Table 4. Impact of type, presentation and organ involvement of chronic GVHD on chronic GVHD-specific survival

Characteristics	*Chronic GVHD-specific survival*		
	HR	*95% CI*	*P-value*
Type of chronic GVHD			
Limited	1.00		
Extensive	2.60	(1.67–4.05)	<0.001
Presentation of chronic GVHD			
de novo	1.00		
Progressive	1.73	(1.10–2.72)	0.017
Quiescent	0.76	(0.51–1.13)	0.173
Skin			
None	1.00		
Limited	0.58	(0.41–0.83)	0.002
Extensive	1.34	(1.01–1.78)	0.043
Oral cavity			
No	1.00		
Yes	0.97	(0.76–1.25)	0.840
Eye			
No	1.00		
Yes	1.03	(0.78–1.35)	0.859
Liver			
No	1.00		
Yes	1.17	(0.91–1.51)	0.225
Lung			
No	1.00		
Yes	1.29	(0.96–1.74)	0.091
Joint			
No	1.00		
Yes	0.93	(0.52–1.66)	0.795
Intestine/genitals			
No	1.00		
Yes	2.15	(1.66–2.78)	<0.001
Others			
No	1.00		
Yes	1.34	(0.85–2.11)	0.206

Abbreviations: CI = confidence interval; HR = hazard ratio. Hazard ratios were adjusted by type of stem cell source, recipient age, disease risk and grade II–IV acute GVHD.

Several limitations of this study should be noted. First, in this study, acute and chronic GVHD were diagnosed on the basis of traditional criteria, whereas chronic GVHD was diagnosed and classified on the basis of NIH criteria in recent studies.[36–39] Therefore, our results cannot be compared with those reported in other studies. In addition, it is possible that late onset acute GVHD was classified as chronic GVHD or early onset of chronic GVHD was defined as acute GVHD. This may bias the association between acute and chronic GVHD. Second, there is a possibility that chronic GVHD that developed a few years after SCT was not reported or was missed. Furthermore, detailed information on the clinical course of GVHD and on the onset of each chronic GVHD organ manifestation was not available; therefore, chronic GVHD-specific survival should be cautiously interpreted. Fourth, because organ involvement of chronic GVHD was not defined in detail in this large retrospective studies, there is a possibility of misclassification regarding organ involvement. Further, the information on intestinal or genital involvement was not separately collected in the questionnaire. Lastly, incidence of chronic GVHD in the present study was relatively low as compared with that in Caucasian cohorts, suggesting that the genetic differences between races may affect occurrence of chronic GVHD. Therefore, the results should be cautiously interpreted when the result is applied for non-Asian populations.

In conclusion, extensive chronic GVHD was less frequently observed in the U-CB group. In addition, among patients who developed chronic GVHD, oral cavity, eye, liver, lung and joint involvement were less frequently observed in the U-CB group. Although limited type of skin GVHD was frequently observed, it remains within the range of limited chronic GVHD. Therefore, the quality of life may be better for long-term survivors of the U-CB group than those of the MR-BM group or the other groups. Progressive onset, extensive chronic GVHD or intestinal or genital involvement was associated with lower chronic GVHD-specific survival, which suggests the need to intensify treatment for patients with these chronic GVHD characteristics. Finally, a prospective study using NIH criteria is needed to compare the

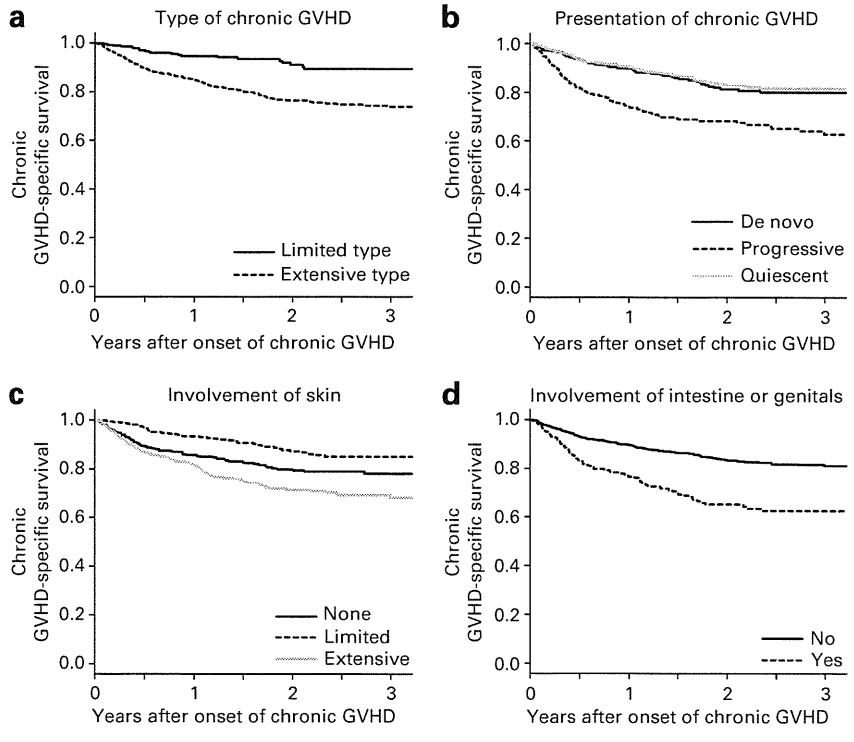

Figure 3. Chronic GVHD-specific survival stratified by type (**a**), presentation (**b**), involvement of skin (**c**) and involvement of intestine or genitals (**d**).

incidences of patients with chronic GVHD between Japan and other countries.

CONFLICT OF INTEREST

The authors declare no conflict interest.

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ORIGINAL ARTICLE

Impact of pretransplant body mass index on the clinical outcome after allogeneic hematopoietic SCT

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To elucidate the impact of pretransplant body mass index (BMI) on the clinical outcome, we performed a retrospective study with registry data including a total of 12 050 patients (age ⩾ 18 years) who received allogeneic hematopoietic SCT (HSCT) between 2000 and 2010. Patients were stratified as follows: BMI < 18.5 kg/m^2, Underweight, $n = 1791$; 18.5 ⩽ BMI < 25, Normal, $n = 8444$; 25 ⩽ BMI < 30, Overweight, $n = 1591$; BMI ⩾ 30, Obese, $n = 224$. The median age was 45 years (range, 18–77). A multivariate analysis showed that the risk of relapse was significantly higher in the underweight group and lower in the overweight and obese groups compared with the normal group (hazard ratio (HR), 1.16, 0.86, and 0.74, respectively). The risk of GVHD was significantly higher in the overweight group compared with the normal group. The risk of non-relapse mortality (NRM) was significantly higher in the overweight and obese group compared with the normal group (HR 1.19 and HR 1.43, respectively). The probability of OS was lower in the underweight group compared with the normal group (HR 1.10, $P = 0.018$). In conclusion, pretransplant BMI affected the risk of relapse and NRM after allogeneic HSCT. Underweight was a risk factor for poor OS because of an increased risk of relapse. Obesity was a risk factor for NRM.

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INTRODUCTION

Obesity has become an important health issue worldwide.[1] On the other hand, malnutrition is an important problem in cancer patients.[2] The impact of pretransplant obesity (high body mass index (BMI)) and malnutrition (low BMI) on the clinical outcome after allogeneic hematopoietic SCT (HSCT) is still controversial. Sorror *et al.*[3] reported that obesity (BMI > 35 kg/m^2) as a factor in the hematopoietic cell transplant-specific comorbidity index was associated with an increased risk of non-relapse mortality (NRM). A large retrospective study from the Center for International Blood and Marrow Transplant Research (CIBMTR) showed that the probability of OS in patients with low BMI (BMI < 18.5 kg/m^2) was inferior to that in patients with a normal BMI in patients who received stem cells from either related or unrelated donors, mainly because of the increased risk of relapse.[4] A limitation of this CIBMTR study was the limited number of patients with low BMI (32 of 2041 patients (1.6%) who received related HSCT and 33 of 1801 patients (1.8%) who received unrelated HSCT). We previously reported that there was a trend toward an increased risk of acute GVHD and NRM in patients with high BMI, and the risk of relapse was higher in patients with low BMI using registry data from the Japanese Marrow Donor Program.[5] However, this study was limited by the small number of patients with high BMI (BMI ⩾ 30 kg/m^2) in this population (61 of 3935 patients (1.6%)). A larger database is needed to increase the statistical power, so that it would be sufficient to clarify the impact of both low BMI and high BMI simultaneously using a single database. In addition, a previous study did not reveal the characteristics of post transplant morbidity and mortality in patients with each risk factor.[3] If we can clarify the details regarding the cause of failure in patients with low or high BMI, we may be able to improve the overall outcome after allogeneic HSCT. For this purpose, we assessed the impact of pretransplant BMI using a database from the Japan Society for Hematopoietic Cell Transplantation (JSHCT).[6]

PATIENTS AND METHODS

This study was approved by the Institutional Review Board of National Cancer Center, Tokyo, Japan. The patients in this analysis were aged 18 years or older, had received a first allogeneic HSCT between 2000 and 2010, and had data regarding pretransplant BMI. The patients' clinical data were obtained from the JSHCT database.[6] Excluding patients without data regarding OS ($n = 30$) as well as patients who received cord blood transplant ($n = 3621$), 12 050 patients met the inclusion criteria and were included in the analysis. Patients were classified into four groups based on pretransplant BMI values according to consensus weight designations from the World Health Organization[7] and the National Heart Lung and Blood Institute Expert Panel,[8] as follows: underweight (BMI < 18.5 kg/m^2, $n = 1791$), normal (18.5 ⩽ BMI < 25 kg/m^2, $n = 8444$), overweight (25 ⩽ BMI < 30 kg/m^2, $n = 1591$) and obese (BMI ⩾ 30 kg/m^2; $n = 224$).

The study endpoints included GVHD, NRM, OS and relapse. Incidences of grade II–IV or III–IV acute and chronic or extensive chronic GVHD were based on classical criteria.[9,10] OS was defined as time to death from any cause. NRM was defined as death from any cause in continuous CR or no progression. Relapse was defined as the time to onset of hematologic recurrence or disease progression.

A descriptive statistical analysis was performed to assess the patients' characteristics. Medians and ranges are provided for continuous variables and percentages are shown for categorical variables. The patients'

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characteristics were compared using the Chi-squared test for categorical variables. The probability of OS was calculated by the Kaplan–Meier method. A Cox proportional hazards regression model was used to analyze OS. The cumulative incidences of NRM and GVHD were evaluated using the Fine and Gray model for univariate and multivariate analyses. In the competing risk models for GVHD, relapse and death before these events

Table 1. Patients' characteristics

Variable	*Underweight* *BMI < 18.5* N *(%)*	*Normal* *18.5 ⩽ BMI < 25* N *(%)*	*Overweight* *25 ⩽ BMI < 30* N *(%)*	*Obesity* *30 ⩽ BMI* N *(%)*	P-*value*
Number of patients	1791	8444	1591	224	
Median age, years (range)	42 (18–73)	46 (18–77)	44 (18–72)	37 (18–70)	< 0.001
Sex					
Female	1057 (59.0)	3400 (40.3)	434 (27.3)	87 (38.8)	< 0.001
Male	734 (41.0)	5043 (59.7)	1157 (72.7)	137 (61.2)	
Missing	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	
Performance status					
0–1	1410 (78.7)	6970 (82.5)	1355 (85.2)	197 (87.9)	< 0.001
2–4	263 (14.7)	771 (9.1)	105 (6.6)	15 (6.7)	
Missing	118 (6.6)	703 (8.3)	131 (8.2)	12 (5.4)	
Stem cell source					
Related BM	350 (19.5)	1409 (16.7)	258 (16.2)	31 (13.8)	< 0.001
Related PBSC	496 (27.7)	2037 (24.1)	317 (19.9)	58 (25.9)	
Unrelated BM	945 (52.8)	4998 (59.2)	1016 (63.9)	135 (60.3)	
HLA mismatch					
Match	1395 (77.9)	6685 (79.2)	1267 (79.6)	177 (79.0)	0.56
Mismatch	368 (20.5)	1632 (19.3)	309 (19.4)	43 (19.2)	
Missing	28 (1.6)	127 (1.5)	15 (0.9)	4 (1.8)	
Donor/recipient sex combination					
Female to male	277 (15.5)	1799 (21.3)	358 (22.5)	37 (16.5)	< 0.001
Others	1484 (82.9)	6519 (77.2)	1217 (76.5)	187 (83.5)	
Missing	30 (1.7)	126 (1.5)	16 (1.0)	0 (0)	
Underlying disease					
AML	660 (36.9)	3395 (40.2)	659 (41.4)	86 (38.4)	< 0.001
ALL	370 (20.7)	1450 (17.2)	260 (16.3)	48 (21.4)	
MDS	163 (9.1)	927 (11.0)	232 (14.6)	23 (10.3)	
Lymphoma	323 (18.0)	1446 (17.1)	230 (14.5)	27 (12.1)	
Non-malignant	132 (7.4)	388 (4.6)	53 (3.3)	13 (5.8)	
MPD including CML	116 (6.5)	708 (8.4)	137 (8.6)	24 (10.7)	
Others	27 (1.5)	130 (1.5)	20 (1.3)	3 (1.3)	
Disease risk					
Standard	836 (46.7)	4082 (48.3)	842 (52.9)	125 (55.8)	< 0.001
High	906 (50.6)	4106 (48.6)	712 (44.8)	94 (42.0)	
Missing	49 (2.7)	256 (3.0)	37 (2.3)	5 (2.2)	
Time from diagnosis to transplant					
Median, day	256	278	317	362	< 0.001
Conditioning regimen					
Myeloablative	1139 (63.6)	5396 (63.9)	1080 (67.9)	166 (68.0)	< 0.001
TBI-Cy-based	824 (46.4)	3968 (47.2)	796 (50.2)	123 (55.2)	
Bu-Cy-based	188 (10.6)	1014 (12.1)	212 (13.4)	26 (11.7)	
Reduced-intensity	617 (34.5)	2824 (33.4)	466 (29.3)	55 (24.6)	
Missing	35 (2.0)	224 (2.7)	45 (2.8)	3 (1.3)	
GVHD prophylaxis					
CSP-based	887 (49.5)	3959 (46.9)	737 (46.3)	97 (43.3)	0.12
TAC-based	868 (48.5)	4315 (51.1)	833 (52.4)	123 (54.9)	
Missing	36 (2.0)	170 (2.0)	21 (1.3)	4 (1.8)	
Year of transplant					
< 2007	884 (49.4)	4402 (52.1)	847 (53.2)	109 (48.7)	0.077
⩾ 2007	907 (50.6)	4042 (47.9)	744 (46.8)	115 (51.3)	

Abbreviations: BMI = body mass index; MDS = myelodysplastic syndrome; MPD = myeloproliferative disorder; TAC = tacrolimus.

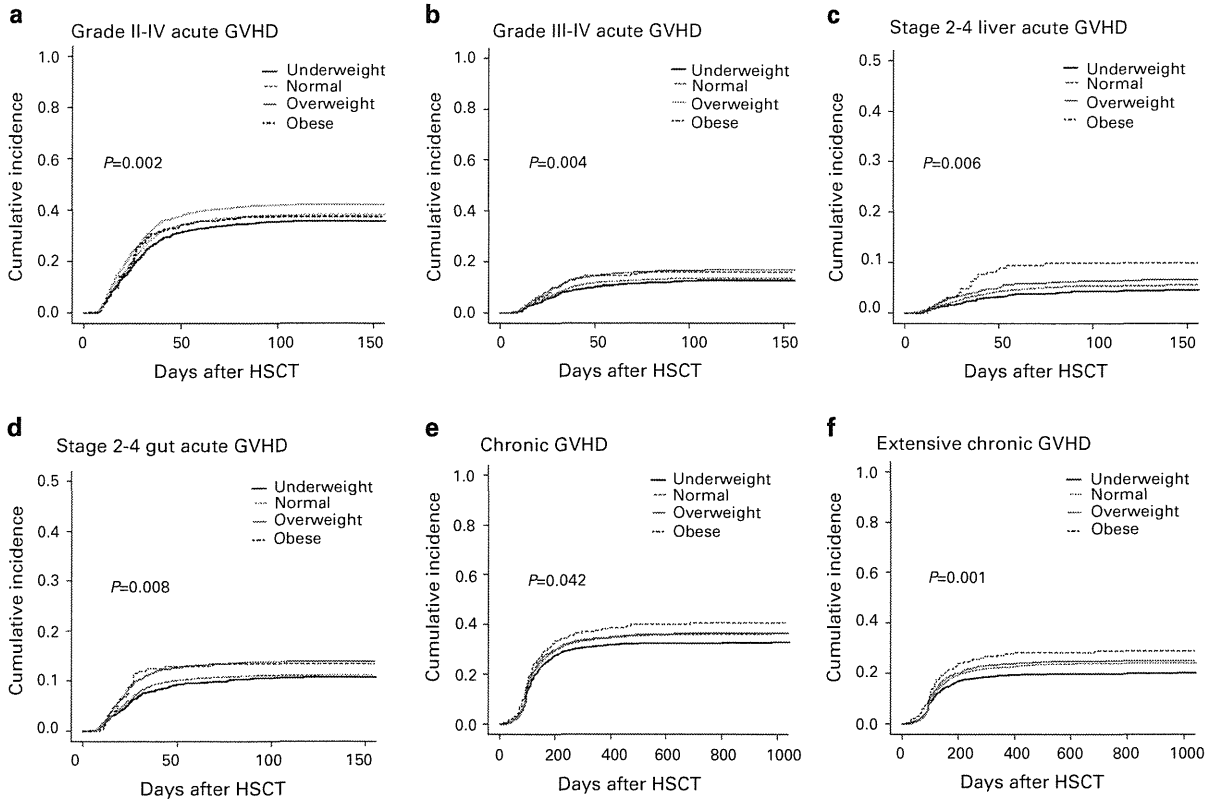

Figure 1. Cumulative incidence of GVHD grouped according to pretransplant BMI. (**a**) grade II–IV acute, (**b**) grade III–IV acute, (**c**) stage 2–4 liver acute, (**d**) stage 2–4 gut acute, (**e**) chronic, (**f**) extensive chronic.

were defined as competing risks. In the competing risk models for NRM, relapse was defined as a competing risk. For each cause-specific NRM, relapse and NRM with other causes were defined as competing risks. Factors that were associated with a two-sided *P* value of less than 0.10 in the univariate analysis were included in a multivariate analysis. We used a backward-stepwise selection algorithm and retained only the statistically significant variables in the final model. A two-sided *P* value of less than 0.05 was considered statistically significant. The variables evaluated in these analyses were as follows: sex mismatch (female to male vs other), patient's age at the time of HSCT (age $\geqslant$ 50 years vs age $<$ 50), disease risk (standard risk vs high risk), performance status (0–1 vs 2–4), stem cell source (related BM vs related PBSC vs unrelated BM), year of transplant ($\geqslant$2007 vs $<$ 2007) and HLA disparity as assessed by serological typing of HLA A, B and DRB1. In the analysis including the hematopoietic cell transplant-specific comorbidity index, we grouped patients into three groups (0 points vs 1–2 points vs $\geqslant$ 3 points).[3] Standard risk was defined as the first or second CR of acute leukemia, the first or second chronic phase of CML, myelodysplastic syndrome refractory anemia or refractory cytopenia with multilineage dysplasia, or nonmalignant disease. High risk was defined as other malignancies. Performance status was defined following ECOG criteria.[11] We considered that the data are missing completely at random, and therefore, all analyses in this study were performed as available-case analyses. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Tochigi, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.0.2).[12]

RESULTS

The patient characteristics are shown in Table 1. The median age was 45 years (range, 18–77). The median follow-up of surviving patients was 1183 days after allogeneic HSCT. The underweight group included more patients with a poor performance status (14.7%) and female patients (59.0%) compared with the normal group. The obese group included younger patients and more patients with a myeloablative conditioning regimen (68.0%) and standard-risk disease (55.8%) compared with the normal group. Female patients had significantly higher BMI (mean, female 22.3 kg/m^2, male 21.1 kg/m^2, $P < 0.001$). Gender-adjusted outcomes were less significant, and therefore gender was not included in the analysis.

The cumulative incidence of grade II–IV acute GVHD at 150 days was 35.7% in the underweight, 38.3% in normal, 42.2% in overweight and 37.6% in obese groups ($P = 0.002$, Figure 1a). A multivariate analysis showed that overweight was associated with an increased risk of grade II–IV acute GVHD (hazard ratio (HR) 1.13, 95% confidence interval (CI) 1.03–1.24, $P = 0.011$, Table 2). The cumulative incidence of grade III–IV acute GVHD was 12.7% in the underweight, 13.5% in normal, 16.8% in overweight and 15.9% in obese groups ($P = 0.004$, Figure 1b). A multivariate analysis showed that being overweight was associated with an increased risk of grade III–IV acute GVHD (HR 1.27, 95%CI 1.10–1.48, $P = 0.002$, Table 2). With regard to the target organ of acute GVHD, the incidence of skin GVHD was not significantly different among the four groups. On the other hand, the incidences of stage 2–4 liver and stage 2–4 gut acute GVHD were higher in patients who were overweight and obese. The cumulative incidence of stage 2–4 acute GVHD in the liver was 4.6% in the underweight, 5.5% in normal, 6.5% in overweight and 9.9% in obese groups ($P = 0.006$, Figure 1c). A multivariate analysis showed that obesity was associated with an increased risk of stage 2–4 acute GVHD in the liver (HR 2.00, 95%CI 1.26–3.17, $P = 0.003$, Supplementary Table 1). The cumulative incidence of stage 2–4 acute GVHD in the gut was 10.7% in the underweight, 11.2% in normal, 14.0% in overweight and 13.5% in obese groups ($P = 0.008$, Figure 1d). A multivariate analysis showed that being overweight was associated with an increased risk of stage 2–4 acute GVHD in the gut (HR 1.30, 95%CI 1.10–1.53, $P = 0.002$,

Table 2. Multivariate analysis of GVHD, outcome and significant factors

	Hazard ratio	*95%CI*	*P-value*
Grade II-IV acute GVHD			
Body mass index			
Underweight	0.94	0.86–1.03	0.21
Normal	1		
Overweight	1.13	1.03–1.24	0.011
Obesity	0.94	0.74–1.20	0.64
GVHD prophylaxis			
CSP-based	1		
TAC-based	0.84	0.77–0.90	< 0.001
HLA mismatch			
Match	1		
Mismatch	1.56	1.44–1.70	< 0.001
Performance status			
0–1	1		
2–4	0.74	0.66–0.83	< 0.001
Conditioning regimen			
Myeloablative	1		
Reduced-intensity	0.85	0.79–0.91	< 0.001
Stem cell source			
Related BM	1		
Related PBSC	1.24	1.12–1.38	< 0.001
Unrelated BM	1.62	1.47–1.78	< 0.001
Disease risk			
Standard	1		
High	1.13	1.06–1.21	< 0.001
Year of transplant			
< 2007	1		
⩾ 2007	0.85	0.80–0.91	< 0.001
Grade III–IV acute GVHD			
Body mass index			
Underweight	0.96	0.82–1.11	0.60
Normal	1		
Overweight	1.27	1.10–1.48	0.002
Obesity	1.17	0.81–1.70	>0.41
HLA mismatch			
Match	1		
Mismatch	1.45	1.28–1.65	< 0.001
Stem cell source			
Related BM	1		
Related PBSC	1.61	1.34–1.93	< 0.001
Unrelated BM	1.52	1.29–1.79	< 0.001
Disease risk			
Standard	1		
High	1.26	1.13–1.41	< 0.001
Year of transplant			
< 2007	1		
⩾ 2007	0.80	0.72–0.89	< 0.001

Abbreviation: TAC = tacrolimus.

Supplementary Table 1). The cumulative incidence of chronic GVHD at 2 years was 32.5% in the underweight, 35.8% in normal, 36.6% in overweight and 40.1% in obese groups ($P = 0.042$, Figure 1e). In a multivariate analysis, BMI was not a significant risk factor for chronic GVHD. The cumulative incidence of extensive chronic GVHD was 19.9% in the underweight, 23.7% in normal, 24.9% in overweight and 28.4% in obese groups ($P = 0.001$, Figure 1f). A multivariate analysis showed that obesity was associated with an increased risk of extensive chronic GVHD (HR 1.32, 95%CI 1.01–1.74, $P = 0.043$, Supplementary Table 1).

The cumulative incidence of NRM at 2 years was 19.5% in the underweight, 21.9% in normal, 25.1% in overweight and 23.0% in obese groups ($P = 0.002$, Figure 2a). A multivariate analysis showed that overweight and obesity were each associated with an increased risk of NRM (HR 1.19, 95%CI 1.06–1.33, $P = 0.004$; HR 1.43, 95%CI 1.08–1.88, $P = 0.012$, Table 3). Only 30 of the 12 050 patients had a BMI > 35 kg/m^2 (0.25%). In these patients, the cumulative incidence of NRM at 2 years was 25.6%. The cumulative incidence of infection-related NRM at 2 years was 5.7% in the underweight, 6.3% in normal, 7.7% in overweight and 5.2% in obese groups ($P = 0.021$, Figure 2b). A multivariate analysis showed that overweight was associated with an increased risk of infection-related NRM (HR 1.34, 95% CI 1.09–1.64, $P = 0.006$). The cumulative incidence of GVHD-related NRM at 2 years was 2.3% in the underweight, 3.1% in normal, 4.5% in overweight and 5.1% in obese groups ($P = 0.002$, Figure 2c). A multivariate analysis showed that obesity was associated with an increased risk of GVHD-related NRM (HR 2.15, 95% CI 1.20–3.86, $P = 0.010$). In patients who developed grade II–IV acute GVHD, the cumulative incidence of 2-year NRM after acute GVHD was 23.8% in the underweight, 28.8% in normal, 32.6% in overweight and 34.1% in obese groups ($P = 0.001$). A multivariate analysis showed that overweight and obesity were each associated with an increased risk of NRM in patients who developed grade II–IV acute GVHD (HR 1.18, 95% CI 1.01–1.39, $P = 0.040$; HR 1.62, 95%CI 1.09–2.42, $P = 0.018$). In patients who developed grade III–IV acute GVHD, the cumulative incidence of 2-year NRM after acute GVHD was 39.7% in the underweight, 49.4% in normal, 53.8% in overweight and 59.0% in obese groups ($P = 0.003$). A multivariate analysis showed that underweight and obesity were associated with a decreased and increased risk of NRM, respectively, in patients who developed grade III–IV acute GVHD (HR 0.72, 95% CI 0.56–0.92, $P = 0.009$; HR 1.65, 95% CI 1.01–2.71, $P = 0.048$).

We also assessed the impact of BMI on NRM in a multivariate analysis that included hematopoietic cell transplant-specific comorbidity index scores. In a multivariate analysis that included hematopoietic cell transplant-specific comorbidity index (0 points vs 1–2 points vs ⩾ 3 points), overweight and obesity were each still associated with an increased risk of NRM (HR 1.26, 95% CI 1.05–1.50, $P = 0.012$; HR 1.54, 95% CI 1.05–2.26, $P = 0.029$).

The cumulative incidence of relapse/progression was 35.6% in the underweight, 30.5% in normal, 23.9% in overweight and 22.6% in obese groups ($P < 0.0001$, Figure 2d). A multivariate analysis showed that underweight was associated with a higher risk of relapse (HR 1.16, 95% CI 1.06–1.28, $P = 0.002$), and overweight and obesity were each associated with a lower risk of relapse (HR 0.86, 95% CI 0.77–0.96, $P = 0.008$; HR 0.74, 95% CI 0.56–0.99, $P = 0.045$, Table 4). In patients with BMI ⩾ 35 kg/m^2, the cumulative incidence of relapse at 2 years was 18.4%. We conducted a subgroup analysis according to the underlying hematological malignancies. In patients with AML, the cumulative incidence of relapse/progression was 43.5% in the underweight, 35.5% in normal, 28.3% in overweight and 28.6% in obese groups ($P < 0.0001$). In patients with ALL, the cumulative incidence of relapse/progression was 31.9% in the underweight, 28.9% in normal, 21.8% in overweight and 22.1% in obese groups ($P = 0.091$).

The probability of OS at 2 years after allogeneic HSCT was 49.4% in the underweight, 53.0% in normal, 54.9% in overweight and 63.5% in obese groups ($P = 0.002$, Figure 2e). A multivariate analysis showed that underweight was associated with a worse OS than that in the normal group (HR 1.10, 95% CI 1.02–1.19, $P = 0.018$, Table 4).

We conducted a subgroup analysis according to the conditioning regimen. In patients who received a conventional CY plus TBI-

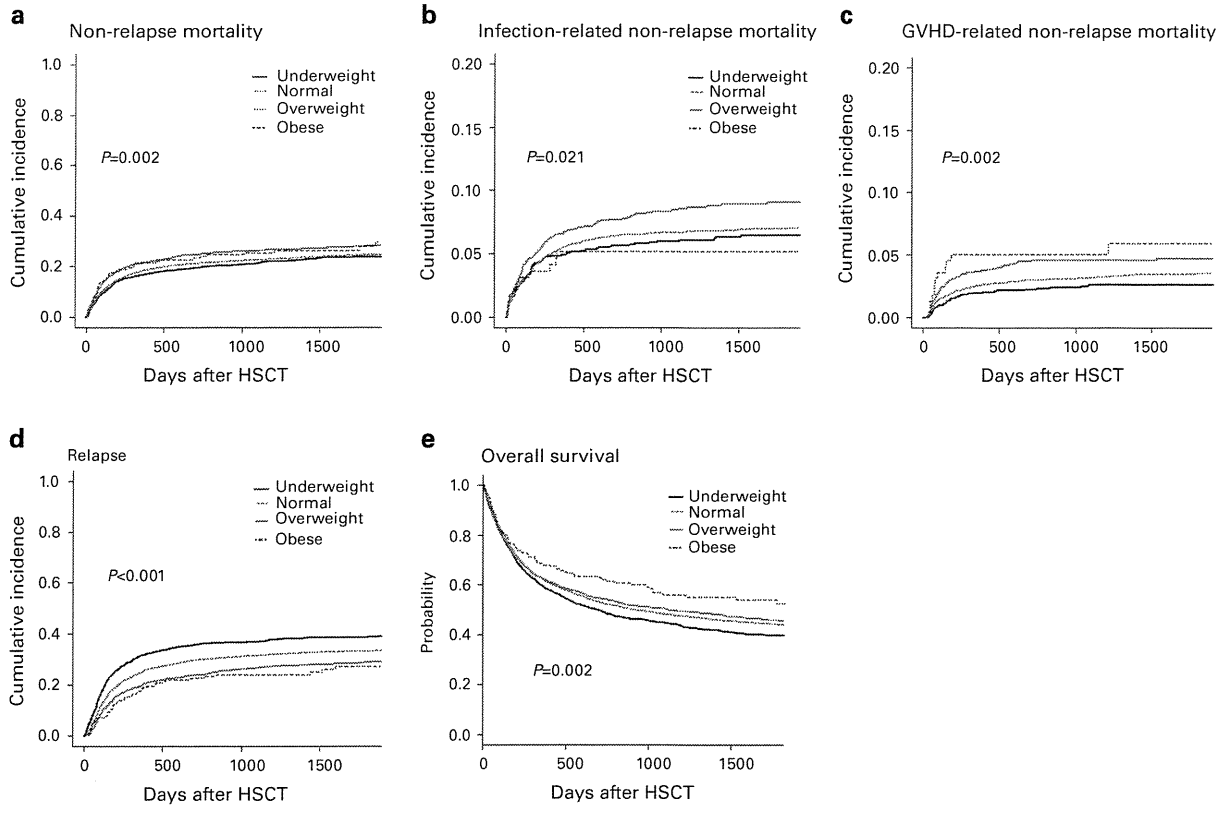

Figure 2. Cumulative incidence of (**a**) NRM (**a**), infection-related NRM (**b**), GVHD-related NRM (**c**) and relapse (**d**), probability of OS (**e**) grouped according to pretransplant BMI.

based myeloablative conditioning regimen, the cumulative incidence of relapse/progression was 33.6% in the underweight, 28.8% in normal, 23.1% in overweight and 23.6% in obese groups ($P < 0.0001$), and the cumulative incidence of NRM was 17.1% in the underweight, 21.0%in normal, 25.3% in overweight and 23.9% in obese groups ($P = 0.003$). In patients who received a BU plus CY-based myeloablative conditioning regimen, the cumulative incidence of relapse/progression was 38.9% in the underweight, 27.2% in normal, 20.7% in overweight and 13.5% in obese groups ($P = 0.001$), and the cumulative incidence of NRM was 18.9% in the underweight, 22.2% in normal, 25.8% in overweight and 17.1% in obese groups ($P = 0.47$). In patients who received a reduced-intensity conditioning regimen, the cumulative incidence of relapse/progression was 35.0% in the underweight, 33.2% in normal, 25.5% in overweight and 22.8% in obese groups ($P = 0.018$), and the cumulative incidence of NRM was 22.0% in the underweight, 21.7% in normal, 25.9% in overweight and 22.4% in obese groups ($P = 0.13$).

DISCUSSION

Here, we demonstrated that pretransplant BMI significantly influenced the post-transplant clinical outcome. To our knowledge, this is the largest study on the impact of pretransplant BMI after allogeneic HSCT. Our study showed that patients with a low BMI had the worst OS because of an increased risk of relapse, whereas patients with a high BMI had the highest NRM because of an increased risk of GVHD-related NRM.

Regarding the impact of obesity, Sorror *et al.*[3] reported that obesity (BMI > 35 kg/m^2) was associated with an increased risk of NRM. However, in Japan and many other countries, the prevalence of patients with BMI > 35 kg/m^2 is rather low, as shown in this study and previous reports.[1,5] A previous study showed that the mean BMIs in the US and Japan were 28 kg/m^2 and 22 kg/m^2, respectively, which shows that there is a huge difference in BMI between the two countries.[1] In the current study, only 30 of the 12 050 total patients had BMI > 35 kg/m^2 (0.25%). Although the risk of NRM in patients with BMI > 35 kg/m^2 tended to be higher than that in patients with normal BMI (2-year NRM 25.6% vs 21.9%), this difference was not statistically significant, possibly because of the limited number of patients. Theoretically, Japanese patients compared to Caucasian patients should have less GVHD because of less HLA gene variability and less obesity because of diet. Therefore, the findings of this study could be even more pronounced in Caucasian patients, which should be assessed using data of Caucasian patients.

In the current study, obese patients (BMI ⩾ 30 kg/m^2) had a higher risk of NRM, and particularly GVHD-related NRM, compared with those with normal BMI. In addition, obese patients had a worse outcome than those with normal BMI when patients developed grade II–IV or grade III–IV acute GVHD. One possible reason why obese patients had a higher risk of GVHD-related death is the higher incidences of hepatic and gut acute GVHD in comparison with patients with normal BMI, which have been reported to be associated with a poor response to GVHD therapy and an increased risk of NRM.[13–16] One hypothesis is that the greater tissue damage caused by the higher dose of chemotherapy in obese patients may contribute to the induction of cytokine storms, which leads to severe acute GVHD.[17] Another hypothesis is that the different immune status in obesity affects the functional status of immune cells after allogeneic HSCT. It has been reported that, in obese patients, the number of adipose tissue-resident immune cells, such as macrophages, CD8$^+$ T cells and IFN-γ Th1$^+$ cells, is increased, and the number of regulatory T cells is decreased.[18–20] Such an obesity-induced shift in adipose tissue-resident immune cells might increase the alloimmune reaction

Table 3. Multivariate analysis of NRM, outcome and significant factor

	Hazard ratio	*95%CI*	*P-value*
NRM			
Body mass index			
Underweight	0.93	0.83–1.06	0.28
Normal	1		
Overweight	1.19	1.06–1.33	0.004
Obesity	1.43	1.08–1.88	0.012
Age			
Age < 50	1		
Age ⩾ 50	1.62	1.47–1.77	< 0.001
HLA mismatch			
Match	1		
Mismatch	1.45	1.31–1.60	< 0.001
Sex combination			
Female to male	1.30	1.18–1.43	< 0.001
Others	1		
Performance status			
0–1	1		
2–4	1.44	1.26–1.63	< 0.001
Stem cell source			
Related BM	1		
Related PBSC	1.14	0.99–1.31	0.073
Unrelated BM	1.70	1.50–1.92	< 0.001
Conditioning regimen			
Myeloablative	1		
Reduced-intensity	0.90	0.81–0.99	0.027
Year of transplant			
< 2007	1		
⩾ 2007	0.72	0.67–0.79	< 0.001
Infection-related NRM			
Body mass index			
Underweight	0.9	0.71–1.13	0.35
Normal	1		
Overweight	1.34	1.09–1.64	0.006
Obesity	1.05	0.57–1.92	0.89
Age			
Age < 50	1		
Age ⩾ 50	1.82	1.56–2.13	< 0.001
HLA mismatch			
Match	1		
Mismatch	1.49	1.24–1.78	< 0.001
Sex combination			
Female to male	1.30	1.09–1.55	0.004
Others	1		
Performance status			
0–1	1		
2–4	1.45	1.16–1.80	0.001
Stem cell source			
Related BM	1		
Related PBSC	1.15	0.88–1.49	0.31
Unrelated BM	1.64	1.30–2.06	< 0.001
Year of transplant			
< 2007	1		
⩾ 2007	0.71	0.61–0.83	< 0.001
GVHD-related NRM			
Body mass index			
Underweight	0.79	0.55–1.12	0.18
Normal	1		
Overweight	1.26	0.93–1.72	0.14
Obesity	2.15	1.20–3.86	0.010
HLA mismatch			
Match	1		
Mismatch	1.44	1.11–1.87	0.007
Disease risk			
Standard	1		
High	1.44	1.15–1.82	0.002
Stem cell source			
Related BM	1		
Related PBSC	1.40	0.94–2.07	0.098
Unrelated BM	1.67	1.18–2.36	0.004
Year of transplant			
< 2007	1		
⩾ 2007	0.74	0.59–0.93	0.009

Abbreviation: NRM = non-relapse mortality.

after allogeneic HSCT as reported in the field of organ transplantation, as reviewed previously.[21] Intriguingly, previous studies have reported that Caucasian patients had an increased risk of acute GVHD compared to Asian patients.[22,23] The huge difference in BMI among races might at least partially influence the incidence of acute GVHD.

The obese patients in this study had a substantially increased risk of stage 2–4 acute GVHD in the liver (HR 2.00, 95% CI 1.26–3.17). Considering the mortality associated with hepatic acute GVHD, we should intervene to reduce the risk of hepatic acute GVHD in obese patients.[13–16] It is well-known that a prominent obesity-induced immune shift in the liver, so-called non-alcoholic steatohepatitis, causes inflammation in the liver, which might contribute to the subsequent increased risk of hepatic acute GVHD.[18,24] Practically, careful monitoring and early institution of high-dose immunosuppression are suggested. As a possible intervention, weight loss by diet and exercise could be a safe option, and has been shown to dose-dependently improve histological disease activity in non-alcoholic steatohepatitis associated with obesity.[25,26]

In terms of the impact of being underweight, several previous studies have also reported that being underweight was associated with a poor outcome after allogeneic HSCT.[4,27,28] Navarro *et al.*[4] has reported that OS in AML patients with BMI at transplant < 18 was inferior to that in patients with a normal BMI in patients who received stem cells from related donors, but not in the unrelated donor group. In terms of relapse, the relative risk of relapse was reduced for the overweight (relative risk 0.82, 95%CI 0.68–0.99, $P = 0.044$) and obese (relative risk 0.76, 95% CI 0.0.60–0.96, $P = 0.022$) groups. However, in terms of disease-free survival (Figure 2b in Navarro *et al.*[4]), there was a clear trend that the outcome in AML patients with BMI at transplant < 18 was inferior to that in patients with a normal BMI in patients who received stem cells from unrelated donors. The lack of statistical significance in unrelated HSCT might be because of a lack of power in the study (33 in 1801 patients). Underweight patients may have had more advanced disease compared with those with higher BMI, even though the proportion of patients with advanced disease was the same in the underweight and normal groups in this study. Shorter interval between diagnosis and transplant in the underweight group might suggest the aggressive nature of underlying disease. In a multivariate analysis, being underweight was associated with an increased risk of relapse independent of

Table 4. Multivariate analysis of relapse and OS, outcome and significant factor

	Hazard ratio	*95%CI*	P-*value*
Relapse			
Body mass index			
Underweight	1.16	1.06–1.28	0.002
Normal	1		
Overweight	0.86	0.77–0.96	0.008
Obesity	0.74	0.56–0.99	0.045
Age			
Age < 50	1		
Age ⩾ 50	1.11	1.03–1.20	0.001
Sex combination			
Female to male	0.89	0.81–0.97	0.007
Others	1		
Performance status			
0–1	1		
2–4	1.77	1.60–1.96	< 0.001
Conditioning regimen			
Myeloablative	1		
Reduced-intensity	0.86	0.80–0.93	< 0.001
Stem cell source			
Related BM	1		
Related PBSC	1.1	1.00–1.22	0.061
Unrelated BM	0.77	0.70–0.85	< 0.001
Disease risk			
Standard	1		
High	2.52	2.34–2.72	< 0.001
Year of transplant			
< 2007	1		
⩾ 2007	1.11	1.04–1.19	0.003
OS			
Body mass index			
Underweight	1.10	1.02–1.19	0.018
Normal	1		
Overweight	1.02	0.94–1.11	0.67
Obesity	0.95	0.76–1.19	0.67
Age			
Age < 50	1		
Age ⩾ 50	1.51	1.42–1.60	< 0.001
HLA mismatch			
Match	1		
Mismatch	1.33	1.25–1.43	< 0.001
Sex combination			
Female to male	1.10	1.03–1.18	0.005
Others	1		
Conditioning regimen			
Myeloablative	1		
Reduced-intensity	0.81	0.76–0.86	< 0.001
Performance status			
0–1	1		
2–4	2.31	2.14–2.49	< 0.001
Stem cell source			
Related BM	1		
Related PBSC	1.19	1.09–1.30	< 0.001
Unrelated BM	1.23	1.14–1.34	< 0.001
Year of transplant			
< 2007	1		
⩾ 2007	0.94	0.89–0.99	0.027

performance status and disease risk. When we performed a subgroup analysis that included only patients with high-risk disease, being underweight was still independently associated with a poor OS because of a significantly increased risk of relapse compared with the normal group (HR 1.11, 95% CI 1.01–1.22, $P = 0.027$). Furthermore, even when we grouped patients according to the conditioning regimen, the cumulative incidence of relapse was significantly higher in the underweight group compared with the other groups, irrespective of the type of the conditioning regimen. One possible explanation for why underweight patients had an increased risk of relapse is the insufficient dosage of chemotherapy compared with those in the other groups. In underweight patients, actual body weight is usually used to calculate the dose of chemotherapy. Therefore, the dose of chemotherapy in underweight patients should be lower than those in patients with normal or heavier body weight, considering the dose per ideal body weight. However, it is uncertain whether the adjusted dose of chemotherapy using an ideal body weight in patients with low BMI could lead to a better outcome without an increased risk of morbidities. In addition, several previous reports showed that the status of nutrition had an impact on the metabolism of the chemotherapeutic drugs.[29,30] For instance, nutritional status was reported to affect the level of cytochrome P450 enzymes which are responsible for the metabolism of the chemotherapeutic drugs. It was reported that there was a correlation between total body weight and plasma half-life of CY, which means that the concentration of CY is higher in obese patients compared with the normal weight patients.[31] Such changes in the metabolism of chemotherapeutic drugs might affect the risk of relapse and NRM in the setting of allogeneic HSCT.

An intervention that may improve the outcome is the amelioration of body weight loss before allogeneic HSCT. In general nutrition screening, BMI < 18.5 kg/m^2 is defined as an impaired nutritional status according to the European Society of Parenteral and Enteral Nutrition guidelines for 2002.[32] It may be possible to at least partially prevent pretransplant weight loss with some intervention including lifestyle modification, such as intensive nutritional support and exercise during induction and consolidation chemotherapy.[33,34] Exercise is important for maintaining skeletal muscle mass, and sufficient nutritional support is essential for preventing catabolism, since previous reports have demonstrated a high prevalence of sarcopenia before allogeneic HSCT.[33–35]

This study has some limitations. Because of the nature of the registry database, we were not able to assess the policies regarding adjustment of the conditioning regimen dose for patients with obesity, which will likely vary among the transplant centers. Another important limitation is that we included almost exclusively Japanese patients. Therefore, it is uncertain whether similar findings would be seen in other countries/regions. Our findings should be reassessed using other databases. Furthermore, because of the nature of the registry database, we were not able to assess the change of body weight and anthropometric measures before allogeneic HSCT. Although no standardized nutritional screening tool has been designed specifically for use in patients who undergo allogeneic HSCT, weight loss and anthropometric measures is in general regarded as an integral part of nutritional screening in most nutritional screening tool.[32,36,37] A recent study reported that pretransplant low arm muscle area was a stronger predictor than BMI of poor outcomes after HCT in children with hematologic malignancies.[38] The impact of pretransplant BMI, anthropometric measures and change of body weight should be assessed in the future studies.

In conclusion, we demonstrated that pretransplant BMI significantly affected the major post-transplant outcome. A prospective study to assess the impact of intervention including nutritional support and exercise is warranted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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A Descriptive Analysis of Post-Chemotherapy Development of Interstitial Lung Disease Using Spontaneous Reporting Data in Japan

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Abstract: This descriptive study used the Japanese spontaneous reporting data to investigate the time taken (TTILD) to development of interstitial lung disease (ILD) after initiation of chemotherapy and the death rates attributed in part to post-chemotherapy ILD (i.e., DR) for anticancer drugs. We evaluated TTILD and DR endpoints for 36 anticancer drugs, which are widely used for treating 11 solid and 3 hematological cancers, and are suspected of causing ILD, by using 8-year spontaneous reporting data recording for 2,553 patients in the reporting system of the relevant Japanese regulatory agency. The median TTILD and overall DR attributable to post-chemotherapy ILD for the drugs were 1.8 months and 29%, respectively. For most drugs, the median TTILDs were between 1 to 4 months, and the DRs attributable to post-chemotherapy ILD were <40%; however, TTILDs were as long as 4 to 6 months and DRs attributable to post-chemotherapy ILD were ≥40% for several other drugs. Of the 36 drugs, we identified those that may trigger post-chemotherapy late-onset ILDs or result in high DRs. The anticancer drugs that may have triggered late-onset ILDs were defined as those that caused ILD development after approximately 4 months from the initial drug administration.

Keywords: Adverse drug-reaction reporting, anticancer drug, epidemiology, interstitial lung disease, post-marketing surveillance, spontaneous report.

INTRODUCTION

Drug-induced lung injury includes involvement of the airways, lung parenchyma, media stinum, pleura, pulmonary vasculature, the neuromuscular system, or any combination of these. The most common form of drug-induced lung injury is drug-induced interstitial lung disease (DILD). DILD, which is a notable adverse drug reaction for both patients and the physicians, is a life-threatening disease, with risks increasing following chemotherapy. DILD particularly caused alarm in Japan after a high death rate was noted in non-small-cell lung cancer (NSCLC) patients receiving gefitinib.

The Japanese regulatory agency approved gefitinib for treating advanced NSCLC in July 2002. Between July and October 2002, more than 7,000 patients received gefitinib. DILD was observed in 26 patients and 13 of those died of DILD. Based on evaluation of clinical data from these patients, the Japanese health authority determined that DILD developed at an early stage after gefitinib administration and that patients' conditions deteriorated rapidly [1]. The health authority immediately published an emergency safety report on gefitinib safety in October 2002.

Thenceforth, many other studies evaluated DILDs due to several other anticancer drugs. Some have focused on DILD incidence rates and identification of risk factors particularly associated with epidermal growth factor receptor-tyrosine kinase inhibitors, including gefitinib and erlotinib [2-6]. DILD caused by tyrosine-kinase-inhibitor therapy for NSCLCs has also been discussed [7, 8].

However, DILDs-associated with other molecularly targeted (MT) or cytotoxic drugs have not been investigated in detail. Some previous reports were generally case series [9-13]. Furthermore, the documented DILDs in the literature were reported to develop within 3 months [2-4, 6] while these studies focused on rapid-onset DILD after treatment initiation.

We occasionally encounter patients who develop DILD after long-term treatment (e.g., 3 or 4 months after starting treatment). It is useful to record the time from the start of drug administration to DILD development (TTDILD) and the death rates attributed in part to the ILD due to widely

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used anticancer drugs. However, gathering a sufficient number of patients who developed DILD for evaluating TTDILD and death rates for every anticancer drug is difficult.

To address this issue, we used the spontaneous reporting data collected by the Japanese Adverse Drug Event Reporting System (JADERS), a database containing information on adverse drug reactions submitted to the Japanese regulatory agency. However, some limitations exist when analyzing time taken to post-chemotherapy interstitial lung disease (ILD) development (TTILD) and the death rates partially attributed to the post-chemotherapy ILD (i.e., DR) by using spontaneous reports (as discussed in the Methods and Discussion sections). Using spontaneous reports, we identified 36 anticancer drugs suspected of causing ILDs and used for treating 11 solid and 3 hematological cancers. We further defined the drugs as those that may trigger late-onset post-chemotherapy ILDs or yield high DRs attributed partially to post-chemotherapy ILD. We analyzed the TTDILD and DRs for each drug in a descriptive manner.

METHODS

Spontaneous Reporting Data Recorded by JADERS

To ensure that a novel or clinically important risk factor is not overlooked or reported too late, health authorities in the United States (US), the European Union (EU), Japan, and elsewhere require toxicity information to be reported promptly and periodically. For investigated drugs, suspected or unexpected toxicity findings that are life threatening or result in death require mandatory reporting to the US, EU, Japanese, and other regulatory authorities within 7 days; all other suspected or unexpected serious events must be reported within 15 days. Regulations for post-marketing reporting are similar but slightly different. For unsolicited (for example, spontaneously reported without any prompting from the manufacturer) post-marketing adverse-event reports, a causal relationship is assumed. Insolicited post-marketing information, causality (unlike spontaneous reports) is not assumed. We, therefore, covered patient's spontaneous reporting data upon administration of anticancer drugs and DILD development, because the anticancer drugs described in the spontaneous reports were suspected to cause ILDs.

For example, if an NSCLC patient received gefitinib and developed ILD, the patient's physicians must examine the causal relationships between gefitinib and the ILD development based on clinical, laboratory, and imaging data. If a causal relationship cannot at least be denied, the physicians will send a spontaneous report, including the information shown in Table **1**, to the JADERS. In this case, this ILD would be reported as a gefitinib-induced ILD. Notably, the ILD definition and diagnosis, and additional methods used to determine the causality between the drugs and ILD development would not be uniform among reporters.

Recently, the Japanese regulatory agency publically released the spontaneous reporting data gathered from April 2004. The data set we analyzed in this study can be downloaded from http://www.info.pmda.go.jp/fukusayou/consentDownLoad.html (in Japanese). In this study, we focused on 36 anticancer drugs that reportedly cause ILD and are widely used for treating 11 solid and 3 hematological cancers (Table **2**). Among the spontaneous reports between April 2004 and March 2012, we extracted 3,480 reports of 2,553 patients, who received at least 1 of the 36 drugs, had any 1 of the 14 cancers, and subsequently developed ILD likely as a result of drug treatment. For each spontaneous report, we collected the following data: (1) primary cancer, age, and sex; (2) the anticancer drug used for treating the primary cancer and suspected of causing ILD; (3) the time from initiation of drug administration to ILD development, which was defined as TTILD; and (4) information on whether the patient had died and if the patient's death was attributed partially to DILD.

When 2 or more drugs were used as combination chemotherapy, the "drug's reported role in the event" was reported for each drug under the Drug category in Table **1**. For example, when a patient received a combination chemotherapy including drugs A, B and C, and subsequently developed ILD possibly due to any of the drugs, the suitable role in ILD was selected for each drug among the 4 variables (i.e., primary suspect drug, suspect drug, concomitant, or

Table 1. Information contained in the spontaneous reports.

Category	Variable
Demographics	Report identification number (unique number identifying a JADERS report; a patient may have 1 or more reports. If correctly linked, a follow-up report would have the same case number as the initial report); patient's sex (unknown, male, female, or not specified); patient's age, weight, and height at onset of an adverse drug reaction; fiscal year and quarter reports were sent; and reporter's occupation (physician, pharmacist, other healthcare professional, lawyer, or consumer).
Drug	Report identification number; drug's reported role in event (primary suspect drug, suspect drug, concomitant, or interacting); drug name; drug administration route (for example, oral intake, intravenous injection, or intramuscular injection); date therapy was started (or re-started) for this drug (YYYYMMDD, YYMM, or YY format); date therapy was stopped for this drug (YYYYMMDD, YYMM, or YY format); number of times drug administration occurred during a single cycle; reason for the drug usage; drug treatment (stopped, decreased, increased, no change in dose, unknown, or does not apply); and reaction recurrence if the drug therapy was restarted (yes, no, or unknown).
Adverse drug reaction	Report identification number; preferred term ("preferred term" level medical terminology describing the event, using the Medical Dictionary for Regulatory Activities (MedDRA); patient outcome (cured, improvement, improvement with a persistent symptom or dysfunction, non-improvement, death attributed in part to an adverse drug reaction, or unknown); and date adverse drug reaction occurred or began (YYYYMMDD, YYMM, or YY format).
Disease	Report identification number; disease information (primary disease, complication, and other).

Table 2. List of the 36 suspected drugs likely responsible for ILD, as well as their TTILD and DR attributed in part to post-chemotherapy ILD. A patient who received multiple drugs was included in each drug category; for example, in case a patient received a combination therapy with gemcitabine and carboplatin for lung cancer, the patient was counted in both drug categories.

RN	Cancer	Classification	Drug	Total	Death	DR	TTILD	RN	Cancer	Classification	Drug	Total	Death	DR	TTILD
1	Breast	Antimetabolite	Capecitabine	19	5	26.3	10.9	45	Pancreas	Small molecule	Erlotinib*	1	0	0	1.8
2	Breast	Alkylating	Cyclophosphamide	51	6	11.8	2.5	46	Pancreas	Antimetabolite	Gemcitabine	161	36	22.4	2.5
3	Breast	Microtubule	Docetaxel	48	11	22.9	2	47	Prostate	Microtubule	Docetaxel	77	39	50.6	2.1
4	Breast	Microtubule	Eribulin	8	1	12.5	0.9	48	Ovarian	Platinum	Carboplatin	7	2	28.6	0.9
5	Breast	Antimetabolite	Fluorouracil	25	2	8	2.2	49	Ovarian	Platinum	Cisplatin	4	2	50	3.8
6	Breast	Antimetabolite	Gemcitabine	6	2	33.3	0.5	50	Ovarian	Microtubule	Docetaxel	6	0	0	2
7	Breast	Small molecule	Lapatinib*	3	0	0	6.8	51	Ovarian	Topoisomerase	Doxorubicin	10	1	10	1.6
8	Breast	Microtubule	Paclitaxel	61	10	16.4	1.7	52	Ovarian	Antimetabolite	Gemcitabine	7	1	14.3	1.8
9	Breast	Antibody	Trastuzumab*	52	9	17.3	1.8	53	Ovarian	Microtubule	Paclitaxel	9	2	22.2	0.9
10	Breast	Microtubule	Vinorelbine	15	3	20	2.5	54	Uterine	Platinum	Carboplatin	6	0	0	1.9
11	Colon	Antibody	Bevacizumab*	91	22	24.2	4.7	55	Uterine	Platinum	Cisplatin	6	2	33.3	5.1
12	Colon	Antimetabolite	Capecitabine	34	12	35.3	3.2	56	Uterine	Microtubule	Docetaxel	5	0	0	2.4
13	Colon	Antibody	Cetuximab*	19	13	68.4	1.6	57	Uterine	Antimetabolite	Gemcitabine	6	0	0	2.6
14	Colon	Antimetabolite	Fluorouracil	214	61	28.5	4.8	58	Uterine	Microtubule	Paclitaxel	10	1	10	1.4
15	Colon	Topoisomerase	Irinotecan	118	38	32.2	1.5	59	Leukemia	Antimetabolite	Cytarabine	6	1	16.7	0.9
16	Colon	Platinum	Oxaliplatin	213	72	33.8	5	60	Leukemia	Antimetabolite	Fludarabine	2	0	0	0.6
17	Colon	Antibody	Panitumumab*	7	2	28.6	2.8	61	Leukemia	Small molecule	Imatinib*	43	4	9.3	4.6
18	Colon	Antimetabolite	TGO	46	11	23.9	2	62	Leukemia	Small molecule	Nilotinib*	2	1	50	5.8
19	Esophageal	Platinum	Cisplatin	4	1	25	4.2	63	ML	Alkylating	Bendamustine	3	2	66.7	4.8
20	Esophagus	Microtubule	Docetaxel	26	11	42.3	1.6	64	ML	Alkylating	Cyclophosphamide	78	11	14.1	2.5
21	Esophagus	Antimetabolite	Fluorouracil	9	3	33.3	3.3	65	ML	Topoisomerase	Doxorubicin	42	4	9.5	3
22	Gastric	Platinum	Cisplatin	10	4	40	6	66	ML	Topoisomerase	Etoposide	7	0	0	2.5
23	Gastric	Microtubule	Docetaxel	20	5	25	2.1	67	ML	Antimetabolite	Fludarabine	1	1	100	1.1
24	Gastric	Antimetabolite	Fluorouracil	3	2	66.7	0.8	68	ML	Antibody	Rituximab*	113	19	16.8	1.9
25	Gastric	Topoisomerase	Irinotecan	19	4	21.1	2	69	ML	Microtubule	Vincristine	55	9	16.4	2.6
26	Gastric	Platinum	Oxaliplatin	2	2	100	2.8	70	MM	Small molecule	Bortezomib*	47	6	12.8	0.5
27	Gastric	Microtubule	Paclitaxel	63	26	41.3	1.4	71	MM	Other	Lenalidomide	2	1	50	1
28	Gastric	Antimetabolite	TGO	104	37	35.6	2								
29	Renal	Small molecule	Everolimus*	6	0	0	2.6								
30	Renal	Small molecule	Sorafenib*	6	2	33.3	0.5								
31	Renal	Small molecule	Sunitinib*	13	1	7.7	1								
32	Hepatic	Small molecule	Sorafenib*	35	16	45.7	1.6								
33	Lung	Topoisomerase	Amrubicin	43	10	23.3	0.6								
34	Lung	Antibody	Bevacizumab*	24	6	25	2.5								
35	Lung	Platinum	Carboplatin	91	42	46.2	1.4								
36	Lung	Platinum	Cisplatin	28	12	42.9	1.8								
37	Lung	Microtubule	Docetaxel	133	47	35.3	1.3								
38	Lung	Small molecule	Erlotinib*	96	32	33.3	0.7								
39	Lung	Small molecule	Gefitinib*	607	209	34.4	0.9								
40	Lung	Antimetabolite	Gemcitabine	114	34	29.8	1.8								
41	Lung	Topoisomerase	Irinotecan	37	12	32.4	1.4								
42	Lung	Microtubule	Paclitaxel	68	27	39.7	1.2								
43	Lung	Antimetabolite	Pemetrexed	84	26	31	1.2								
44	Lung	Microtubule	Vinorelbine	89	22	24.7	1.4								

RN, reference number; TTILD, time to post-chemotherapy ILD development (months); DR, death rate (%);TGO, tegafur, gimeracil, and oteracil; MM, multiple myeloma; ML, malignant lymphoma; *, Molecularly targeted agent.

interacting). We, therefore, could identify a primary (i.e., most relevant) drug suspected of causing the ILD. However, we included all the suspected drugs (i.e., both of "primary suspect drug" and "suspect drug") into the analysis in this study because the criterion on determination of "primary suspect drug" would be varied depending on different reporters.

Working Definitions of Post-Chemotherapy ILD and DR

In this study, we extracted 3,480 reports of cancer patients who received anti-cancer drug(s) and subsequently developed ILDs likely due to the drug(s) used. Each included drug was either a "primary suspect drug" or "suspect drug" in the spontaneous reports. We defined the ensuing ILD as "post-chemotherapy ILD." Notably, the term "post-chemotherapy ILD" does not necessarily mean drug-induced ILD, the presence of which should be rigorously determined based on physical examinations, symptoms, pulmonary function tests, and imaging data.

Furthermore, from the report, we extracted the outcome of the post-chemotherapy ILD (i.e., cured, improvement, improvement with a persistent symptom or dysfunction, non-improvement, death attributed in part to an adverse drug reaction, or unknown; Table **1**, Adverse drug reactions). Therefore, we could determine whether the death is attributed in part to post-chemotherapy ILD. We defined DR as the proportion of reported patients whose deaths were attributed in part to post-chemotherapy ILD, among the reports of patients who developed post-chemotherapy ILD.

Statistical Analyses

TTILD and DR were calculated for a total of 36 suspected anticancer drugs, which included 12MT and 24 non-MT drugs. We compared the TTILD and DR data between the MT and non-MT drugs. We also assessed the association of sex (male or female), age (<40, 40-59, 60-79, or ≥80 years), and drug class (alkylating, antimetabolite, topoisomerase, platinum, microtubule, antibody, small molecule, or other) with TTILD (or DR). The TTILD and DR data were compared using the Wilcoxon rank sum test (or Kruskal-Wallis test) and χ^2 test, respectively. A two-sided *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using the SAS software (version 9.3, SAS Institute Inc., Cary, NC, USA).

RESULTS

Sex and Age

Among the 2,553 patients in the 3,480 reports, 1,723 (68%) were men, and 830 (32%) were women. With respect to age distribution, the number of patients aged <30, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79, and ≥80 years were 12 (0.5%), 27 (1%), 91 (4%), 351 (14%), 793 (31%), 1,023 (40%), and 256 (10%), respectively.

Time to ILD Development

The median values of TTILD for all 36 drugs (3,480 reports), the 24 non-MT drugs (2,450 reports), and the 12 MT drugs (1,030 reports) were 1.8 months (inter-quartile range [IQR], 0.8-3.4 months), 2.1 months (IQR, 1.1-4.1 months), and 1.1 months (IQR, 0.5-2.8 months), respectively. The TTILDs for the MT drugs were significantly shorter than those for non-MT drugs ($P< 0.001$).

Fig. (**1**) shows the scatter plot for the TTILD and DR of each drug and cancer. The reference number shown in Fig. (**1**) corresponds to that shown in Table **2**. We found that the TTILDs for most drugs were between 1 and 4 months, while they were as long as approximately 4-6 months for several drugs, including (1) capecitabine and lapatinib for breast cancer; (2) bevacizumab, fluorouracil, and oxaliplatin for colon cancer; (3) cisplatin for esophageal, gastric, ovarian, and uterine cancers; (4) imatinib and nilotinib for leukemia; and (5) bendamustine for multiple lymphoma. Since fluorouracil and oxaliplatin are used as a well-known combination therapy in colon cancer as folinic acid, fluorouracil, and oxaliplatin (FOLFOX), their corresponding TTILDs were also similar. Cisplatin may commonly trigger a longer TTILD in esophageal, gastric, ovarian, or uterine cancers, although the sample size for each cancer was ≤10.

Death Rates

The DRs for all 36 drugs, the 24 non-MT drugs, and the 12 MT drugs were 29% (1,018/3,480), 28% (708/2,450), and 30% (310/1,030), respectively. The DRs between the MT and non-MT drugs were not significantly different ($P= 0.488$).

According to Fig. (**1**), the DRs for most drugs were <40%, whereas DRs were ≥40% for several drugs, including (1) cetuximab for colon cancer; (2) docetaxel for esophageal cancer; (3) cisplatin, fluorouracil, oxaliplatin, and paclitaxel for gastric cancer; (4) sorafenib for hepatic cancer; (5) carboplatin and cisplatin for lung cancer; (6) docetaxel for prostatic cancer; (7) cisplatin for ovarian cancer; (8) nilotinib for leukemia; (9) bendamustine and fludarabine for malignant lymphoma; and (10) lenalidomide for multiple myeloma. We also noted that for colon cancer, the DRs for all drugs were between 20% and 40%. In the case of lung cancer, the DRs for all the drugs were also between 20% and 40%, which was likely because many of the drugs were generally given in combination.

ASSOCIATION BETWEEN PATIENT CHARACTERISTICS AND ILD-RELATED OUTCOMES

We assessed the association of sex, age, and drug class with TTILD (or DR) (Table **3**). Increased age, male gender, and drug class were significantly associated with death rate. ILD, which developed 1.8 months after the administration of chemotherapy (median value obtained from 3,480 reports), did not significantly associate with death. Additionally, the times to post-chemotherapy ILD were similar between sexes and age groups, while there were significant differences depending on the drug class. Among the drug classes, TTILD was the shortest for small molecule agents (1 month), while it was the longest for platinum agents (3.7 months).

DISCUSSION

This is the first study to compare descriptively the TTILD and DRs across different drugs and cancers by using

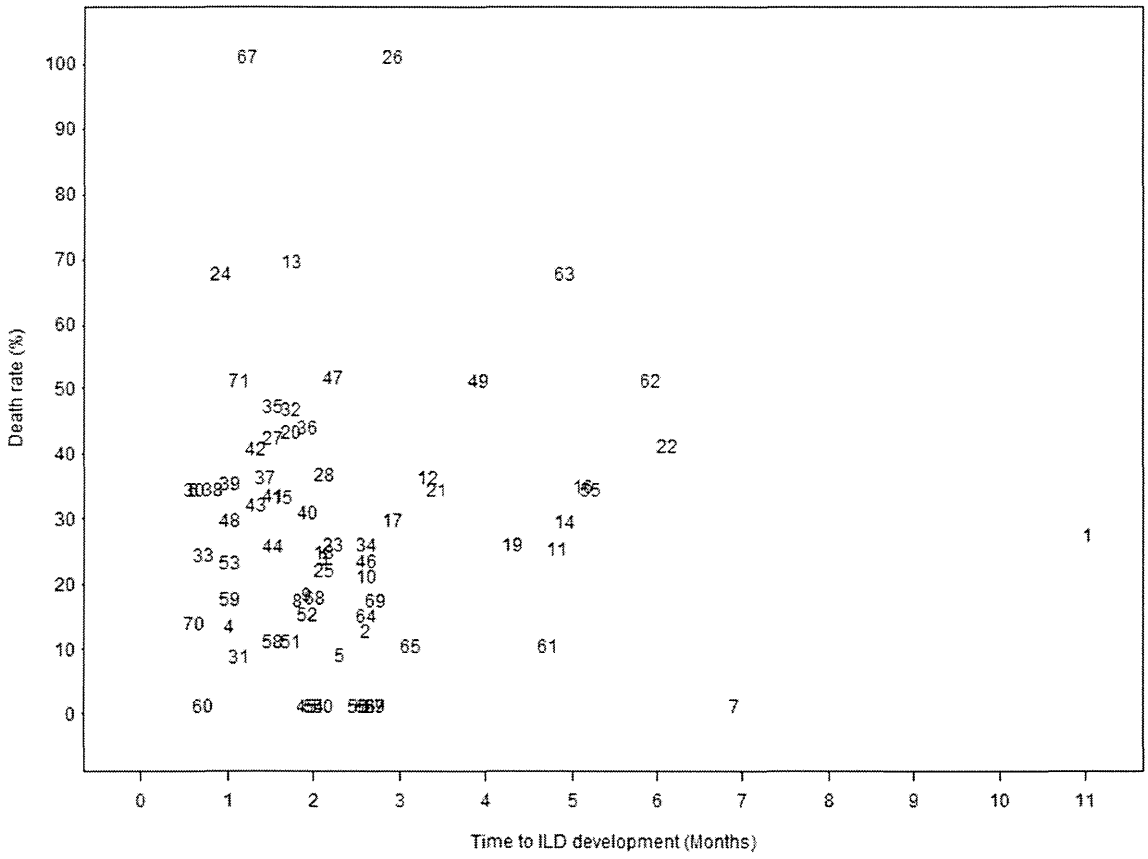

Fig. (1). Scatter plot of the time to post-chemotherapy ILD and DR for each drug and cancer. The reference numbers shown in Fig. (**1**) correspond to those in Table **2**.

the Japanese spontaneous reporting data. We defined the anticancer-drugs-mediated late-onset ILD as ILD that developed after approximately 4 months from the initiation of drug administration. After excluding the drugs that had spontaneous reports as low as 10, our results may indicate that we should pay particular attention to late-onset post-chemotherapy ILD in patients who received the following: (1) capecitabine for breast cancer; (2) FOLFOX (corresponding to fluorouracil and oxaliplatin) with or without bevacizumab for colon cancer; and (3) imatinib for leukemia. We only found a few case reports on these drugs [14, 15].

Our study also showed that DRs attributed in part to post-chemotherapy ILD were approximately 20-40% for most drugs, similar to previous reports on gefitinib [3, 6]. This result indicates the need for careful drug monitoring, as in the case of gefitinib. After excluding the drugs that had spontaneous reports as low as 10, we found anticancer drugs that may yield high DRs≥40%, including (1) cetuximab for colon cancer, (2) docetaxel for esophageal or prostatic cancers, (3) paclitaxel for gastric cancer, (4) sorafenib for hepatic cancer, and (5) cisplatin and carboplatin for lung cancer.

Little is known about DILD associated with widely used anticancer drugs in standard chemotherapies. The global ILD incidence is not clearly known, but 2.5-3% of cases are drug-induced [16, 17]. Schwaiblmair *et al.* [18], showed that the major representatives of DILD-causing agents were anticancer drugs. The drugs we covered in our study were not included in the drug list presented by Schwaiblmair *et al.* [18]. These included amrubicin, bendamustine, capecitabine, carboplatin, cisplatin, eribulin, everolimus, fluorouracil, irinotecan, lenalidomide, nilotinib, oxaliplatin, panitumumab, pemetrexed, sorafenib, sunitinib, tegafur-gimeracil-oteracil, vincristine, and vinorelbine.

Schwaiblmair *et al.* [18], also reported that both extremes of age (i.e., childhood and old age) were generally associated with an increased risk of drug toxicity, but there is no scientific evidence in the literature that the gender influences the risk of DILD. Perez-Alvarez *et al.* [19], evaluated the characteristics of patients with ILD due to biological therapies and identified age over 65 years, later onset of ILD, frequent use of immunosuppressive drugs, and previous diagnosis of ILD as the risk factors of death attributable to ILD, whereas it was not associated with sex. On the other hand, Kelly *et al.* [20], evaluated the rheumatoid arthritis-related ILD (RA-ILD) and found that male gender and age were independently associated with RA-ILD. This higher frequency of RA-ILD in men may be due to the fact that smoking is strongly associated with ILD in men. The association of age and sex with ILD has been discussed in other diseases as well [21-23]. In this study, increased age was associated with death and the frequency of death in men was higher than that in women by 10% (Table **3**). Drug classification was also significantly associated with death. Thus, careful attention may be needed to the possibility of

Table 3. Association of patient characteristics with ILD-related outcomes.

Patient Characteristics		Number of Reports	Death n, %	P-Value	Time to ILD, Median, Months	P-Value
Sex	Male	2366	765 (32%)	<.0001	1.8	0.834
	Female	1114	253 (23%)		1.8	
Age (Years)	<40	64	8 (13%)	<.0001	1.9	0.551
	40-59	614	133 (22%)		1.8	
	60-79	2494	762 (31%)		1.8	
	≥80	308	115 (37%)		1.9	
Drug Classification	Alkylating	132	19 (14%)	<.0001	2.5	<.0001
	Antimetabolite	841	234 (28%)		2.5	
	Topoisomerase	276	69 (25%)		1.7	
	Platinum	371	139 (38%)		3.7	
	Microtubule	693	214 (31%)		1.6	
	Antibody	306	71 (23%)		2.5	
	Small molecule	859	271 (32%)		0.9	
	Other	2	1 (50%)		1.0	
Time to Post-Chemotherapy ILD	<1.8 months	1706	524 (31%)	0.063	-	-
	≥1.8 months	1774	494 (28%)		-	

deaths due to post-chemotherapy ILD in elderly or male patients after the use of platinum, microtubule targeting, or small molecule agents, although their use need not necessarily be restricted. High-resolution CT, KL-6, and surfactant protein-D (SP-D) before or during the treatment would be helpful in the assessment of benefit/risk of using anti-cancer drugs.

Although spontaneous reporting data do not include the patterns of ILD encountered, the Guideline for the Management of Drug-Induced Lung Disease by the Japanese Respiratory Society includes the imaging patterns most typical for each drug [24]. According to this guideline, acute interstitial pneumonia (AIP) and diffuse alveolar damage (DAD) are frequently encountered with the use of drugs including cyclophosphamide, gefitinib, erlotinib, cetuximab, panitumumab, and methotrexate; and cryptogenic organizing pneumonia (COP) and bronchiolitis obliterans organizing pneumonia (BOOP), with drugs such as bleomycin, methotrexate, and cyclophosphamide. Non-specific interstitial pneumonia (NSIP) and hypersensitivity pneumonia (HP) often occur with the use of methotrexate and gefitinib, respectively. Endo *et al.* [25], reported imaging patterns of gefitinib-related ILD using data from the West Japan Thoracic Oncology Group. According to this report, the following 2 patterns are mainly encountered with the use of gefitinib: (A) a nonspecific area with ground-glass attenuation, and (B) extensive bilateral ground-glass attenuation or airspace consolidations with traction bronchiectasis, such as in AIP. Thus, the above-mentioned patterns might be frequently occurring imaging patterns spontaneously reported to JADERS after treatment with anti-cancer drugs. In addition, Schwaiblmair *et al.* [18], reported histopathological patterns of interstitial pneumonia for numerous drugs.

There were several limitations in our approach of using the spontaneous reporting data from JADERS. The spontaneous reporting data primarily have reporting and selection biases; therefore, the results of this study should be interpreted carefully. Our TTILD and DR findings may be confounded by the disease prognosis with the drugs used; for example, because of the use of first-line drugs, patients with better prognoses who received first-line chemotherapies potentially had much longer TTILDs and lower DRs simply because their overall survival was generally much longer. The TTILD and DR may also be biased due to other confounding variables such as performance status, cumulative dose, and other prognostic or time-dependent variables. Although we compared TTILDs and DRs between MT and non-MT drugs, the differences might be confounded by indication. The spontaneous reports were not sufficiently detailed (e.g., clinical, laboratory, or imaging data) to properly define and diagnose ILDs and the additional causal relationships between the drugs used and ILD development. Therefore, those might vary depending on the reporters. Finally, pharmaceutical companies, medical institutions, patients, or any combination of these may possibly report the ILD simultaneously by chance; for example, rarely, 2 or more ILDs may be reported for the same patient.

Considering the above-mentioned limitations, our findings are hypothetical and should be verified in future investigations, such as a prospective cohort study. However, the list of the 36 suspected anticancer drugs, as well as the TTILDs and DRs, provides valuable information on drug-associated DILDs that escaped attention thus far by healthcare professionals involved in using these drugs for therapy. As we found that DR and TTILD varied depending on the drug class, we also recommend that patients who develop post-chemotherapy ILD should be managed depending on the class of the drug administered. For example, small molecule and platinum agents are similar in that they showed more than 30% of DRs, but TTILD between these agents are quite different. Furthermore, large, prospective, post-marketing studies including patients without post-chemotherapy ILD as controls would be

beneficial in order to examine the impact of drug class on ILD-related outcomes.

CONFLICT OF INTEREST

Dr. Hirakawa has received lecture fees and honoraria from Ono Pharmaceutical Co. Ltd., lecture fees from Taiho Pharmacuticals, and lecture fees and honoraria from Novartis Pharma KK, irrelevant to the submitted work.

Dr. Yonemori has received lecture fees from Taiho Pharmacuticals, irrelevant to the submitted work.

Dr. Kuwatsuka, Dr. Kodaira, Dr. Yamamoto, Dr. Yunokawa, Dr. Hamada, and Dr. Tamura have nothing to disclose.

Dr. Shimizu has received honoraria from Eisai, Novartis, Takeda Pharmaceutical, Astra Zeneca, and Roche-Chugai, and a grant from Boehringer-Ingelheim, irrelevant to the submitted work.

Dr. Gemma has received grants and lecture fees from Pfizer, and lecture fees from Chugai, irrelevant to the submitted work.

Dr. Fujiwara has received honoraria from AstraZeneca KK; honoraria from Eisai Co. Ltd.; honoraria from Ono Pharmaceutical Co. Ltd.; grants and honoraria from Kyowa Hakko Kirin Co. Ltd.; grants and honoraria from GlaxoSmithKline KK; grants and honoraria from Sanofi-Aventis KK; grants and honoraria from Daiichi Sankyo Co. Ltd.; grants and honoraria from Taiho Pharmaceutical Co. Ltd.; grants from Takeda Bio Development Center Ltd.; grants and honoraria from Chugai Pharmaceutical Co. Ltd.; honoraria from Eli Lilly Japan KK; grants from Nihon Boehringer Ingelheim Co. Ltd.; grants and honoraria from Novartis Pharma KK; grants from Pfizer Japan; honoraria from Bristol-Myers KK; grants from Janssen Pharmaceutical KK; grants from Kissei Pharmaceutical Co. Ltd.; and grants from Nippon Kayaku Co. Ltd, irrelevant to the submitted work.

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PATIENT CONSENT

Declared none.

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ORIGINAL ARTICLE

Positive impact of chronic graft-versus-host disease on the outcome of patients with *de novo* myelodysplastic syndrome after allogeneic hematopoietic cell transplantation: a single-center analysis of 115 patients

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Abstract

To evaluate the impact of graft-versus-host disease (GVHD) and prognostic factors for patients with myelodysplastic syndrome (MDS) after allogeneic hematopoietic cell transplantation (allo-HCT), we retrospectively reviewed 115 patients with MDS or acute myeloid leukemia with multilineage dysplasia (AML-MLD) after allo-HCT at our center. Eighty one patients received reduced-intensity conditioning (RIC) regimens, whereas 34 received myeloablative conditioning regimens. Although the RIC group was significantly older and included more patients with poor cytogenetic risk, no difference in 4-yr overall survival (OS) was seen between the two groups. In a multivariate analysis, covariates associated with a worse OS were the French-American-British stage of refractory anemia excess blasts in transformation/AML-MLD at peak, poor cytogenetic risk, bone marrow blasts of 20% or higher at HCT and the absence of chronic GVHD (cGVHD). By using semi-landmark analyses, we found that the presence of cGVHD significantly improved OS in high-risk patients or the RIC group. However, there was no difference in OS between those with and without cGVHD among low-risk MDS patients. These findings suggest that the graft-versus-leukemia effect may be more beneficial in high-risk patients who do not receive intensive preparative regimens.

Key words myelodysplastic syndrome; allogeneic hematopoietic cell transplantation; graft-versus-host disease; graft-versus-leukemia effect

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Allogeneic hematopoietic cell transplantation (allo-HCT) has been assumed to be the only treatment modality with curative potential for patients with myelodysplastic syndrome (MDS). However, about 90% of MDS cases occur in elderly patients above the age of 60 yrs (1) and a substantial proportion of them are more likely to have a worse performance status and an increased comorbidity. As a result, myeloablative conditioning (MAC) regimens are less commonly used for patients with MDS because of an increased risk of non-relapse mortality (NRM). However, some studies have reported that the dose intensity of the conditioning regimen plays an important role in controlling the disease after allo-HCT for MDS or acute myeloid leukemia (AML) (2, 3). Reduced-intensity conditioning regimens (RIC) have been developed to decrease the risk of NRM with less-intensive conditioning for elderly or less-fit patients while preserving a graft-versus-leukemia (GVL) effect by an alloimmune reaction as an antitumor effect (4, 5). The European Group for Blood and Marrow Transplantation reported that, among patients with MDS who underwent allo-HCT from a sibling donor, the RIC group was associated with a lower incidence of NRM and a higher risk of relapse in comparison with the

MAC group, whereas overall survival (OS) was similar in both groups (6).

Although an alloimmune reaction by donor T-cells is important for disease control after allo-HCT, especially in the RIC setting, the significance of this effect has not been well documented in patients with MDS. Therefore, we retrospectively reviewed the medical records of 115 patients with *de novo* MDS or AML with multilineage dysplasia (AML-MLD) who underwent their first allo-HCT at our center, and evaluated the impact of graft-versus-host disease (GVHD) and prognostic factors for the outcome in patients with MDS after allo-HCT.

Patients and methods

Patients

This study included patients with *de novo* MDS or AML-MLD who underwent their first allo-HCT at our center between January 2000 and December 2009. The study protocol was reviewed and approved by the institutional ethics committee. Therapy-related MDS and cord blood transplant recipients were excluded. Therapy-related MDS was defined as disease arising in patients who were treated with irradiation, chemotherapy, or both for hematologic malignancies or other cancers. Disease stages were categorized according to the French-American-British (FAB) classification (7). AML-MLD was defined as AML with more than 30% bone marrow (BM) myeloblasts and morphological features of myelodysplasia, or a prior history of MDS. Patients with MDS were classified into two diagnostic groups (Low/Intermediate-1 and Intermediate-2/High) at diagnosis and at peak according to the International Prognostic Scoring System (IPSS) (8). Cytogenetic risk groups were determined according to IPSS using the cytogenetic information at diagnosis. Matching between the donor and recipient was determined according to donor–recipient HLA-A, HLA-B, and HLA-DR compatibility.

Myeloablative conditioning regimens included cyclophosphamide (Cy, 60 mg/kg for 2 d) plus busulfan (Bu, orally 4 mg/kg for 4 d or i.v. 3.2 mg/kg for 4 d) (Bu/Cy) or total body irradiation (TBI, 12 Gy) (TBI/Cy). RIC regimens included Bu (orally 4 mg/kg for 2 d or i.v. 3.2 mg/kg for 2 d) plus fludarabine (Flu, 30 mg/m^2 for 6 d) (Flu/Bu) or cladribine (2-CdA, 0.11 mg/kg for 6 d) (2-CdA/Bu). In a subset of patients who received RIC, low-dose TBI (2 or 4 Gy) and/or low-dose antithymocyte globulin (ATG) (total dose 5–10 mg/kg Fresenius or 2.5–5 mg/kg Thymoglobulin) were added. GVHD prophylaxis included either cyclosporine or tacrolimus alone or a combination of either of the calcineurin inhibitors and methotrexate. The decision regarding the intensity of the conditioning regimen and GVHD prophylaxis for each patient was made at the discretion of the attending physicians based on a review of the patient's age, disease status, comorbidities, performance status and HLA compatibility.

Neutrophil and platelet engraftment dates were defined as the first of three consecutive days with an absolute neutrophil count of 0.5×10^9/L or higher and an untransfused platelet count of 2.0×10^9/L or higher. Acute and chronic GVHD (cGVHD) were diagnosed and graded according to standard criteria (9). Response and relapse of the disease were defined according to standard hematologic criteria.

Statistical analysis

We used the Chi-square analysis and Fisher's exact test to compare categorical covariates and the Mann–Whitney *U* test to compare continuous covariates. OS was estimated by the Kaplan–Meier method, and differences between groups were evaluated by the log-rank test. Relapse and NRM were considered as competing risk events for each other. The probabilities of relapse and NRM were estimated by the cumulative incidence functions, and differences between groups were evaluated by the Gray test (10, 11). OS and the incidences of relapse and NRM were estimated as probabilities at 4 yrs from allo-HCT. To evaluate the effect of cGVHD on OS, we performed semi-landmark analyses (12). For patients with cGVHD, OS was estimated as the probability from the onset of cGVHD by the Kaplan–Meier method. A landmark comparison group consisted of survivors without cGVHD at day 138 (landmark day), which was the median time of the onset of cGVHD with OS for this group estimated as the probability from the landmark day. The Cox proportional hazards regression model was used for univariate and multivariate analyses, and a hazard ratio was calculated in conjunction with a 95% confidence interval (CI). For the assumption of proportional hazards over time, acute GVHD (aGVHD) and cGVHD were treated as time-dependent covariates (13). For multivariate analyses, we decided to include covariates with a *P*-value of <0.1 in univariate analyses. In addition, we included conditioning regimens and GVHD in these models to evaluate their effects on the outcome. The statistical analysis was performed with R-Project (version 2.2.1; http://www.r-project.org/).

Results

Patient characteristics

The characteristics of a total of 115 patients are summarized in Table 1. The median age was 55 yrs (range: 19–68) and the median follow-up of surviving patients was 40 months (range: 4–130). Eighty one patients (70%) received RIC regimens, whereas 34 (30%) received MAC regimens. According to the FAB stage at peak, the proportions of patients with refractory anemia (RA)/refractory anemia with ringed sideroblasts (RARS), refractory anemia

Table 1 Patient characteristics

No. of patients	All $N = 115$	MAC $N = 34$	RIC $N = 81$
Period of HCT (%)			
2000–2004	71 (62)	18 (53)	53 (65)
2005–2009	44 (38)	16 (47)	28 (35)
Age at HCT, median (range)	55 (19–68)	46 (23–57)	57 (19–68)
Age at HCT, yrs			
≧50 yrs (%)	84 (73)	10 (29)	74 (91)
Patient sex, male (%)	82 (71)	24 (71)	58 (72)
FAB stage at diagnosis (%)			
RA/RARS	45 (39)	13 (38)	32 (40)
RAEB/CMMoL	44 (38)	12 (36)	32 (40)
RAEB-T/AML-MLD	26 (23)	9 (26)	17 (20)
IPSS at diagnosis (%)			
Low/Intermediate-1	37 (32)	13 (38)	24 (30)
Intermediate-2/High	64 (56)	16 (47)	48 (59)
Unknown	14 (12)	5 (15)	9 (11)
FAB stage at peak (%)			
RA/RARS	22 (19)	6 (18)	16 (20)
RAEB/CMMoL	38 (33)	10 (29)	28 (34)
RAEB-T/AML-MLD	55 (48)	18 (53)	37 (46)
IPSS at peak (%)			
Low/Intermediate-1	24 (21)	6 (18)	18 (22)
Intermediate-2/High	77 (67)	23 (68)	54 (67)
Unknown	14 (12)	5 (14)	9 (11)
Cytogenetic risk group (%)			
Good/Intermediate	75 (65)	27 (79)	48 (59)
Poor	40 (35)	7 (21)	33 (41)
BM blasts at HCT, median (range)	5 (0–78)	3 (0–46)	4 (0–78)
≦4%	60 (52)	18 (53)	42 (52)
5–19%	38 (33)	10 (29)	28 (35)
≧20%	10 (9)	3 (9)	7 (8)
Unknown	7 (6)	3 (9)	4 (5)
Disease duration, months, median (range)	9 (1–200)	8 (2–200)	10 (1–172)
Karnofsky score at HCT (%)			
90–100	96 (83)	29 (85)	67 (83)
Transfusion dependence (%)	89 (77)	27 (79)	62 (77)
Prior chemotherapy (%)	68 (59)	22 (65)	46 (57)
Donor (%)			
Related	55 (48)	12 (35)	43 (53)
Unrelated	60 (52)	22 (65)	38 (47)
HLA matching (%)			
HLA match (6/6)	101 (88)	31 (91)	70 (86)
HLA mismatch (5/6)	14 (12)	3 (9)	11 (14)
Source of stem cells (%)			
Peripheral blood	52 (45)	11 (32)	41 (51)
BM	63 (55)	23 (68)	40 (49)
Sex mismatch (%)			
Female donor/Male recipient	36 (31)	13 (38)	23 (28)
Other combination	79 (69)	21 (62)	58 (72)
Follow-up duration for survivors, months, median (range)	40 (4–130)	40 (4–130)	47 (4–125)
Conditioning regimen			
MAC (%)			
CY/TBI		15 (44)	
Bu/CY		19 (56)	
Reduced intensity conditioning			
Flu/Bu-based			65 (80)
2-CdA/Bu-based			16 (20)
TBI-containing			23 (28)
ATG-containing			26 (32)
GVHD prophylaxis (%)			
CSP			26 (32)
CSP+MTX		24 (71)	37 (46)
TAC			2 (2)
TAC+MTX		10 (29)	16 (20)

MAC, myeloablative conditioning; RIC, reduced intensity conditioning; HCT, allogeneic hematopoietic cell transplantation; FAB, French-American-British; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts; CMMoL, chronic myelomonocytic leukemia; RAEB-T, refractory anemia with excess blasts in transformation; AML-MLD, acute myeloid leukemia with multilineage dysplasia; BM, bone marrow; mons, months; CY, cyclophosphamide; TBI, total body irradiation; Bu, busulfan; ATG, antithymocyte globulin; Flu, fludarabine; 2-CdA, cladribine; CSP, cyclosporine; MTX, methotrexate; TAC, tacrolimus; GVHD, graft-versus-host disease; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome.

with excess blasts (RAEB)/chronic myelomonocytic leukemia (CMMoL), and refractory anemia excess blasts in transformation (RAEB-T)/AML-MLD were 19%, 33%, and 48%, respectively. According to the cytogenetic risk at diagnosis, the proportions of patients with good/intermediate and poor risk were 65% and 35%, respectively. According to the IPSS risk at peak, the proportions of patients with Low/Intermediate-1 and Intermediate-2/High were 21% and 67%, respectively, and 12% of the patients did not have evaluable data. BM blast counts at allo-HCT were 4% or less in 52%, 5–19% in 33%, 20% or higher in 9%, and not evaluable in 6%. The RIC group was significantly older than the MAC group (median, 57 vs. 46 yrs, $P < 0.001$) and included more patients with poor cytogenetic risk (41% vs. 21%, $P = 0.03$).

Conditioning regimen and GVHD prophylaxis

The conditioning regimen and GVHD prophylaxis are shown in Table 1. The MAC group included either Bu/CY or TBI/CY, followed by a combination of methotrexate and tacrolimus or cyclosporine. The RIC group included Flu/Bu or 2-CdA/Bu, followed by either cyclosporine or tacrolimus alone or a combination of either of the calcineurin inhibitors and methotrexate.