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Pretransplant-corrected QT dispersion as a predictor of pericardial effusion after pediatric hematopoietic stem cell transplantation

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Keywords
cardiac tamponade, fenestration, hemolytic uremic syndrome, pericardiocentesis, thrombotic microangiopathy, thrombotic thrombocytopenic purpura.

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Summary

Pericardial effusion is a potentially fatal complication following hematopoietic stem cell transplantation (HSCT). Therefore, the identification of risk factors could improve the outcome. Prolonged QT dispersion (QTD) and corrected QTD (QTcD) are associated with serious arrhythmias and sudden death in many forms of heart disease. However, no study has evaluated the efficacy of QTD and QTcD to predict pericardial effusion post-HSCT. We studied 89 pediatric HSCT patients to identify preoperative risk factors for pericardial effusion with particular focus on QTD and QTcD. Pericardial effusion occurred in 15 patients (cumulative onset rate: 17.4%) within one year post-HSCT, of which 8 (9.2%) were symptomatic. Patients with pericardial effusion following allogeneic HSCT showed significantly lower overall survival; however, pericardial effusion was not the direct cause of death in any patient. Univariate and multivariate analyses revealed that transplantation-associated thrombotic microangiopathy (TA-TMA) was an independent risk factor for post-HSCT pericardial effusion. In addition, pretransplant QTcD was significantly prolonged in the pericardial effusion group. These results suggest that pediatric patients with abnormally prolonged QTcD before the preparative regimen for HSCT should be regularly followed-up by echocardiography to detect pericardial effusion, particularly when accompanied by complications including TA-TMA.

Introduction

Hematopoietic stem cell transplantation (HSCT) is used successfully to treat a variety of malignancies and immunodeficiency disorders. Cardiac and cardiovascular complications are among the most severe adverse events and may appear around the time of treatment or months to years later [1]. Serious post-HSCT cardiac complications with early onset include heart failure, cardiac tamponade, and cardiac arrhythmias [2].

The onset frequency of cardiac tamponade or severe pericardial effusion following HSCT is 0.8–1.0% in adults [3,4] and 4.4–17.0% in children [5–7]. Furthermore, in two previous studies including both adults and children, all

patients who developed cardiac tamponade or pericardial effusion following HSCT were younger than 16 years, which may suggest that children are particularly prone to this complication [8,9]. The onset time of cardiac effusion in patients indicated for HSCT varies markedly from before to >1 year post-HSCT [2–9]. Reported causes include reaction to allogeneic HSCT, the conditioning regimen, graft-versus-host disease (GVHD), infection, primary disease relapse, iron overload, and reaction to sirolimus or any immunosuppressant [3,7–18]. Several studies have reported that increased age, high-risk status, myeloablative conditioning, delayed neutrophil engraftment, and cytomegalovirus (CMV)-positive serostatus of the recipient are significant risk factors for cardiac effusion prior to or following HSCT [5,6]. Primary treatments for cardiac tamponade include emergency drainage and fenestration [2–11,13–15,17]. In addition, treatment of the underlying cause is important, for example, immunosuppression for GVHD [3,7,14,17]. However, most reports on tamponade associated with HSCT are from single cases, while few studies have attempted to identify the risk factors predictive of tamponade in HSCT patients in a larger case series.

Prolonged QT dispersion (QTD) and prolonged corrected QT dispersion (QTcD) have been associated with serious arrhythmias and sudden death in many forms of heart disease [19–22]. Both QTD and QTcD are evaluable by electrocardiography alone prior to detection of any myocardial damage on the echocardiogram. Recently, QTD and QTcD were reported to be predictive of acute heart failure after high-dose chemotherapy used for conditioning regimens prior to HSCT [23,24]. In addition, significant predictive utility of QTD and QTcD for heart failure and arrhythmia during and after preparative conditioning was reported in pediatric HSCT patients [25]. However, no study has evaluated the efficacy of QTD and QTcD for the prediction of cardiac tamponade or pericardial effusion following HSCT.

We conducted a retrospective cohort study of pediatric HSCT patients to identify risk factors for pericardial effusion with a particular focus on QTD and QTcD.

Materials and methods

Patient selection

This retrospective study included pediatric HSCT patients (age: ≤18 years) treated at Nagano Children's Hospital from December 1993 to December 2013. The inclusion criteria were as follows: (i) no past cardiac disease history, no abnormalities detected on chest X-ray, standard 12-lead electrocardiogram at rest, or echocardiogram at diagnosis and within one month prior to the initiation of preparative conditioning, (ii) repeated cardiovascular surveillance post-HSCT, including at least one evaluation more than 60 days post-HSCT regardless of whether heart complications were suspected or not, and (iii) no past history of HSCT. Although a total of 113 patients received HSCT in this period, based on these criteria, 89 patients were enrolled in this study. Five patients meeting the pretransplant examination criteria were excluded because re-evaluation was not performed for more than 60 days post-HSCT.

Advanced disease (high-risk disease) was defined as follows: (i) refractory hematological disorders [noncomplete remission (non-CR)] in which the bone marrow (BM) exhibited ≥5% blast cells just prior to preparative regimens, (ii) more than third complete remission (CR3), or (iii) progression of solid tumors. Other malignancies were classified as standard risk.

The study protocol was approved by the Institutional Review Board of Nagano Children's Hospital.

Cardiovascular surveillance

We performed cardiovascular surveillance for all patients prior to HSCT. Subsequently, we re-evaluated them at least once 60 days post-HSCT in the absence of symptoms. If a patient exhibited any symptoms for cardiovascular problems, we performed extraordinary evaluations as appropriate. All relevant data on echocardiography were collected for this study.

We analyzed left ventricular fractional shortening (LVFS) for the evaluation of systolic function, mitral valve (MV) E/A ratio for the evaluation of diastolic function, and LV Tei index for the evaluation of both systolic and diastolic function [25].

QTD was analyzed by a method described previously [25]. In brief, two observers unaware of the diagnosis measured the QT interval defined from the initial deflection of the QRS complex to the point at which a tangent crossed the isoelectric line on every lead using a digitizer. The QT interval was then corrected with Fridericia's formula ($QTc = QT/RR^{1/3}$) [26]. QTD and QTcD were calculated by subtracting the shortest QT and QTc values from the longest corresponding values across all 12 electrocardiographic leads simultaneously. Pretransplant-QTD was analyzed retrospectively after HSCT, so no therapeutic intervention was performed on the basis of the results. The normal mean QTD for children is 27.8 ± 2.0 (range: 15.0−40.0) ms, and normal QTcD is 33.7 ± 2.4 (range: 20.4−50.4) ms [25].

We calculated the cumulative anthracycline dose according to a previously reported formula [25].

Definition and severity grading of pericardial effusion

Pericardial effusion was evaluated on the basis of echocardiography results by a pediatric cardiologist. Severity

was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.0. Grade 0 indicates no pericardial effusion, and grades II to V indicate effusion of increasing severity. Specifically, grade II is defined as the asymptomatic effusion of mild-to-moderate severity, III as effusion with physiological consequences, IV as effusion with life-threatening consequences requiring urgent intervention, and V as fatal effusion.

Definition and toxicity grading of transplantation-associated thrombotic microangiopathy (TA-TMA)

Transplantation-associated thrombotic microangiopathy (TA-TMA) was defined by the diagnostic criteria described previously [27]. All of the following should be present: (i) increased percentage (>4%) of schistocytes in peripheral blood; (ii) de novo, prolonged, or progressive thrombocytopenia (platelet count $<50 \times 10^9$/L or a 50% or greater decrease from previous counts); (iii) sudden and persistent increase in LDH; (iv) decrease in hemoglobin concentration or increased red blood cell transfusion requirement; (v) decrease in serum haptoglobin concentration. Usually, we screened for TA-TMA using schistocyte counts once a week. In addition, in cases where other symptoms appeared, such as thrombocytopenia, increase in LDH, progressive anemia, leading to a suspicion of TA-TMA, we performed further evaluations for TA-TMA.

Toxicity was graded according to the Blood and Marrow Transplant Clinical Trials Network Toxicity Committee [28]. The details of grading were as follows: grade I, evidence of red blood cell (RBC) destruction (schistocytosis) without clinical consequences; grade II, evidence of RBC destruction with increased creatinine levels ≤3 times the upper limit of normal (ULN); grade III, evidence of RBC destruction with creatinine levels >3 times the ULN but not requiring dialysis; grade IV, evidence of RBC destruction with renal failure requiring dialysis and/or accompanied by encephalopathy. We judged TA-TMA positivity as ≥grade II, so all patients diagnosed with TA-TMA in this study had some renal dysfunctions.

Monitoring of virus infection

From December 1993 to June 1999, CMV pp65 antigenemia was monitored once a week after engraftment. As of July 1999, peripheral blood was monitored by PCR every week during the peritransplant period for CMV, Epstein–Barr virus (EBV), and human herpes virus 6 (HHV-6) irrespective of symptoms. All post-transplant reactivations and primary infections were monitored.

Statistical analysis

Candidate risk factors for pericardial effusion were evaluated by Fisher's exact test and logistic regression analysis. Potential factors with at least borderline significance ($P < 0.15$) according to univariate analysis were included in multivariate analysis. Differences in cardiovascular parameters between pericardial effusion and no-effusion groups were compared using the unpaired *t*-tests and Mann–Whitney *U*-tests. The utility of the marker for predicting pericardial effusion was also tested by receiver operating characteristic (ROC) curve analysis as expressed by the area under the curve (AUC). We used a log-rank test to evaluate differences in pericardial effusion development and overall survival (OS). All statistical analyses were performed using EZR [29]. Statistical significance was defined as $P < 0.05$.

Results

Incidence and clinical outcome of pericardial effusion after pediatric HSCT

Of the 89 pediatric HSCT patients included in the study, pericardial effusion occurred in 15 patients [cumulative onset rate: 17.4%, 95% confidence interval (CI): 9.0–25.1]. Of these 15 patients, eight showed symptomatic grade III or IV pericardial effusion (9.2%, 95% CI: 4.3–16.5) and seven showed asymptomatic grade II pericardial effusion (8.2%, 95% CI: 3.6–15.3). The median onset delay was 61 days (range: 1–319 days) post-HSCT. All cases developed within 1 year of transplant. Detailed information on these pericardial effusion patients is shown in Table 1. In total, eight of the 15 patient (53.3%) had another effusion (pleural effusion and/or ascites) when pericardial effusion was detected. No patients developed veno-occlusive disease at effusion onset. General fluid management was administered in all cases, and the pericardial fluid exclusion method for urgent pericardiocentesis was performed in all four grade IV cases (26.7%). Pericardial fluid was analyzed in these four cases (Patients 1−4). No evidence of infection was found in three of these cases, while HHV-6 was detected in the fluid sample of one patient (Patient 2) who had systemic HHV-6 infection. Two patients (Patients 6 and 10) required milrinone for reduced cardiac function. Six patients (Patients 2–4, 6, 12, and 14) with suspected GVHD were treated with prednisolone; only one patient (Patient 14) showed an apparent response to prednisolone. Ganciclovir was used for two patients (Patients 2 and 6) with HHV-6 infection. Plasma exchange was performed for four patients with TA-TMA (Patients 2, 3, 6, and 8), and continuous hemodiafiltration was necessary for the two patients (Patients 3 and 8) with severe renal dysfunction related to TA-TMA. Pericardial effusion was mitigated by

Table 1. Characteristics of patients with pericardial effusion.

Pt. No	Age	Sex	Disease	Disease Status	QTcD (ms)	Donor/ Source	HLA mismatch	Preparative regimen	GVHD prophylaxis	GVHD		Viral infection†			TA-TMA*	Pericardial effusion*	Treatment‡	Outcome, cause of death
										Acute*	Chronic	EBV	CMV	HHV-6				
1	4	Male	NB	CR	74.2	A/PB	–	MEC	–	–	–	ND	+	ND	III (+14 days)	IV (+13 days)	Pericardiocentesis	Death (+797 days) Disease progression
2	12	Female	ALL	non-CR	21.0	U/CB	1/6	TBI 12 Gy, Flu, Mel	CsA, mPSL, MMF	II (+33 days)	Ex	–	–	+	II (+329 days)	IV (+319 days)	Pericardiocentesis PSL, GCV, PE	Death (+446 days) TA-TMA, Sepsis
3	13	Female	AML	CR	68.4	U/BM	0/6	TBI 3 Gy, Flu, Mel	Tac, sMTX, MMF	0	No	–	–	–	IV (+163 days)	IV (+162 days)	Pericardiocentesis PSL, CHDF, PE	Death (+261 days) Disease progression
4	17	Male	ALL	non-CR	66.8	U/CB	2/6	TBI 12 Gy, AraC, Cy	CsA, sMTX	III (+35 days)	No	–	+	–	II (+40 days)	IV (+40 days)	Pericardiocentesis PSL	CR (+5401 days)
5	5	Male	ALL	non-CR	55.3	U/CB	2/6	Bu, Flu, Mel	CsA, PSL	III (+18 days)	NA	–	+	ND	II (+17 days)	III (+35 days)	–	Death (+64 days) *Aspergillus* pneumonia
6	14	Female	MDS	non-CR	45.0	M/BM	2/6	TBI 3 Gy, Flu, Mel	Tac	III (+12 days)	Lo	–	–	+	IV (+22 days)	III (+15 days)	PSL, GCV, PE Milrinone	CR (+3104 days)
7	4	Female	NB	PR	57.6	A/PB	–	MEC	–	–	–	–	–	–	II (+9 days)	III (+15 days)	–	CR (+2597 days)
8	2	Male	NB	PR	55.3	A/PB	–	MEC	–	–	–	–	–	–	IV (+9 days)	III (+1 day)	CHDF, PE	CR (+665 days)
9	3	Male	ALL	non-CR	54.7	F/BM	2/6	TBI 3 Gy, Flu, Mel	Tac, sMTX	III (+23 days)	No	–	+	–	I (+25 days)	II (+307 days)	–	Death (+309 days) Disease progression, Sepsis
10	2	Female	NB	PR	25.9	A/PB	–	MEC	–	–	–	–	+	–	No	II (+125 days)	Milrinone	Death (+130 days) Disease progression, CMV pneumonia
11	2	Male	NB	PD	59.0	A/BM	–	TBI 10 Gy, MEC	–	–	–	ND	+	ND	II (+19 days)	II (+61 days)	–	Death (+111 days) Disease progression
12	11	Female	ALL	non-CR	24.2	F/BM	1/6	Bu, Mel	CsA, sMTX	III (+10 days)	No	ND	+	ND	IV (+17 days)	II (+102 days)	PSL	Death (+106 days) TA-TMA
13	16	Male	ALL	>CR3	42.7	A/PB	–	Bu, Mel	–	–	–	ND	–	ND	No	II (+7 days)	–	CR (+6331 days)
14	8	Male	ALL	CR1	31.8	S/BM	0/6	Bu, Mel	CsA	III (+9 days)	Ex	–	–	–	III (+12 days)	II (+101 days)	PSL	CR (+3737 days)
15	11	Female	ALL	CR2	55.0	U/BM	1/6	TBI 8 Gy, Flu, Cy	Tac, sMTX, mPSL	III (+23 days)	Ex	–	+	+	II (+60 days)	II (+75 days)	–	CR (+3588 days)

A, autologous; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AraC, cytarabine; BM, bone marrow; Bu, busulfan; CB, cord blood; CHDF, continuous hemodiafiltration; CMV, cytomegalovirus; CR, complete remission; CR1, first complete remission; CR2, second complete remission; CR3, third complete remission; CsA, cyclosporine A; Cy, cyclophosphamide; EBV, Epstein–Barr virus; Ex, extensive type; F, father; Flu, fludarabine; GCV, ganciclovir; GVHD, graft-versus-host disease; HHV-6, human herpesvirus 6; HLA, human leukocyte antigen; Lo, localized type; M, mother; MDS, myelodysplastic syndrome; MEC, melphalan + etoposide + carboplatin; Mel, melphalan; MMF, mycophenolate mofetil; mPSL, methylprednisolone; NA, not applicable; NB, neuroblastoma; ND, no data; non-CR, refractory disease; PB, peripheral blood stem cells; PD, progressive disease; PE, plasma exchange; PR, partial response; PSL, prednisolone; S, sibling; sMTX, short-term methotrexate; Tac, tacrolimus; TBI, total body irradiation; TA-TMA, transplantation-associated thrombotic microangiopathy; U, unrelated.

*Grade, onset delay post-hematopoietic stem cell transplantation.

†Peripheral blood was monitored by CMV antigenemia or PCR for each virus every week during the peritransplant period.

‡Treatment (other than fluid management) provided for pericardial effusion and other symptoms after the development of pericardial effusion.

treatment in all cases, but three patients died of the primary disease shortly after the development of pericardial effusion (Patients 9, 10, and 11) and one died after sustained drainage (Patient 2). In total, eight of the 15 patients (53.3%) with pericardial effusion following HSCT died; however, pericardial effusion was not the direct cause of death in any of these cases. Rather, the cause of death was the underlying disease in five cases, *Aspergillus* pneumonia in one case, TA-TMA in one case, and sepsis with TA-TMA in one case. Pericardial effusion did not affect OS for patients receiving autologous HSCT as indicated by the log-rank test ($P = 0.290$) (Fig. 1a). However, OS was significantly reduced by effusion in patients treated by allogeneic HSCT (44.4%, 95% CI 13.6–71.9 vs. 79.7%, 95% CI 53.1–92.2; $P = 0.026$) (Fig. 1b).

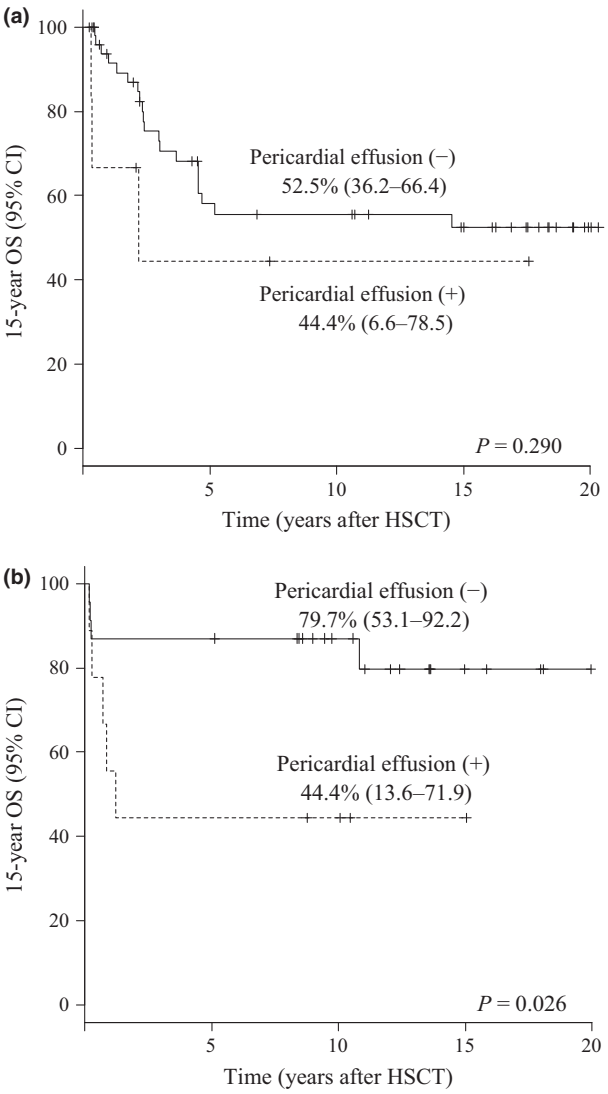

Figure 1 (a) Influence of post-treatment pericardial effusion on OS of pediatric patients treated by autologous HSCT (log-rank test). Post-HSCT pericardial effusion did not reduce OS in these patients. (b) Influence of post-treatment pericardial effusion on OS of pediatric patients treated by allogeneic HSCT (log-rank test). Post-HSCT pericardial effusion significantly reduced OS in allogeneic HSCT patients. CI, confidence interval; HSCT, hematopoietic stem cell transplantation; OS, overall survival.

Demographic and noncardiovascular risk factors for pericardial effusion after pediatric HSCT

We then examined the associations between the cumulative incidence of pericardial effusion (percentage of subgroup) and various demographic and clinical parameters using univariate analysis (Table 2). Of these candidate risk factors, a disease other than solid tumor (solid tumors 8.8% vs. other diseases 31.2%; $P = 0.016$), disease status (advanced risk 36.8% vs. standard risk/nonmalignant disease 11.4%; $P = 0.015$), transplant donor (autologous 10.5% vs. syngeneic/sibling/related 18.2% vs. unrelated 50.0%; $P = 0.013$), transplant source (BM 20.0% vs. cord blood 75.0% vs. peripheral blood stem cells 10.0%; $P = 0.009$), human leukocyte antigen (HLA) mismatch (autologous 10.5% vs. 0/6 mismatch 11.1% vs. ≥1/6 mismatch 50.0%; $P = 0.004$), acute GVHD (autologous 10.5% vs. grade 0/I 6.3% vs. grade ≥II 50.0%; $P = 0.001$), chronic GVHD (autologous 10.5% vs. no/localized type 18.8% vs. extensive type 50.0%; $P = 0.037$), and TA-TMA (grade 0/I 4.1% vs. grade ≥II 80.0%; $P < 0.001$) were significantly associated with pericardial effusion by univariate analysis. Multivariate analysis revealed that of these parameters, only TA-TMA ≥grade II was a significant independent risk factor for pericardial effusion ($P < 0.001$) (Table 2).

Cardiovascular function parameters as risk factors for pericardial effusion

Parameters of cardiovascular function were measured both before HSCT and at least once 60 days or more post-HSCT. Prior to HSCT, the following parameters did not significantly differ between the pericardial effusion and no-effusion patient groups by unpaired *t*-tests: total anthracycline dose (207.2 ± 114.9 mg/m^2 vs. 150.3 ± 133.7 mg/m^2, $P = 0.129$), heart rate at rest (99.4 ± 24.3 beats/min vs. 98.3 ± 22.9 beats/min, $P = 0.864$), systolic function (LVFS) (0.336 ± 0.057 vs. 0.357 ± 0.048, $P = 0.161$), diastolic function (MV E/A ratio) (1.554 ± 0.401 vs. 1.659 ± 0.320, $P = 0.346$), and combined function (LV Tei index) (0.214 ± 0.114 vs. 0.240 ± 0.108, $P = 0.453$). In addition, there were no significant differences in mean QT (336.0 ± 44.0 ms vs. 334.5 ± 41.3 ms, $P = 0.898$) and mean QTc (392.8 ± 24.9 ms vs. 389.4 ± 22.2 ms, $P = 0.602$) prior to HSCT between the groups. However, pretransplant mean QTD and QTcD were significantly pro-

Table 2. Analysis of risk factors for the development of pericardial effusion: (A) univariate analysis (B) multivariate analysis.

(A) Univariate analysis

Variable	Number of patients (total $N = 89$)	Number of patients with pericardial effusion ($N = 15$, %)	P
Age			
≥6 years	43	8 (18.6)	0.780
<6 years	46	7 (15.2)	
Sex			
Male	44	8 (18.2)	0.784
Female	45	7 (15.6)	
Disease			
Solid tumor	57	5 (8.8)	0.016
Others	32	10 (31.2)	
Disease status			
Advanced risk	19	7 (36.8)	0.015
Standard risk, non-malignant disease	70	8 (11.4)	
Conditioning regimen			
Myeloablative	74	12 (16.2)	0.712
Reduced intensity	15	3 (20.0)	
Conditioning including irradiation			
TBI, TLI	30	7 (23.3)	0.250
No	59	8 (13.6)	
Donor			
Autologous	57	6 (10.5)	0.013
Syngeneic, Sibling, Related	22	4 (18.2)	
Unrelated	10	5 (50.0)	
Source			
BM	35	7 (20.0)	0.009
CB	4	3 (75.0)	
PBSCs	50	5 (10.0)	
HLA mismatch			
Autologous	57	6 (10.5)	0.004
0/6	18	2 (11.1)	
≥1/6	14	7 (50.0)	
Acute GVHD			
Autologous	57	6 (10.5)	0.001
Grade 0, I	16	1 (6.3)	
Grade ≥ II	16	8 (50.0)	
Chronic GVHD			
Autologous	57	6 (10.5)	0.037
No, Lo	16	3 (18.8)	
Ex	6	3 (50.0)	
TA-TMA			
Grade 0, I	74	3 (4.1)	<0.001
Grade ≥ II	15	12 (80.0)	
EBV infection*			
Positive	7	0 (0.0)	0.175
Negative	33	9 (27.3)	
CMV infection			
Positive	28	8 (28.6)	0.066
Negative	61	7 (11.5)	
HHV-6 infection*			
Positive	14	3 (21.4)	1.000
Negative	23	6 (26.1)	

(B) Multivariate analysis

Variables	Odds ratio (95% CI)	P
TA-TMA (Grade ≥ II)	69.00 (10.50–451.00)	<0.001
QTcD	1.06 (1.00–1.13)	0.049

BM, bone marrow; CB, cord blood; CI, confidence interval; CMV, cytomegalovirus; EBV, Epstein–Barr virus; Ex, extensive type; GVHD, graft-versus-host disease; HHV-6, human herpesvirus 6; HLA, human leukocyte antigen, Lo, localized type; PBSCs, peripheral blood stem cells; QTcD, corrected QT dispersion; TA-TMA, transplantation-associated thrombotic microangiopathy; TBI, total body irradiation; TLI, total lymphoid irradiation.

*PCR analaysis for EBV and HHV-6 only available since July 1999, so not all patients were evaluated.

longed in the pericardial effusion group (QTD: 36.5 ± 15.7 ms vs. 25.9 ± 12.6 ms, $P = 0.006$; QTcD: 49.1 ± 16.7 ms vs. 32.4 ± 14.3 ms, $P < 0.001$. Similarly, median QTD and QTcD values were significantly longer in the pericardial effusion group as assessed by Mann–Whitney U-test (Fig. 2). Together with previous risk factors, TA-TMA ≥grade II (hazard ratio: 69.00, 95% CI: 10.50–451.00; $P < 0.001$) and prolonged QTcD (hazard ratio: 1.06, 95% CI: 1.00–1.13; $P = 0.049$) were significant independent risk factors for pericardial effusion (Table 2). The ROC curve of QTcD also predicted pericardial effusion after HSCT. A cut-off value of 55.0 ms for prolonged QTcD had a sensitivity of 60.0% and a specificity of 93.7% for distinguishing the effusion from the noneffusion group (AUC of 0.777, 95% CI: 0.632–0.923) (Fig. 3).

Discussion

The incidence of pericardial effusion has varied markedly across studies. Rhodes *et al.* reported a pericardial effusion onset frequency of 4.4% in pediatric HSCT patients. In that study, routine echocardiography was conducted for all patients 100 days post-transplant, and more thorough cardiac examinations were conducted for patients with clinical signs [7]. In contrast, two studies that examined only patients with clinical signs after pediatric HSCT reported pericardial effusion onset frequencies of 16.9% and 17% [5,6]. In our study, the cumulative pericardial effusion onset frequency after pediatric HSCT was 17.4% when both

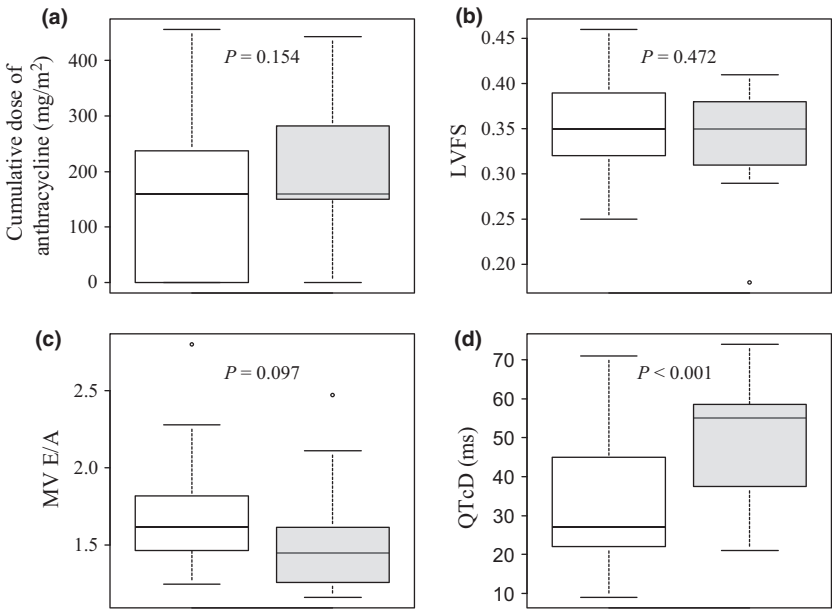

Figure 2 Parameters of cardiovascular surveillance before hematopoietic stem cell transplantation in patients with or without post-treatment pericardial effusion (Mann–Whitney *U*-test). White box: no pericardial effusion group, Gray box: pericardial effusion group. Difference in (a) the cumulative dose of anthracycline (mg/m^2), (b) systolic function: left ventricular fractional shortening (LVFS), (c) diastolic function: mitral valve (MV) E/A ratio, (d) corrected QT dispersion (QTcD) (ms).

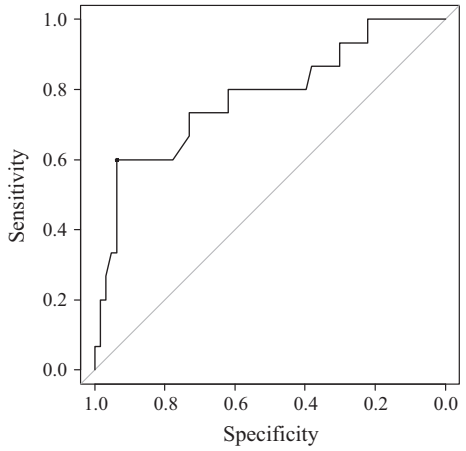

Figure 3 Receiver operating characteristic (ROC) curve of corrected QT dispersion (QTcD) (ms) for the detection of pericardial effusion after hematopoietic stem cell transplantation.

symptomatic and asymptomatic cases were included, but was reduced by almost half (9.2%) when only patients with clinical signs (≥ grade III) were included. One study found no cases of pericardial effusion following autologous HSCT [5]. In contrast, several reports have demonstrated the occurrence of pericardial effusion after autologous HSCT consistent with our result [6,7,30]. Thus, in addition to onset frequency, clinical characteristics are also heterogeneous across studies, possibly due to influences of uncontrolled variables such as patient disease, transplant conditions, and post-treatment complications. It is possible that many previous studies did not report nonsymptomatic cases with mild pericardial effusion. If such cases were included, undoubtedly the reported onset frequency would have been higher. The most parsimonious conclusion is that approximately 1 in six pediatric HSCT patients will develop pericardial effusion, of which about half will be symptomatic. The concern is that pericardial effusion can progress after HSCT, reaching a potentially fatal cardiac tamponade. Thus, it is critical that the risk factors for pericardial effusion be identified, particularly in pediatric patients who show a significantly higher incidence than adult HSCT patients.

Diseases other than solid tumor, advanced disease, unrelated transplant donor, CB cell source, HLA mismatch, acute GVHD, chronic GVHD, and TA-TMA were significant risk factors for pericardial effusion in univariate analysis. Although several of these factors were also found to be associated in previous studies (e.g., advanced disease, unrelated transplant donor, and GVHD) [6,7], most of these factors were not significant in multivariate analysis. One possible reason for this discrepancy is the limited number of allogeneic HSCT patients in the current study. Only TA-TMA was a significant risk factor for pericardial effusion after HSCT in both univariate and multivariate analyses. Although the pathogenic association between TA-TMA and pericardial effusion is unclear, several risk factors for

TA-TMA development [31,32] were also shown to be risk factors for pericardial effusion after HSCT, including advanced primary disease, unrelated donor, conditioning regimen, HLA mismatch, GVHD, and infection [5,6]. Therefore, it is possible that many cases of pericardial effusion are associated with an earlier development of TA-TMA. In fact, when we reperformed univariate analysis with related versus unrelated donors (excluding syngeneic donors from the first group) and acute GVHD grade 0, vs. I–II vs. III–IV, acute GVHD was a significant predictor of developing of TA-TMA ($P < 0.001$).

TA-TMA belongs to the family of thrombotic microangiopathies that also includes hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) [33]. Kondo *et al.* [30] reported 10 cases of HUS in 193 HSCT enforcement cases (including both allogeneic and autologous transplants for pediatric malignancies), and pericardial effusion developed in six of these 10 cases. Although pericardial effusion in TA-TMA may be secondary to third spacing and edema due to nephropathy, seven of the 15 effusion patients in the current study did not have another pleural effusion or ascites. Other possible reasons for the development of pericardial effusion in these patients are HUS and TTP, both of which are accompanied by heart complications such as myocardial ischemia, myocardial infarction, depressed myocardial function, myocarditis, congestive heart failure with dilated cardiomyopathy, and pericardial effusion with tamponade [34–36]. Cardiac microvascular thrombi, hemorrhage, and/or necrosis are also regarded as pathological causes of pericardial effusion [34,35]. It is possible that pericardial effusion developed through mechanisms similar to those involved in conventional HUS and TTP as suggested by an autopsy study after HSCT by Cazin *et al.* [11], who reported marked edema, separation of the muscle fibers with extravasation of blood and small capillary thrombosis, and focal areas of necrosis in two cases. Recently, Dandoy *et al.* [37] reported that raised right ventricular pressure at day 7 after HSCT was associated with TA-TMA and pericardial effusion. For this reason, they also suggested early vascular injury in the lung. Although we do not have enough available data so early after HSCT, this report may also be helpful to understand the pathogenic mechanism of post-HSCT pericardial effusion.

In the present study, both mean and median baseline QTcD were significantly prolonged in patients who developed post-HSCT pericardial effusion; thus, prolonged preoperative QTcD may be predictive of pericardial effusion. One possible cause of prolonged QTD and QTcD before HSCT is a history of anthracycline treatment [22,38–40]. Most of the patients in our study had a history of anthracycline treatment before HSCT, although there were differences in total drug dose. Anthracycline-induced cardiotoxicity appears to involve free radical formation and oxidative stress [39]. Although increased QTD and QTcD are believed to reflect anthracycline-induced abnormal ventricular depolarization and repolarization [39,41], cardiac function, as evaluated by echocardiographic screening, was comparatively normal before transplant in the pericardial effusion group. However, echocardiography may not detect the early stages of anthracycline-induced cardiotoxicity [38,42]. In contrast, QTD and QTcD abnormalities may appear even in patients with a low anthracycline dose, underscoring the role of individual variability [22,25,38]. In fact, we could not find any relationship between the cumulative dose of specific drugs before HSCT (including anthracycline and other drugs) and prolongation of QTC and QTcD (Pearson's product–moment correlation). Although the total anthracycline dose did not differ between the groups in our study, QTcD was significantly prolonged before HSCT in the pericardial effusion group. Further analysis of effusion patients showed that QTD was significantly longer prior to transplant compared with initial diagnosis (Wilcoxon signed rank sum test, $P = 0.016$), suggesting that many patients in the pericardial effusion group had a relatively high anthracycline sensitivity and thus were at an increased risk of potential myocardial toxicity even before HSCT. Furthermore, cumulative effects of the primary disease and treatments prior to transplant could be additional predisposing factors for prolonged QTcD and subsequent consequences of transplant conditioning, the transplant procedure, and post-transplant treatments in this patient group. Therefore, although the effusion group showed no differences in most measures of cardiac function before HSCT relative to the noneffusion group, suggesting only mild myocardial dysfunction, these mild disorders may have contributed to pathological changes in the myocardium following HSCT that eventually resulted in pericardial effusion. The risk of pericardial effusion may be further elevated by the risk factors identified in this and previous studies. Thus, special attention should be paid to HSCT candidates with risk factors such as TA-TMA and prolonged QTcD before the preparative regimen, and careful follow-up is recommended in patients with an elevated risk in order to facilitate timely detection and treatment of pericardial effusion.

Overall survival was significantly reduced by pericardial effusion in allogeneic HSCT patients (Fig. 1b), although it was not the direct cause of death in any patient. Thus, patients with pericardial effusion had other complications beforehand, the poor control of which enhanced the risk of pericardial effusion (Table 1). Disease severity was a significant risk factor for pericardial effusion in univariate analysis. Several studies have shown that severe pericardial effusion can be a direct cause of death [2,8,42]; however, others have reported no patient death directly due to

pericardial effusion [3,4,6,7,30]. Early identification and rapid treatment at the time of cardiac tamponade onset have likely prevented such fatalities, as has aggressive treatment of the underlying causes [3,7,14–17].

In conclusion, pericardial effusion developed in 17.4% of patients within one year post-HSCT, and half of these patients were symptomatic and a quarter required urgent treatment. TA-TMA ≥grade II was a significant risk factor as revealed by both univariate and multivariate analyses. In addition, prolonged QTcD before HSCT was predictive of post-treatment pericardial effusion. These results suggest that patients with abnormally prolonged QTcD before the preparative regimen should be monitored by regular follow-up echocardiography, particularly when accompanied by additional risk factors for pericardial effusion. However, larger case studies are necessary to confirm the prognostic efficacy of TA-TMA, long QTD, and long QTcD.

Authorship

RY and EI: participated in research design and writing of article. NM and SY: participated in data analysis. DM, KS, and MS: participated in data collection. MT and YH: did the statistical analysis. NK, EH, and YO: participated in performance of the research. TN and SY: commented on and approved the final version.

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