syndrome (SIRS). Arterial blood gas analysis revealed a progressive deterioration in tissue perfusion within hours of HCU admission, as evidenced by a marked elevation in lactic acid (from 2.5 to 9.1 mmol/L), a significant decrease in BE (from -1.1 to -9.6 mmol/L), and a slight decline in pH (from 7.40 to 7.33). By 21:00 that evening, her Mean Arterial Pressure (MAP) had stabilized above 65 mmHg following a combination of norepinephrine and aramine therapy.

During the subsequent two days of HCU treatment (Table 1), her condition continued to deteriorate, with progressive multi-organ dysfunction, including worsening liver injury, myocardial injury, heart failure, and new-onset acute kidney injury, accompanied by SIRS, as high fever, myalgias, tachycardia, and markedly elevated IL-6 (>5000 pg/mL). In the absence of severe infection, septic shock or sepsis-associated cytokine release syndrome (CRS) was initially excluded. According to the LEE staging/grading system⁶, the patient was diagnosed with grade 4 CRS. Tocilizumab (8 mg/kg) was administered on days 2 and 3, and the dose of Methylprednisolone

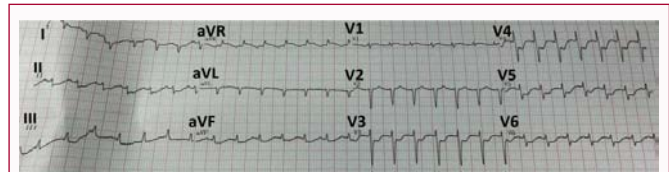


Figure 1: Initial electrocardiogram on HCU admission.

(MP) was escalated to 2 mg/kg. Given the presence of pulmonary edema, dyspnea, and a decreased oxygen index, High-Flow Nasal Cannula Oxygen Therapy (HFNC) was initiated. Concurrently, Continuous Renal Replacement Therapy (CRRT) coupled with cytokine adsorption (CVVH+CA330) was implemented to reduce vascular preload, alleviate pulmonary edema, and cytokine adsorption. From day 4 to day 9 of the HCU treatment course (Table 1), her body temperature normalized, and organ function improved, with LVEF recovering to normal (55%). However, the NT-proBNP values consistently exceeded the reference limit due to substantial myocardial damage. Meanwhile, the MP dose was rapidly tapered, and vasoactive medications were gradually reduced and discontinued. By the ninth day of the HCU treatment course, the patient was transferred to the general ward. Engraftment of neutrophils occurred on day +15 and platelets on day +25. The patient subsequently developed severe invasive fungal pneumonia secondary to immunocompromised status. Fortunately, after two months of effective antifungal therapy, the patient eventually recovered and was discharged from the hospital.

Discussion

We described a young child with SAA who exhibited both Cy-induced severe cardiotoxicity, and grade 4 CRS-induced multiple-organ damage and refractory shock. Despite clinical deterioration in the initial three days of HCU treatment, her condition ultimately stabilized with glucocorticoids, tocilizumab and CRRT.

Cy-induced severe cardiotoxicity and AHF are uncommon in pediatric populations, with the existing literature predominantly focusing on adult cases. To the best of our knowledge, there was only one documented case of AHF associated with standard-dose Cy in a 4-year-old HSCT patient with β-thalassemia [7]. Histopathological and ultrastructural evaluation of the myocardium demonstrated extensive coagulative necrosis of cardiomyocytes, endothelial injury, and subendothelial/interstitial fibrin thrombi. Endothelial injury is considered the most probable pathogenesis driving thrombotic microangiopathy and resulting in ischemic tissue injury. In a retrospective analysis of 4302 adult patients treated with Cy, 8 34 (0.8%) developed severe cardiac events after receiving a median Cy dose of 100 mg/kg and were admitted to the ICU 6.5 (4-12) days later. Among these 34 cases, 24 (70.6%) occurred within 2 weeks after CY administration, predominantly in the context of allo-HSCT. 53% (18 patients) developed cardiogenic shock, 59% (20 patients) required invasive mechanical ventilation, and 14% (5 patients) needed CRRT. Sixteen patients died. Most survivors experienced an improvement or fully recovered in cardiac function within a month. Consistent with the literature, our patient's 5-day onset of severe cardiac events emphasizes the importance of close monitoring early after Cy administration. Data regarding the recovery from Cy-induced cardiotoxicity are sparse. However, available evidence suggests a recovery period ranging from several days to weeks [2-9].

Table 1: Laboratory test results during the HCU period.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Normal range	
Treatment	MP 40 mg	MP 40 mg	MP 80 mg	MP 80 mg	MP 80 mg	MP 80 mg	MP 70 mg	MP 60 mg	MP 50 mg	/	
			TCZ 320 mg	TCZ 320 mg							
			CVVH+CA330	CVVH	CVVH	CVVH	CVVH	CVVH			
			HFNC	HFNC	HFNC	HFNC	HFNC	HFNC			
ALT	91.8	239	940	806	836	752	669	590	376	11-66 (U/L)	
TBIL	122	116	78	74.3	57.9	49.6	42	54.6	37.6	3-22 (umol/L)	
Creatinine	82	73	123	135	106	114	91	86	89	>110 (umol/L)	
cTN-I	3489	11709	13113	7113	5221	4318	4355	2915	2746	0-34.2 (pg/mL)	
NT-proBNP	>35000	>35000	>35000	>35000	>35000	>35000	>35000	>35000	>35000	>35000	0-300 (pg/mL)
LVEF	40	30	/	/	/	/	/	/	55	50-70 (%)	
IL-6	500	>5000	>5000	>5000	>5000	>5000	1544	549	97	0-7 (pg/mL)	
PCT	0.61	2.23	6.54	6.12	4.37	2.4	3	1.7	1.36	0-0.3 (ng/mL)	
BT	38.2	37.8	37.6	normal	normal	normal	normal	normal	normal	< 37.0 (□)	
MAP	45	67	88	92	74	74	77	75	70	≥65 (mmHg)	
HR	147	133	132	136	125	108	97	86	90	60-100 (bpm)	
Lactic acid	2.5	9.4	12.2	5.2	4.2	4.2	4.4	3.7	1.8	<2 (mmol/L)	
SOFA	8	9	11	10	9	10	10	7	5	0 (point)	

Abbreviation: ALT: Alanine Aminotransferase; BT: Body Temperature; CVVH: Continuous Veno-Venous Hemofiltration; cTN-I: Cardiac Troponin I; HFNC: High-Flow Nasal Cannula Oxygen Therapy; HR: Heart Rate; LVEF: Left Ventricular Ejection Fraction; MAP: Mean Arterial Pressure; MP: Methylprednisolone; NT-proBNP, N-Terminal Pro-Brain Natriuretic Peptide; PCT: Procalcitonin; SOFA: Sequential Organ Failure Assessment; TBIL, Total Bilirubin; TCZ: Tocilizumab

CRS frequently complicates the immediate post-HSCT. A single-center retrospective analysis of 75 consecutive cases of peripheral blood allo-HSCT performed with Granulocyte colony-stimulating factor-mobilized T-cell replete grafts [10]. Sixty-five (75%) patients met the CRS criteria, with 56 (65%) experiencing mild (grade 1-2) CRS and 9 (12%) suffering from severe (grade 3-4) CRS. Seven patients developed severe CRS before day +7. Upon observing relative improvement in the patient's circulatory status, we promptly initiated CRRT treatment. The integration of CRRT and cytokine adsorption therapy facilitated rapid clinical improvement, achieved efficient cytokine clearance, and effectively prevented the deterioration of multiple organ dysfunction in severe CRS [11]. Meanwhile, it reduced preload in AHF, improved organ and pulmonary edema, and was beneficial for controlling infections; CRRT was highly effective in continuously correcting metabolic acidosis and maintaining internal environment stability; and it allowed for safe parenteral nutrition delivery without inducing volume overload. The initial etiology of refractory shock in this patient remained ambiguous (CRS vs. cardiogenic shock). However, following effective immunotherapy and CRRT-mediated cytokine adsorption which successfully controlled CRS, circulatory stability was restored. Consequently, the refractory shock was primarily attributed to distributive shock driven by CRS, with concurrent diminished cardiac function exacerbating the clinical course.

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