Pathol. Oncol. Res. (2012) 18:11–16
DOI 10.1007/s12253-011-9383-x

RESEARCH

Clinical Impact of Pre-transplant Pulmonary Impairment on Survival After Allogeneic Hematopoietic Stem Cell Transplantation

Kazuhiko Kakihana · Kazuteru Ohashi · Yuka Hirashima · Yutaka Murata · Takeshi Kobayashi · Takuya Yamashita · Hisashi Sakamaki · Hideki Akiyama

Received: 5 January 2011 / Accepted: 8 March 2011 / Published online: 1 April 2011

Abstract We retrospectively analyzed the clinical outcomes of patients with pulmonary impairment before undergoing allogeneic hematopoietic stem cell transplantation (HSCT) for the first time. Among 297 evaluable patients who underwent their first HSCT, 23 had restrictive, obstructive or mixed ventilatory impairment (n=9, 13 and 1, respectively). Males predominated among the patients with pulmonary impairment (p=0.037) and received a reduced intensity conditioning (RIC) regimen more frequently, although the difference did not reach statistical significance (p=0.05). Among 23 patients with pulmonary impairment, 9 underwent post-transplant pulmonary function tests and obstructive ventilatory impairment progressed only in 2 patients, both of whom developed bronchiolitis obliterans. Kaplan-Meier estimates of 3-year overall (OS) among patients with and without pulmonary impairment were 57% and 47%, respectively, and those of relapse-free survival (RFS) were 70%, and 68%, respectively, with no significant differences between the groups (OS, p=0.235; RFS, p=0.287). The rates of non-relapse mortality also did not significantly differ (p=0.835). Our results suggest that allogeneic HSCT is safe for patients with pulmonary impairment. The lower frequency of fatal pulmonary complications after HSCT and the RIC regimen might contribute to favorable survival rates.

Keywords Fatal pulmonary complication · Obstructive ventilatory impairment · Restrictive ventilatory impairment · Reduced intensity conditioning regimen

K. Kakihana (✉) · K. Ohashi · Y. Murata · T. Kobayashi · T. Yamashita · H. Sakamaki · H. Akiyama
Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital,
3-18-22 Honkomagome, Bunkyo-ku,
Tokyo 113–8677, Japan
e-mail: kakihana@cick.jp

Y. Hirashima
Pharmacy Division, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital,
Tokyo, Japan

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) can potentially cure various hematological diseases and numerous technical advances in HSCT allow HSCT to be applied even for elderly patients and/or those with mild organ dysfunction. However, vital organs must be evaluated using computed tomography (CT), echocardiography, magnetic resonance imaging and pulmonary function tests (PFT) to screen patients for HSCT eligibility because of the risk of life-threatening complications. Since pulmonary complications after HSCT represent major causes of morbidity and mortality, several reports have described post-transplant pulmonary complications such as infection, chronic GVHD of the lung, and changes in pulmonary function. In fact, several reports have described that pulmonary function parameters worsen after HSCT, although some of them are partially reversible [1–5]. Some investigations have also associated abnormal pre-transplant PFT with post-transplant pulmonary complications such as air flow obstruction [6–8]. However, the impact of pre-transplant pulmonary impairment on survival has not yet been determined. Thus, we retrospectively analyzed the clinical outcomes of patients with pulmonary impairment before HSCT.

Patients and Methods

Among the 319 patients who underwent a first allogeneic HSCT at our hospital between January 2004 and December 2009, we retrospectively reviewed the records of 297 who were evaluable. Those who underwent a second HSCT were excluded from the analysis. The median age of the patients was 42 (range: 16–67) years. All patients underwent spirometry immediately before HSCT, as well as pre-transplant evaluation by echocardiography, systemic CT and brain MRI. Pulmonary function parameters including vital capacity (VC), total lung capacity, residual volume, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and peak expiratory flow were measured, but we did not routinely determine the diffusing capacity of the lung for carbon monoxide (DLCO).%VC was defined as the ratio of predicted VC and FEV1% as a ratio of FVC. Restrictive, obstructive and mixed ventilatory impairment was defined as%VC<80%, FEV1%<70% and both%VC and FEV1%<80% and <70%, respectively [1, 9].

Patients underwent preparative therapies according to the primary disease and type of transplantation. Most patients with a lymphoid malignancy were conditioned with a myeloablative regimen comprising total body irradiation (TBI, 12 Gy) plus cytarabine (8 g/m^2) and cyclophosphamide (CY, 120 mg/kg). Most patients with myeloid malignancy were conditioned with a regimen comprising busulfan (BU, 16 mg/kg orally or 12.8 mg/kg intravenously) and CY (120 mg/kg). Total lymphoid irradiation (TLI, 7 Gy) was added to the BU/CY regimen for patients undergoing human leukocyte antigen (HLA)-mismatched or unrelated transplantation. Patients with severe aplastic anemia were also conditioned using a regimen that included TLI. Most patients undergoing the reduced intensity conditioning (RIC) regimen, received fludarabine (125 mg/m^2) and melphalan (120 mg/m^2), or fludarabine (180 mg/m^2) and busulfan (6.4 mg/kg intravenously), and 1 day TBI (4Gy). Prophylaxis for acute graft versus host disease (GVHD) consisted of a short course of methotrexate and cyclosporin A or tacrolimus (FK). Patients undergoing either unrelated or HLA-mismatched transplantation also received FK.

Continuous baseline characteristics were compared using the Mann–Whitney test and categorical characteristics were compared using the χ^2 test. Overall survival (OS) was calculated from the first transplantation to final follow-up or death. Relapse-free survival (RFS) was calculated from the first transplantation to the last follow-up or the date when underlying diseases relapsed. Non-relapse mortality

Table 1 Patients' characteristics

		Patients with normal pulmonary function n=274	Patients with pulmonary impairment n=23	Total n=297	P value
Age (y)	Median (range)	42 (16–67)	47 (18–66)	42 (16–67)	0.738
Gender	Male	154	18	172	0.037
	Female	121	5	126	
Regimen intensity	Myeloablative	243	17	260	0.05
	Reduced intensity	31	6	37	
TBI in conditioning regimen	Yes	118	17	135	0.113
	No	156	6	162	
HLA	Matched	179	19	198	0.091
	Mismatched	95	4	99	
Donor	Related	77	3	80	0.118
	Unrelated	197	20	217	
Diagnosis	Acute myeloid leukemia	117	11	128	0.329
	Myelodysplastic syndrome	37	3	40	
	Acute lymphoblastic leukemia	53	1	54	
	Chronic myeloid leukemia	23	1	24	
	Multiple myeloma	5	1	6	
	Other lymphoid malignancies[a]	19	4	23	
	Aplastic anemia and myelofibrosis	20	2	22	

[a] Other lymphoid malignancies include non-Hodgkin's lymphoma, Hodgkin's lymphoma and adult T cell leukemia/lymphoma.

HLA human leukocyte antigen; *TBI* total body irradiation

Table 2 Clinical characteristics of 23 patients with pulmonary impairment

Patient No	Age/ Gender	Primary disease	Conditioning regimen	Type of pulmonary impairment	Type of HSCT	Smoking history (number/ day *year)	Cause of pulmonary impairment	%VC before HSCT (%)	FEV1% before HSCT (%)	%VC after HSCT (%)	FEV1% after HSCT (%)	Inspection date (days after HSCT)	LONIPCs	Outcome (months)	Cause of death
1	53/M	AML	BU+Flud	M	UBMT	Yes (20*20)	Pulmonary tuberculosis	52.3	51.7				-	6†	Relapse
2	24/M	NHL	CA+CY	R	UBMT	No	Unknown	59	93.4				-	5†	Cardiomyopathy
3	54/M	AML	BU+CY	R	UBMT	Yes (30*30)	Unknown	63	79				-	6†	NA
4	32/F	HD	BU+CY	R	UBMT	No	Unknown	64.2	93				-	55	
5	21/M	AML	BU+CY	R	RPBSCT	No	Unknown	67.2	86.7	83.7	110.6	82	BO	57	
6	18/F	AML	BU+CY	R	UBMT	No	Unknown	72.6	96.3				-	9†	Relapse
7	47/F	AML	BU+CY	R	UBMT	Yes (15*26)	Unknown	75.8	88.9				-	16	
8	54/M	ATLL	L-PAM +Flud	R	UBMT	No	Metastatic calcification	76.1	71.7	79.6	88.6	145	-	8†	Relapse
9	18/M	AML	BU+CY	R	UBMT	No	Unknown	76.3	78.2				-	3†	Relapse
10	34/F	MM	CY	R	UBMT	No	Unknown	78.8	80.3	70.7	94.4	300	-	59	
11	54/M	ATLL	CY	O	UBMT	Yes	Emphysema, asthma	95	58.8				-	5†	Bacterial pneumonia
12	50/M	MDS	BU+CY	O	UBMT	NA	Emphysema, atelectasis	96.7	67.7				-	39	
13	61/M	AML	L-PAM +Flud	O	UCBSCT	Yes, (50*40)	Emphysema	99.2	67.7	92.7	72.9	64	-	13	
14	26/M	SAA	CY	O	UBMT	Yes, (10*3)	Unknown	105.2	63.8				-	71	
15	33/M	AML	IVBU+CY	O	UBMT	NA	Unknown	107.4	68.9				-	12†	Relapse
16	66/M	MDS	L-PAM +Flud	O	UCBSCT	Yes, (25*45)	Emphysema	110.3	67.7				-	4†	Engraftment failure
17	23/M	SAA	Flud+CY +ATG	O	UBMT	No	Unknown	112.6	64.1	106.2	65	172	-	20	
18	46/M	AML	CA+CY	O	RPBSCT	Yes	Emphysema	115.2	68.8				-	49†	Relapse
19	54/M	AML	BU+CY	O	UBMT	Yes, (40*30)	Emphysema	119.7	63				-	4†	Relapse
20	57/M	CML	BU+CY	O	RBMT	Yes, (30*35)	Emphysema	122.2	64.8	74.3	41.6	154	BO	67	
21	56/F	MDS	BU+CY	O	UBMT	No	Unknown	129.5	64.5	94.4	49.6	314	BO	18	
22	38/M	ALL	CA+CY	O	UBMT	Yes, (20*20)	Mycobacterium avium infection	137	69.8	129	77.2	440	OP	67	
23	62/M	AML	BU+Flud	O	UBMT	Yes, (50*45)	Emphysema	151.3	65.9	145	72.1	105	-	7†	Fungal pneumonia

M mixed; *O* obstructive; *R* restrictive. *HSCT* hematopoietic stem cell transplantation; *VC* vital capacity; *FEV* forced expiratory volume; *LONIPCs* late onset non-infectious pulmonary complications; *AML* acute myeloid leukemia; *NHL* non-Hodgkin's lymphoma; *HL* Hodgkin's lymphoma; *ATLL* adult T cell leukemia/lymphoma; *MM* multiple myeloma; *MDS* myelodysplastic syndrome; *SAA* severe aplastic anemia; *CML* chronic myelogenous leukemia; *ALL* acute lymphoblastic leukemia; *BU* busulfan; *Flud* fludarabine; *CA* cytosine arabinoside; *CY* cyclophosphamide; *L-PAM* melphalan; *ATG* anti-thymocyte globulin; *UBMT* unrelated bone marrow transplantation; *RPBSCT* related peripheral blood stem cell transplantation; *UCBSCT* unrelated cord blood stem cell transplantation; *RBMT* related bone marrow transplantation; *BO* bronchiolitis obliterans; *OP* organizing pneumonia; *NA* not available.

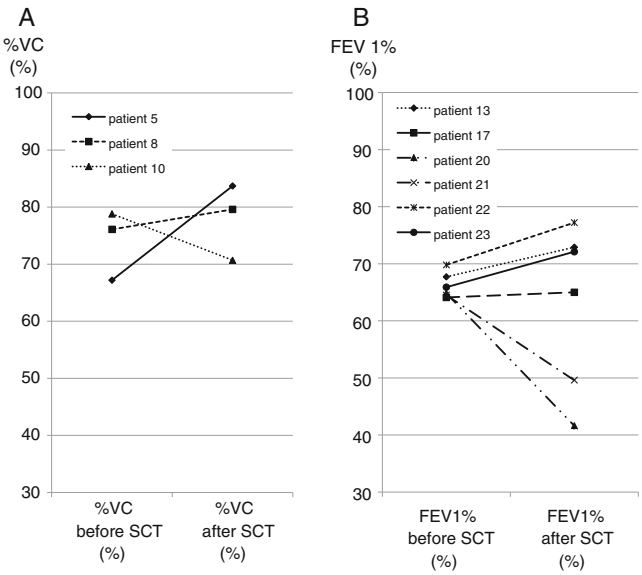

Fig. 1 Changes in pulmonary function. **a**,%VC in patients with restrictive pulmonary impairment; **b**, FEV1% in patients with obstructive pulmonary impairment

(NRM) was defined as death in the absence of relapse. Outcomes were estimated using Kaplan-Meier methods and compared using the log-rank test. All data were analyzed using PSPP II software (SPSS, Chicago, IL). All statistical tests were two-sided, and $p<0.05$ was considered statistically significant.

Results

Table 1 summarizes the patients' characteristics. Of 23 patients with pulmonary impairment before HSCT, 9, 13 and 1 had restrictive, obstructive and mixed ventilatory impairment, respectively. The median ages were 47 (range: 18–66) and 42 (rage: 16–67) years for those with and without pulmonary impairment, respectively. Age, use of TBI, HLA disparity, donor type and diagnosis did not significantly differ between patients with and without pulmonary impairment. Male patients predominated in the

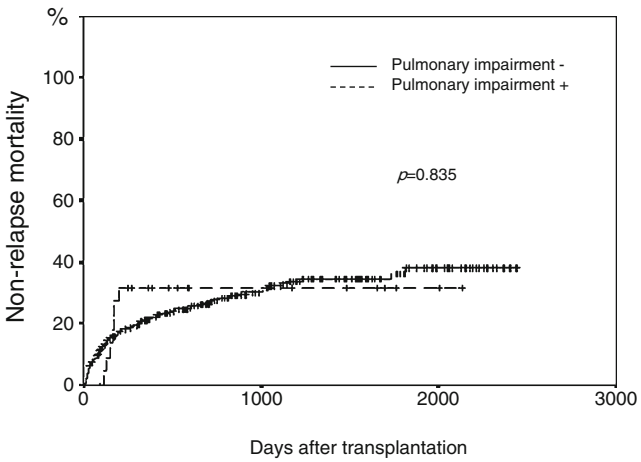

Fig. 3 Non-relapse mortality among patients with (solid line) or without (dotted line) pulmonary impairment

group with pulmonary impairment ($p=0.037$) and underwent the RIC regimen more frequently, although the value did not reach statistical significance ($p=0.05$). Nine of the 13 patients with obstructive ventilatory impairment had a smoking history. Emphysema was the main cause of the pulmonary impairment in 8 patients, of whom 7 had a smoking history, whereas the causes remained obscure in 8 patients with restrictive ventilatory impairment among whom only three had a smoking history (Table 2). Spirometry was performed after HSCT in 9 of 23 patients with pulmonary impairment (restrictive and obstructive ventilatory impairment, $n=3$ and $n=6$, respectively). Spirometric findings did not significantly change in most patients after HSCT (Fig. 1a and b). The FEV1% obviously worsened after HSCT in patient Nos. 20 (64.8% to 41.6%) and 21 (64.5% to 49.6%), both of whom developed bronchiolitis obliterans (BO), which is a sign of chronic GVHD. Twelve patients with pulmonary impairment died during the study (disease relapse, $n=7$; pulmonary complications, $n=2$; Table 2).

Kaplan-Meier estimates of 3-year OS and RFS were 57% and 70%, respectively for patients with normal pulmonary function and 47% and 68%, respectively for

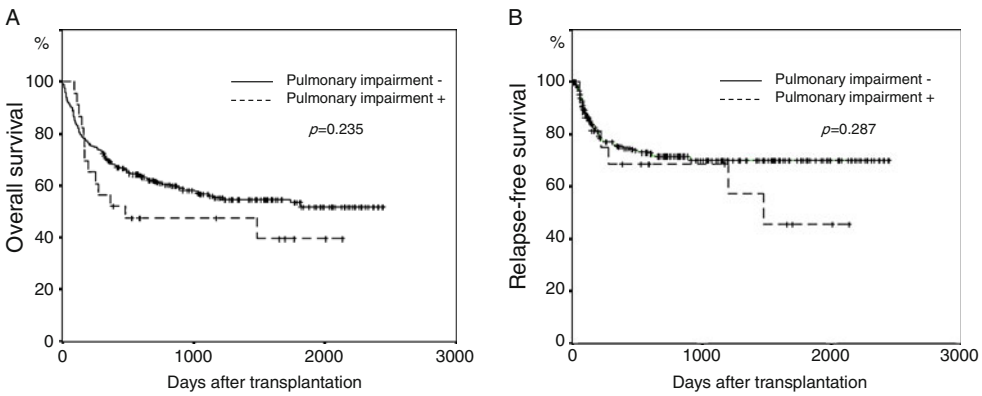

Fig. 2 Overall (**a**) and relapse-free (**b**) survival in patients with (solid line) or without (dotted line) pulmonary impairment

those with pulmonary impairment (no significant differences: OS, p=0.235; RFS, p=0.287; Fig. 2a and b) and NRM also did not significantly differ between the groups (p=0.835, Fig. 3).

Discussion

We retrospectively analyzed the clinical outcomes of patients with pulmonary impairment before HSCT. Among 297 evaluable patients, 23 (7.7%) had pulmonary impairment before HSCT. Although both OS and RFS tended to be inferior to those in patients with normal pulmonary function, the differences did not reach statistical significance. Thus, our results suggest that patients with pulmonary impairment can safely undergo allogeneic HSCT. The predominance of males with pulmonary impairment seemed attributable to smoking rates, which are about 4-fold higher among men than women in Japan. Among the 13 patients with obstructive ventilatory impairment, emphysema was the most frequent cause (n=8), and most (n=7) of these had a history of smoking.

Several reports have described a negative impact of HSCT on pulmonary function, especially among patients with pre-transplant pulmonary impairment [6–8]. One study found a higher risk of pulmonary complications after HSCT among patients with pre-transplant pulmonary impairment, although the incidence of fatal pulmonary complications was not significantly increased [10]. Of the 12 patients who died during the period of the present study, 7 died of disease relapse and only two died of pulmonary complications. Patients with pulmonary impairment tended to receive the RIC regimen more frequently although the difference did not reach statistical significance (p=0.05, Table 1). The RIC regimen is less toxic and non-myeloablative regimens minimally impact post-transplant pulmonary function in patients with CML [11]. Although the periods from HSCT to post-transplant PFT were quite variable in our cohort (median, 172 days after HSCT; range, 64–440 days; Table 2), FEV1% deteriorated in only two of the nine patients who received PFT after HSCT. These two developed BO as a sign of chronic GVHD, which seemed to be a main cause of a decline in PFT. Thus, the RIC regimen and a lower frequency of fatal pulmonary complication after HSCT might contribute to favorable patient survival and post-transplant pulmonary function.

Goldberg et al. studied early non-relapse mortality after HSCT and found that FEV1, performance status, serum creatinine and serum bilirubin were independent factors associated with early toxic death [12]. Furthermore, worsening FEV1 and DLCO are key definitions of comorbidity in the hematopoietic cell transplantation specific comorbidity index (HCT-CI) that can predict non-relapse mortality and survival [13]. Although the NRM in our study also did not significantly differ (Fig. 3), this might be partly due to a difference in the method by which pulmonary function was evaluated. We evaluated obstructive impairment using FEV1%, whereas both of the above reports used %FEV as a ratio of predicted FEV. Of 13 patients with obstructive ventilatory impairment, only 4 of them had a %FEV <80% (data not shown). However, emphysema was the cause of the obstructive ventilatory impairment in 9 of 13 of our patients; thus, evaluation based on FEV1% reflected respiratory status in our cohort. The HCT-CI scores other than pulmonary function were 0 or 1 in all patients with pulmonary impairment (score 0 in 14 patients, 1 in 9 patients, data not shown). This also might contribute to better outcome.

In summary, we analyzed clinical outcomes in patients with pulmonary impairment. Our data demonstrated a favorable clinical outcome and that HSCT can be safe in appropriate conditions depending on other comorbidities and the toxicity of conditioning regimen as well. A minimal number of fatal pulmonary complications after HSCT and the RIC regimen might have contributed to the favorable outcome. However, since this retrospective study investigated a small cohort, further studies are warranted to confirm the clinical impact of pre-transplant pulmonary function on patient survival.

Acknowledgments This study was supported in part by a grant for clinical cancer research from the Ministry of Health, Labor and Welfare of Japan. We would like to thank the staff of the Hematology Division at Tokyo Metropolitan Cancer and the Infectious Diseases Center, Komagome Hospital, for their excellent patient care.

Conflict of interest The authors declare no competing financial interests.

References

1. Marras TK, Szalai JP, Chan CK, Lipton JH, Messner HA, Laupacis A (2002) Pulmonary function abnormalities after allogeneic marrow transplantation: a systematic review and assessment of an existing predictive instrument. Bone Marrow Transplant 30:599–607
2. Badier M, Guillot C, Delpierre S, Vanuxem P, Blaise D, Maraninchi D (1993) Pulmonary function changes 100 days and one year after bone marrow transplantation. Bone Marrow Transplant 12:457–461
3. Gore EM, Lawton CA, Ash RC, Lipchik RJ (1996) Pulmonary function changes in long-term survivors of bone marrow transplantation. Int J Radiat Oncol Biol Phys 36:67–75
4. Chiou TJ, Tung SL, Wang WS, Tzeng WF, Yen CC, Fan FS et al (2002) Pulmonary function changes in long-term survivors of chronic myelogenous leukemia after allogeneic bone marrow transplantation: a Taiwan experience. Cancer Invest 20:880–888
5. Clark JG, Schwartz DA, Flournoy N, Sullivan KM, Crawford SW, Thomas ED (1987) Risk factors for airflow obstruction in recipients of bone marrow transplants. Ann Intern Med 107:648–656

6. El-Khatib M, Bou-Khalil P, Abbas O, Salman A, Jamaleddine G (2007) Value of pretransplant pulmonary function tests in predicting pulmonary complications after autologous peripheral stem cell transplantation. Lung 185:321–324
7. Savani BN, Montero A, Srinivasan R, Singh A, Shenoy A, Mielke S et al (2006) Chronic GVHD and pretransplantation abnormalities in pulmonary function are the main determinants predicting worsening pulmonary function in long-term survivors after stem cell transplantation. Biol Blood Marrow Transplant 12:1261–1269
8. Chien JW, Martin PJ, Gooley TA, Flowers ME, Heckbert SR, Nichols WG et al (2003) Airflow obstruction after myeloablative allogeneic hematopoietic stem cell transplantation. Am J Respir Crit Care Med 168:208–214
9. Chien JW, Madtes DK, Clark JG (2005) Pulmonary function testing prior to hematopoietic stem cell transplantation. Bone Marrow Transplant 35:429–435
10. Ghalie R, Szidon JP, Thompson L, Nawas YN, Dolce A, Kaizer H (1992) Evaluation of pulmonary complications after bone marrow transplantation: the role of pretransplant pulmonary function tests. Bone Marrow Transplant 10:359–365
11. Lee MY, Chiou TJ, Yang MH, Bai LY, Hsiao LT, Chao TC et al (2005) Relatively favorable outcomes of post-transplant pulmonary function in patients with chronic myeloid leukemia receiving non-myeloablative allogeneic hematopoietic stem cell transplantation. Eur J Haematol 74:152–157
12. Goldberg SL, Klumpp TR, Magdalinski AJ, Mangan KF (1998) Value of the pretransplant evaluation in predicting toxic day-100 mortality among blood stem-cell and bone marrow transplant recipients. J Clin Oncol 16:3796–3802
13. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG et al (2005) Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 106:2912–2919