

## Post-Transplant Complications

# Electrocardiogram is very useful for predicting acute heart failure following myeloablative chemotherapy with hematopoietic stem cell transplantation rescue

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### Summary:

A prospective study was conducted in 71 evaluable patients who received myeloablative hematopoietic stem cell transplantation (HSCT) at our facility from 1995 to 2002, to find a sensitive marker for post-transplant heart failure, including echocardiographic systolic and diastolic markers and QTc interval. QTc was found to be an independent and significant risk factor for acute heart failure (AHF) on multivariate logistic regression analysis (OR 1.5,  $P = 0.01$ , 95% confidence interval (CI) 1.1–2.0), while no significant differences between patients with AHF and those without AHF were found in age, sex, treatment history, type of conditioning regimen, and echocardiographic systolic and diastolic markers. On further analysis, post-transplant risk of AHF appeared to be increased as QTc was prolonged. The post-transplant risk of AHF in the group with longest QTc on multivariate logistic regression analysis was found to be 9.8 times that in the group with shortest QTc ( $P = 0.04$ , 95% CI 1.0–100). These results suggest that echocardiographic markers are less valuable predictors of post-transplant AHF, but that prolongation of the QTc, an ECG marker, before HSCT is strongly associated with onset of AHF after HSCT.

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aplastic anemia. However, myeloablative chemotherapies are known to be responsible not only for hematological toxicity, from which rescue by HSCT is possible, but also for nonhematological toxicities involving various organs and tissues. Of nonhematological toxicities, acute heart failure (AHF) is a serious complication sometimes observed after transplantation, which is occasionally life threatening.<sup>1</sup> The incidence of cardiotoxicity after HSCT has been reported to vary from 2.0 to 28.0%, depending on patient number, conditioning regimen, and medical institution.<sup>1–5</sup>

In addition, some anticancer agents used in conditioning regimens for HSCT are known to be cardiotoxic.<sup>6–10</sup> Other studies additionally have reported that dimethylsulfoxide used to freeze grafts is responsible for cardiac dysfunction.<sup>11</sup>

For safe transplantation, it is of critical importance to predict the occurrence of AHF prior to treatment of individual patients. To meet this goal, several approaches to predict the onset of cardiotoxicity have been proposed. One has indicated that the cumulative dose of anthracyclines prior to high-dose therapy before HSCT may be associated with increased risk of cardiotoxicity.<sup>4</sup> On the other hand, it has been reported that patients with <50% ejection fraction tended to develop severe cardiotoxicity after transplantation.<sup>12</sup> However, various subsequent studies have shown that both of these conventional markers are clearly insufficient to predict the onset of acute heart failure accurately.<sup>13–15</sup>

Recent findings for anthracycline-induced cardiomyopathy suggest that diastolic dysfunction of the heart progresses prior to the development of systolic dysfunction in many cases,<sup>16,17</sup> suggesting that diastolic markers might be more sensitive markers for early cardiac injury. However, the usefulness of echocardiographic diastolic markers for prediction of AHF following myeloablative therapy and HSCT has not been investigated in detail. In this study, therefore, we first evaluated the usefulness of diastolic markers of echocardiography. We also evaluated the usefulness of corrected QT (QTc) interval, an electrocardiographic marker reported to be another possible

Myeloablative high-dose chemotherapy followed by hematopoietic stem cell transplantation (HSCT) has widely been used for the treatment of hematological malignancies and

marker of hypertensive and/or ischemic cardiac injury.<sup>18,19</sup> In the present prospective study of 71 patients who underwent various types of high-dose chemotherapy and HSCT, we found that QTc interval, but not systolic or diastolic echocardiographic markers, is quite sensitive in predicting the onset of AHF.

## Patients and methods

### Patients

A total of 75 consecutive patients aged 15–63 years with hematopoietic malignancies or disease underwent myeloablative HSCT in our institute from May 1995 to January 2002. We excluded four patients who did not undergo both echocardiography and electrocardiography before conditioning for myeloablative HSCT. Thus, we prospectively evaluated systolic and diastolic function markers of echocardiography and the QTc interval before HSCT in 71 evaluable patients (non-Hodgkin's lymphoma 22 patients, Hodgkin's disease 2, acute T-cell leukemia 2, acute myeloblastic leukemia 21, acute lymphoblastic leukemia 13, chronic myelogenous leukemia 6, myelodysplastic syndrome 1, multiple myeloma 1, EB virus-associated hemophagocytic syndrome 1, aplastic anemia 2; male 43, female 28).

Of these patients, 61 (86%) had been previously treated with chemotherapies including anthracyclines but none had received mediastinal radiotherapy. We calculated cumulative dose of anthracycline as daunorubicin 0.5, pirarubicin 0.8, mitoxantrone 3.4, idarubicin 1.6 epirubicin 0.6, when intensity of the cardiotoxicity of doxorubicin considered to be 1.0, referring to the previous reports.<sup>20,21</sup>

Of the patients 10 (14%) had not received any anthracycline, 13 (18%) had received 1–200 mg/m<sup>2</sup>, 46 (65%) had received 201–500 mg/m<sup>2</sup>, and 2 (3%) had received more than 500 mg/m<sup>2</sup>.

### High-dose chemotherapy and HSCT

In all, 56 of 71 patients (79%) received conditioning regimens including high-dose cyclophosphamide (120 mg/kg or 4800 mg/m<sup>2</sup>) and 24 patients (34%) received regimens including total body irradiation (TBI) (Table 1). As a source of hematopoietic stem cells, autologous grafts were used for 28 patients (27 peripheral blood stem cells and one bone marrow graft), all of which had been cryopreserved before transplantation. Of the 43 patients who received allogeneic grafts (14 peripheral blood stem cell and 29 bone marrow grafts), one had a marrow graft that had been cryopreserved before transplantation.

### Electrocardiographic examination

All the patients who had finished the last course of conventional chemotherapy were evaluated with a standard 12-lead electrocardiogram at rest within a month before high-dose chemotherapy and HSCT. At that time, the QTc interval was measured automatically using a novel recording system (FDX-6521, FUKUDA). In brief, QT intervals were measured for 15 s at 25 mm/s, and the average value of three independent measurements was employed as the QT interval of the patient.<sup>22</sup> QTc was then calculated by correcting the QT interval with Bazett's formula.<sup>23</sup>

### Echocardiographic examination

At time points similar to those of electrocardiographic examination, echocardiographic examination was also

**Table 1** Patient profile

	Acute heart failure		P-value
	Positive (n = 12)	Negative (n = 59)	
Age (years)	33.5 ± 14.4	35.3 ± 12.6	0.660 <sup>a</sup>
Sex (M/F)	6/6	37/22	0.521 <sup>b</sup>
Cumulative anthracyclines (mg/m <sup>2</sup> )	281 ± 166	238 ± 150	0.392 <sup>a</sup>
<i>Electrocardiographic marker before HSCT</i>			
QTc (ms)	443 ± 38.9	417 ± 21.8	0.002 <sup>a</sup>
<i>Echocardiographic markers before HSCT</i>			
Ejection fraction (%)	60.0 ± 8.4	63.1 ± 6.7	0.168 <sup>a</sup>
Fractional shortening (%)	31.6 ± 8.3	34.0 ± 6.3	0.257 <sup>a</sup>
E/A	1.59 ± 0.78	1.28 ± 0.63	0.099 <sup>a</sup>
Deceleration time (ms)	157 ± 24.0	177 ± 37.2	0.144 <sup>a</sup>
Isovolumic relaxation time (ms)	58.0 ± 10.7	66.2 ± 17.6	0.367 <sup>a</sup>
Left ventricle end-diastolic diameter (mm)	46.0 ± 6.1	46.5 ± 4.5	0.821 <sup>a</sup>
Left ventricle end-systolic diameter (mm)	32.2 ± 7.0	30.6 ± 4.7	0.372 <sup>a</sup>
<i>Conditioning regimen and type of graft</i>			
High-dose cyclophosphamide	10 (83%)	46 (78%)	> 0.999 <sup>b</sup>
Total body irradiation	5 (42%)	19 (32%)	0.524 <sup>b</sup>
Cryopreserved graft	6 (50%)	29 (44%)	0.531 <sup>b</sup>

Values are mean ± s.d.

<sup>a</sup>Unpaired *t*-test.

<sup>b</sup>Fisher's exact test.

performed using a Power Vision 6000 (Toshiba) in order to assess both systolic and diastolic function. We analyzed systolic function markers (left ventricular ejection fraction, fractional shortening) and diastolic function markers (early peak flow velocity/atrial peak flow velocity (E/A), deceleration time, isovolumic relaxation time). Gainsetting was optimized to a level just below background noise. Transducer frequency was 2.5 or 3.5 MHz. Cross-sectional imaging was performed in the left ventricular parasternal long axis and apical four- and two-chamber views. Transmitral flow velocity patterns were recorded from the apical-long axis four-chamber view with the pulsed-wave Doppler sample volume positioned at the tips of the mitral leaflets during diastole.<sup>24</sup> Left ventricular ejection fraction was measured by the modified Simpson method from the apical view.<sup>25,26</sup>

### Diagnosis of AHF

In order to minimize the chances of misdiagnosing of heart failure due to symptoms other than those of cardiac origin, AHF was carefully diagnosed based on both clinical criteria and echocardiographic indices. Clinical criteria were decided in accordance with those used in the Framingham study.<sup>27</sup> In brief, we diagnosed AHF when a minimum of two major criteria and two abnormalities on the echocardiogram, or one major and two minor criteria, and two abnormalities on the echocardiogram were present concurrently. Major criteria included orthopnea, pulmonary congestion, pulmonary rales, gallop rhythm, and jugular-venous distention. Minor criteria included tachycardia (rate of >120/min), shortness of breath, ankle edema, and hepatomegaly. Echocardiographic abnormalities included dilatation of the ventricles, decrease in ejection fraction of the left ventricle of more than 20% compared with baseline, and abnormal inflow pattern of the left ventricle. All criteria had to be new in onset after transplantation conditioning.

The patients who had been diagnosed with AHF were subsequently classified for severity from I to IV according to the New York Heart Association (NYHA) classification.

### Statistical analysis

Categorical variables were compared using Fisher's exact test. Differences in mean values between two groups were compared using the unpaired *t*-test. In these analyses,  $P < 0.05$  was considered to indicate statistical significance.

Various pretransplant risk factors for AHF were analyzed by univariate logistic regression analysis, and then multivariate logistic regression analysis was conducted with covariates with  $P$ -values  $< 0.20$  on univariate analysis.

Subsequently, in order to examine whether the post-transplant risk of AHF is increased as QTc is prolonged, all patients were divided into three groups (tertiles 1–3) consisting of an almost equal number of patients from the shortest QTc, to conduct logistic regression analyses, applying their medians in the respective groups to the tertiles. Logistic analysis was conducted with QTc alone as a factor (Crude), QTc adjusted by E/A and deceleration

time with  $P$ -value  $< 0.20$  (Multiple-adjust 1), and the ejection fraction adjusted by adding the E/A and deceleration time to QTc (Multiple-adjust 2). We calculated the 95% CI for each odds ratio. For each analysis, two-sided  $P$ -values  $< 0.05$  were considered statistically significant. All statistical analyses were performed with the SPSS 10.0 software package.

### Results

Of 71 evaluable patients who underwent high-dose chemotherapy and HSCT, 12 (17%) developed AHF according to our criteria. Of these patients, nine developed grade IV, two grade III, and one grade II heart failure according to the NYHA classification. Seven out of these 12 patients responded to the treatment and completely recovered from cardiac failure. However, of the remaining five patients, three died of AHF and two developed chronic heart failure. Ten of these 12 patients developed AHF within 2 weeks after conditioning chemotherapies including high-dose cyclophosphamide, and were thus diagnosed with cyclophosphamide-induced cardiomyopathy. The remaining two patients with non-Hodgkin's lymphoma developed severe AHF on day 18 or day 34 after HST following a regimen including high-dose melphalan.

As shown in Table 1, there were no significant differences between patients with AHF and those without AHF in patient background including age, sex, cumulative doses of anthracyclines before high-dose therapy, and HSCT. Also, use of high-dose cyclophosphamide, TBI and type of graft did not significantly affect the incidence of AHF as a whole (Table 2). We next compared the results of echocardiography and electrocardiography of patients who developed AHF and those who did not. As also shown in Table 1, neither systolic nor diastolic echocardiographic markers differed significantly between the two groups, although  $P$ -values appeared to be lower in the latter. On the other hand, QTc intervals of patients who developed AHF were significantly larger than those of patients who did not.

In order to find independent risk factors for AHF, we next evaluated all the parameters described in Table 2 with univariate logistic regression analysis, and found that QTc, E/A, and deceleration time were associated with  $P$ -values  $< 0.20$  (Table 2). Therefore, we further used these three parameters in multivariate logistic regression analysis, and found that QTc was the only independent risk factor for AHF (OR 1.5, 95% CI 1.1–2.0,  $P = 0.01$ ) (Table 3). Furthermore, on analysis to determine whether post-transplant risk of AHF is increased as QTc is prolonged, significant increase in post-transplant risk of acute heart failure was found with prolongation of QTc (Table 4). The crude cumulative incidences of AHF were 4% for the lowest, 17% for the middle, and 30% for the highest tertile of QTc interval. The crude odds ratio of AHF was 4.4 (95% CI, 0.5–43) in the population of tertile 2 and 9.1 (95% CI 1.0–80) in that of tertile 3, compared with those of tertile 1 ( $P = 0.02$  for trend). After multivariate adjustment for E/A and deceleration time, QTc interval was strongly associated with increased risk of AHF. The multiple-adjusted odds ratio of AHF was 5.0 (95% CI, 0.5–51) for

**Table 2** Univariate analysis of risk factors for acute heart failure

Variables	OR (95% CI)	P
<i>Univariate analysis model</i>		
Age	1.0 (0.9–1.0)	0.66
Male sex	0.6 (0.2–2.1)	0.42
QTc, per 10 (ms)	1.4 (1.1–1.9)	0.01**
TBI (yes)	1.5 (0.4–5.4)	0.53
High-dose cyclophosphamide (yes)	1.4 (0.3–7.3)	0.68
Cumulative dose of anthracycline, per 100 (mg/m <sup>2</sup> )	1.2 (0.8–1.8)	0.39
Cryopreserved graft (yes)	1.6 (0.5–5.4)	0.48
<i>Echocardiographic diastolic function markers</i>		
Left ventricle end-diastolic diameter, per 10 (mm)	0.8 (0.2–3.6)	0.82
Left ventricle end-systolic diameter, per 10 (mm)	1.8 (0.5–7.0)	0.37
Ejection fraction, per 10 (%)	0.5 (0.2–1.4)	0.23
Fractional shortening, per 10 (%)	0.6 (0.2–1.5)	0.26
E/A, per 0.1	1.1 (1.0–1.2)	0.13*
Deceleration time, per 10 (ms)	0.9 (0.7–1.1)	0.18*
Isovolumic relaxation time, per 10 (ms)	0.7 (0.4–1.4)	0.36

OR indicates odds ratio; CI, confidence interval E/A indicates ratio of E and A wave velocities. \*\* $P < 0.05$ , \* $P < 0.2$ .

**Table 3** Multivariate analysis of risk factors for acute heart failure

Variables	OR (95% CI)	P
<i>Multiple-adjusted model</i>		
QTc, per 10 (ms)	1.5 (1.1–2.0)	0.01*
E/A, per 0.1	1.1 (1.0–1.3)	0.11
Deceleration time, per 10 (ms)	0.8 (0.7–1.1)	0.21

\* $P < 0.05$ .

the population of tertile 2 and 11.4 (95% CI 1.2–108) for that of tertile 3 compared with those of tertile 1 ( $P = 0.02$  for trend) (Table 4). Furthermore, after adjustment for E/A, deceleration time and ejection fraction, the odds ratio of AHF was 5.0 (95% CI 0.5–52) for the population of tertile 2 and 9.8 (95% CI 1.0–100) for that of tertile 3 compared with those of tertile 1 ( $P = 0.04$  for trend) (Table 4).

## Discussion

In the present study, we demonstrated that QTc interval was an independent risk factor for development of AHF after HSCT.

During the present study, 12 of 71 patients (17%) developed AHF, an incidence that appeared to be slightly higher than in some other reports.<sup>1–4</sup> As a possible explanation for this observation, one report indicated that a cryopreserved graft may be associated with increased risk of cardiac disorders.<sup>28</sup> Indeed, in our study, a relatively high proportion (41%) received cryopreserved grafts and six of these 29 patients (21%) developed AHF. However, evaluated in greater detail, 19 of these 29 patients had received the modified BEAC regimen<sup>29</sup> using ranimustine instead of carmustine as conditioning for autotransplantation of cryopreserved grafts, and five of them (26%) developed AHF. In contrast, of the other 10 patients who had received cryopreserved grafts following other combination chemotherapies, only one (10%) developed AHF (data

not shown in Results section). Therefore, the high incidence of AHF in the present study might be in part related to the conditioning regimen used in our institute, rather than to the use of cryopreserved grafts. Indeed, use of cyclophosphamide combined with carmustine or of lomustine combined with cytarabine arabinoside has been reported to increase the incidence of cardiotoxicity.<sup>4,29–31</sup> In addition, it has been reported that AHF induced by high-dose cyclophosphamide may often cause AHF with restrictive diastolic impairment.<sup>1</sup> Since the cardiomegaly in these cases is not always prominent, there may be a risk of misdiagnosis of these patients with pneumonia or pulmonary edema of noncardiac origin. In the present study, we used criteria for AHF including diastolic functions, another possible reason for the high incidence of AHF we observed.

In the present study, we prospectively evaluated various markers to predict AHF following myeloablative chemotherapy and HSCT with careful multivariate analysis.

Of these markers, echocardiographic markers of systolic function were found to be quite poor for prediction of AHF after HSCT, in good accordance with most previous reports.<sup>13–15</sup> In addition, although diastolic markers such as E/A and deceleration time were associated with  $P < 0.2$  on univariate analysis, these markers were not statistically significant on subsequent multivariate analysis.

Notably, we found that QTc interval, an electrocardiac marker that can easily be calculated at most hospitals, is an independent and sensitive risk factor for AHF following myeloablative chemotherapy and HSCT. Furthermore, we showed that prolongation of QTc interval is strongly and directly associated with increased risk of AHF (odds ratios increasing nearly 10-fold from tertiles 1 to 3 in Table 4), and these findings were true even after multiple adjustment by covariates. Recently, we reported that QT dispersion, another electrocardiac marker that represents the difference between maximum and minimum QT intervals, was another quite sensitive predictor of AHF for 19 patients who received chemotherapy including high-dose cyclophosphamide with peripheral blood stem cell rescue.<sup>32</sup> Together with the present findings, these findings suggest that the

**Table 4** Odds ratio of acute heart failure after hematopoietic stem cell transplantation according to QTc interval

	n	Cases	%	Odds ratio (95%CI)		
				Crude	Multiple-adjusted 1 <sup>a</sup>	Multiple-adjusted 2 <sup>b</sup>
QTc interval (ms)						
Tertile 1 (370–411)	24	1	4	1.0	1.0	1.0
Tertile 2 (411–427)	24	4	17	4.4 (0.5–43)	5.0 (0.5–51)	5.0 (0.5–52)
Tertile 3 (427–546)	23	7	30	9.1 (1.0–80)	11.4 (1.2–108)	9.8 (1.0–100)
P for trend				0.02*	0.02*	0.04*

<sup>a</sup>Adjusted for deceleration time, E/A, <sup>b</sup>Adjusted for deceleration time, E/A, ejection fraction.  
\*P<0.05.

electrocardiogram may be more valuable than mechanical markers for prediction of AHF following high-dose chemotherapy and HSCT. Although the precise mechanism of usefulness of QTc for prediction of AHF remains to be elucidated, we speculate that the risk of AHF following high-dose chemotherapy (especially after cyclophosphamide) might be strongly dependent on the presence of slight cardiac injury such as local or multifocal degeneration of cardiac muscle, which can be detected only by electrocardiography. We are now planning a multicenter study to generalize the usefulness of electrocardiac markers, in order to completely prevent the onset of AHF following HSCT in the near future.

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