Diffusion Capacity Predicts Long-term Survival After Allogeneic Bone Marrow Transplantation for Acute Lymphoblastic Leukemia

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Background: The aim of this study was to evaluate changes in pulmonary function measures as predictors of outcome in acute lymphoblastic leukemia (ALL) patients after myeloablative allogeneic bone marrow transplantation (BMT).

Methods: Forced expiratory volume in 1 second (FEV_1) and diffusion capacity for carbon monoxide (DLCO) were evaluated before and after allogeneic BMT every 3 months in 32 patients who survived for at least 100 days. General case histories were also examined.

Results: Univariate analysis revealed that decreased post-BMT DLCO was associated with increased overall and event-free survival ($p < 0.05$). While a pre-BMT FEV_1 of $< 70\%$ was associated with significantly decreased overall survival ($p < 0.05$), multiple regression analysis indicated that patients without cytomegalovirus (CMV) infection, having limited chronic graft-versus-host disease (GVHD) and with markedly decreased DLCO had better overall survival ($p < 0.05$). After adjusting for age, gender, chronic GVHD, and CMV infection, patients with decreased DLCO exhibited enhanced overall survival. Two-year survival and event-free survival rates were significantly higher in patients with decreased DLCO.

Conclusion: We conclude that DLCO may be a good long-term predictor of outcome in patients with ALL following BMT. [*J Chin Med Assoc* 2008;71(5):234–240]

Key Words: acute lymphoblastic leukemia, allogeneic bone marrow transplantation, chronic graft-versus-host disease, pulmonary function test

Introduction

Pulmonary complications occur in 40–60% of bone marrow transplantation (BMT) recipients, accounting for 10–40% of all transplant-related deaths.[1] Pulmonary function testing following BMT is useful for predicting survival.[2] Indeed, several reports have noted that small airway obstruction with decreased forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity (FVC) ratio is associated with increased mortality in patients who have received allogeneic BMT.[1]

Airflow obstruction has also been correlated with the occurrence of chronic graft-versus-host disease (GVHD) following BMT.[3–5] Decrease in diffusion capacity of carbon monoxide (DLCO) after BMT has been observed in chronic myelogenous leukemia patients.[6,7] The mechanisms underlying this deterioration remain unclear. The majority of studies assessing the relationship between pulmonary function and long-term survival following BMT have involved non-homogeneous study populations. To our knowledge, a homogeneous acute lymphoblastic leukemia (ALL) population has not been examined in this manner. Therefore, the aim of this study was to determine whether changes in FEV_1, DLCO, and the occurrence of chronic GVHD have any long-term prognostic significance in patients with ALL after allogeneic BMT.

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E-mail: pmchen@vghtpe.gov.tw • Received: October 19, 2007 • Accepted: February 5, 2008

Methods

Patient population

The case records of 55 ALL patients who received allogeneic BMT between August 1983 and February 2005 at our bone marrow unit were retrospectively reviewed. Our investigation was limited to long-term survivors only (defined as surviving for at least 100 days after BMT).[1] Hence, 16 patients who died before 100 days post transplantation and 7 who accepted transplantation before complete remission were excluded. The remaining 32 patients were analyzed.

Twenty-eight patients in the study population accepted induction chemotherapy with OPDL regimen[8] (every 4 weeks with vincristine 1.3 mg/m^2 on day 1, danuomycin 50 mg/m^2 qd on day 1–3, prednisolone 40 mg/m^2 qd till remission) followed by consolidation with cytarabine 1,000 mg/m^2 q12h on day 1–4 and novantrone 6 mg/m^2 qd on day 1–4. Four patients with ALL accepted the hyper-CVAD regimen (cyclophosphamide 300 mg/m^2 bid on day 1–3, vincristine 2 mg on day 4 and day 11, doxorubicin 50 mg/m^2 on day 4, dexamethasone 40 mg on day 1–4 and day 11–14 during courses 1, 3, 5 and 7, and methotrexate 1,000 mg/m^2 on day 1, cytarabine 3,000 mg/m^2 bid on day 2, day 3 during courses 2, 4, 6 and 8). Intrathecal CNS prophylaxis was performed for 6–8 courses with methotrexate 15 mg, cytarabine 45 mg, and decadron 5 mg in each cycle to all patients according to the situation.

BMT procedure

The treatment regimen included conditioning therapy, GVHD prophylaxis, protective isolation, antibiotics, and supportive care. Patients entered isolation units before initiation of conditioning. The conditioning regimen consisted of total body irradiation (TBI) 150 cGy twice daily for 4 days (total dose 1,200 cGy), with isolating transporter to the radiation room, intravenous cyclophosphamide 60 mg/kg once daily on days 1 and 2 (total dose 120 mg/kg), and intravenous mesna 20 mg/kg 7 times daily (total dose 140 mg/kg) following the cyclophosphamide course. Non-TBI conditioning was as follows: busulfan 4 mg/kg *per os* in divided doses daily for 4 days (total dose 16 mg/kg), cyclophosphamide 50 mg/kg daily for 4 days (total dose 200 mg/kg), intravenous mesna 20 mg/kg 7 times daily (total dose 140 mg/kg). Most patients received a combination of radiation therapy and chemotherapy. Patients not allergic to sulfamethoxazole and trimethoprim received prophylactic treatment for 2 weeks before transplantation and from the time of primary discharge after transplantation for at least 6 months, or until peripheral white blood cell counts normalized.[2]

Cytomegalovirus (CMV) infection was monitored with CMV-PCR weekly post transplant until 100 days after the day of transfusion. Diagnosis of CMV colitis was confirmed by histologic examination of colonoscopy biopsy specimens. Diagnosis of CMV pneumonitis was confirmed by histologic examination of pulmonary macrophages obtained by broncholavage.

GVHD prophylaxis, grading and treatment

All patients received the following GVHD prophylaxis: intravenous cyclosporin A 5 mg/kg or 6.25 mg/kg *per os* from day –1 to day +60; intravenous methotrexate 15 mg/m^2 on day +1, and 10 mg/m^2 on days +3, +6 and +11. Acute GVHD was graded according to published criteria.[9] Chronic GVHD was classified as described by Schulman and colleagues.[10]

Acute GVHD was treated with prednisolone 2 mg/kg daily and cyclosporin 6.25 mg/kg daily, adjusted with methylprednisolone at a dose of 20 mg/kg/day for 3–5 days and ATG 30 mg/kg every other day for 6 doses. These doses were increased if improvements were not apparent.

Pulmonary function tests

Pulmonary function tests were performed before, and every 3 months after BMT according to American Thoracic Society guidelines. Measurements were made using the following equipment: between 1983 and 1993, a wet-spirometer (model 750; Med Science Electronics, St Louis, MO, USA) combined with an XY recorder (Hewlett-Packard, Palo Alto, CA, USA) and a 1-second timer; between March 1993 and November 2003, a Sensormedics Autobox 6200 (Sensormedics Co., Yorba Linda, CA, USA); and from December 2003 onwards, a Sensormedics Vmax (Sensormedics Co.). Previously published equations were used to determine predicted FEV_1 values.[11] DLCO was measured using the single-breath technique and corrected for hemoglobin content. Obstruction was categorized as mild (≥ 70% FEV_1), moderate (60–69% FEV_1), moderately severe (50–59% FEV_1), severe (35–49% FEV_1), or very severe (< 35%). Diffusion capacity was categorized as pathological (DLCO < 80% of predicted value), mild (60–80% of predicted value), moderate (40–59% of predicted value), or severe (DLCO < 40% of predicted value) according to European Respiratory Society guidelines. Decreases in FEV_1 or DLCO were defined according to the grading systems of the American Thoracic and European Respiratory Societies (ATS/ERS),[12] and were indicated by an increase of at least 1 severity grade between pre-BMT and 12 months post-BMT (e.g. a shift from mild to moderate, moderate to severe, etc.).

Statistical methods

Overall and event-free survivals were defined as the intervals between diagnosis and death, and between complete remission and disease recurrence, respectively. The Kaplan-Meier method was used to estimate overall survival and event-free survival. Log-rank tests were performed to assess any association between survival and risk factors. A Cox proportional hazard model was then applied to identify prognostic factors that significantly influenced overall survival and event-free survival. All analyses were performed using the SAS 9.01 statistical software package (SAS Institute Inc., Cary, NC, USA). A p value of less than 0.05 was considered to indicate significance.

Results

Patient characteristics and clinical features

The demographic and clinical characteristics of the 32 ALL patients who survived at least 100 days after allogeneic BMT are presented in Table 1.

Pulmonary function, chronic GVHD, and prognosis

The univariate analysis results for overall and event-free survival prognostic factors are presented in Table 2. Both decreased DLCO and a pre-BMT FEV_1 <70% significantly influenced overall survival (both $p<0.05$). Overall survival was significantly higher in patients with decreased DLCO. Mortality risk was almost 5 times higher when pre-BMT FEV_1 was <70% of the predicted value. Neither a decreased FEV_1 score post-BMT, nor development of either acute or chronic GVHD influenced overall survival (all $p>0.05$). Decreased DLCO after BMT was associated with significantly improved event-free survival ($p<0.05$). There were only 6 patients in whom FEV_1 decreased following BMT (relapse was not apparent in any of these individuals); hence, we were unable to establish an association using the Cox proportional model.

Considering the predisposing factors that may influence prognosis, although no apparent significance in univariate analysis was observed in the present study, these factors were enrolled into the multivariate analysis. Multivariate analysis (Table 3) revealed that limited chronic GVHD was associated with a significantly decreased risk of death (HR, 0.14; $p<0.05$), while CMV infection significantly increased risk of death (HR, 21.91; $p<0.05$). After adjusting for age, gender, chronic GVHD and CMV infection status, decreased DLCO was significantly predictive for both increased overall survival and event-free survival ($p<0.05$).

Table 1. Characteristics of 32 acute lymphoblastic leukemia patients who survived at least 100 days after allogeneic bone marrow transplantation (BMT)*

Age at BMT	25 (11.5–50.6)
Adult (> 18 yr)	
No	7 (21.87)
Yes	25 (78.13)
Gender	
Female	15 (46.9)
Male	17 (53.1)
Months to CR1 after diagnosis	1.30 (0.7–5.5)
Months to BMT after diagnosis	6.73 (3.60–44.00)
Overall survival (mo)	43.22 (11.00–173.43)
Event-free survival (mo)	33.62 (7.97–173.43)
Disease status at BMT	
CR1	29 (90.62)
CR2	3 (9.38)
CMV infection	
No	27 (84.37)
Yes	5 (15.63)
Philadelphia chromosome	
Positive	5 (15.63)
Negative	27 (84.37)
Smoking	
No	26 (81.25)
Yes	6 (18.75)
Conditioning regimen	
BU + CY	3 (9.38)
TBI + CY	29 (90.62)
Acute GVHD	
No	24 (75.00)
Grade 1	3 (9.38)
Grade 2	4 (12.50)
Grade 3	1 (3.13)
Chronic GVHD	
No	13 (40.63)
Limited	11 (34.38)
Extensive	8 (25.00)
Pre-BMT FEV_1 grade	
Mild (≥ 70%)	29 (90.63)
Moderate (60–70%)	2 (6.25)
Moderately severe (50–60%)	1 (3.13)
FEV_1 decreased following BMT	
No	26 (81.25)
Yes	6 (18.75)
Pre-BMT DLCO grade	
Mild (80–60%)	6 (18.75)
Moderate (40–60%)	18 (56.25)
Severe (< 40%)	8 (25.00)
DLCO decreased following BMT	
No	17 (53.13)
Yes	15 (46.88)

**Data presented as median (range) or n (%). CR1 = first complete remission; CR2 = second complete remission; CMV = cytomegalovirus; BU = busulfan; CY = cyclophosphamide; TBI = total body irradiation; GVHD = graft-versus-host disease; FEV_1 = forced expiratory volume in 1 second; DLCO = diffusion capacity for carbon monoxide.*

Table 2. Univariate analysis results for overall and event-free survival risk factors in 32 acute lymphoblastic leukemia patients after allogeneic bone marrow transplantation (BMT)

	Overall survival			Event-free survival		
	HR	95% CI	*p**	HR	95% CI	*p**
Age	1.01	(0.96–1.07)	0.72	1.00	(0.94–1.06)	0.98
Sex						
Female	–			–		
Male	0.75	(0.24–2.33)	0.61	1.22	(0.29–5.10)	0.79
Smoking						
No	–			–		
Yes	0.25	(0.03–2.00)	0.19	0.56	(0.07–4.58)	0.59
Months to BMT after diagnosis	1.01	(0.96–1.06)	0.77	1.01	(0.94–1.09)	0.77
Conditioning regimen						
BU + CY	–			–		
TBI + CY	1.77	(0.21–15.29)	0.60	0.73	(0.09–5.96)	0.77
HLA matching						
Siblings	–			–		
MUD	0.85	(0.23–3.17)	0.80	1.04	(0.25–4.37)	0.95
CMV infection						
No	–			–		
Yes	1.93	(0.41–9.12)	0.41	0.81	(0.10–6.64)	0.85
Acute GVHD						
No	–			–		
Yes	0.77	(0.17–3.56)	0.74	0.46	(0.06–3.74)	0.47
Chronic GVHD						
None	–			–		
Limited	1.30	(0.38–4.51)	0.68	0.38	(0.04–3.42)	0.39
Extensive	0.30	(0.06–1.56)	0.15	0.82	(0.18–3.68)	0.79
Pre-BMT $FEV_1 < 70\%$						
No	–			–		
Yes	4.79	(1.19–19.29)	0.03†	3.26	(0.65–16.29)	0.15
FEV_1 decreased after BMT						
No	–			–		
Yes	1.21	(0.33–4.49)	0.77	–	–	–
DLCO decreased after BMT						
No	–			–		
Yes	0.17	(0.04–0.79)	0.02†	0.11	(0.01–0.90)	0.04†

**p value as determined by Cox proportional hazard regression analyses; †a significant risk factor. HR = hazard ratio; CI = confidence interval; BU = busulfan; CY = cyclophosphamide; TBI = total body irradiation; HLA = human leukocyte antigen; MUD = matched unrelated donor; CMV = cytomegalovirus; GVHD = graft-versus-host disease; FEV_1 = forced expiratory volume in 1 second; DLCO = diffusion capacity for carbon monoxide.*

Figure 1 shows the Kaplan-Meier overall and event-free survival curves for patients in whom DLCO did or did not decrease following BMT. The 2-year survival rates were 93% and 64% for patients who did and did not exhibit decreased DLCO scores, respectively. Corresponding 2-year event-free survival rates were 93% and 53%. Both the differences for overall and event-free survivals between the groups were significant ($p < 0.05$).

Discussion

This study primarily assessed measures of pulmonary function as indicators of long-term outcome in patients with ALL following BMT. Our findings suggest that post-BMT DLCO may be such a prognostic factor.

Previous studies have reported that DLCO decreases are apparent in up to 80% of all BMT survivors, including those in good health.[13–18] Further

Table 3. Multivariate analysis for prognostic factors affecting overall and disease-free survival in 32 acute lymphoblastic leukemia patients after allogeneic hematopoietic stem cell transplantation

	Overall survival			Event-free survival		
	HR	95% CI	*p**	HR	95% CI	*p**
Age	1.01	(0.95–1.07)	0.81	0.98	(0.92–1.06)	0.66
Gender						
Female	–			–		
Male	1.09	(0.31–3.81)	0.90	1.75	(0.34–9.01)	0.50
Chronic GVHD						
None	–			–		
Limited	0.14	(0.02–0.90)	0.04†	0.57	(0.10–3.21)	0.52
Extensive	0.45	(0.11–1.85)	0.27	0.14	(0.01–1.59)	0.11
DLCO decreased after BMT						
No	–			–		
Yes	0.05	(0.01–0.43)	0.01†	0.07	(0.01–0.60)	0.02†
CMV infection						
No	–			–		
Yes	21.91	(1.76–273.12)	0.02†	2.12	(0.20–22.34)	0.53

**p value as determined by Cox proportional hazard regression analyses; †a significant risk factor. HR = hazard ratio; CI = confidence interval; GVHD = graft-versus-host disease; DLCO = diffusion capacity for carbon monoxide; BMT = bone marrow transplantation; CMV = cytomegalovirus.*

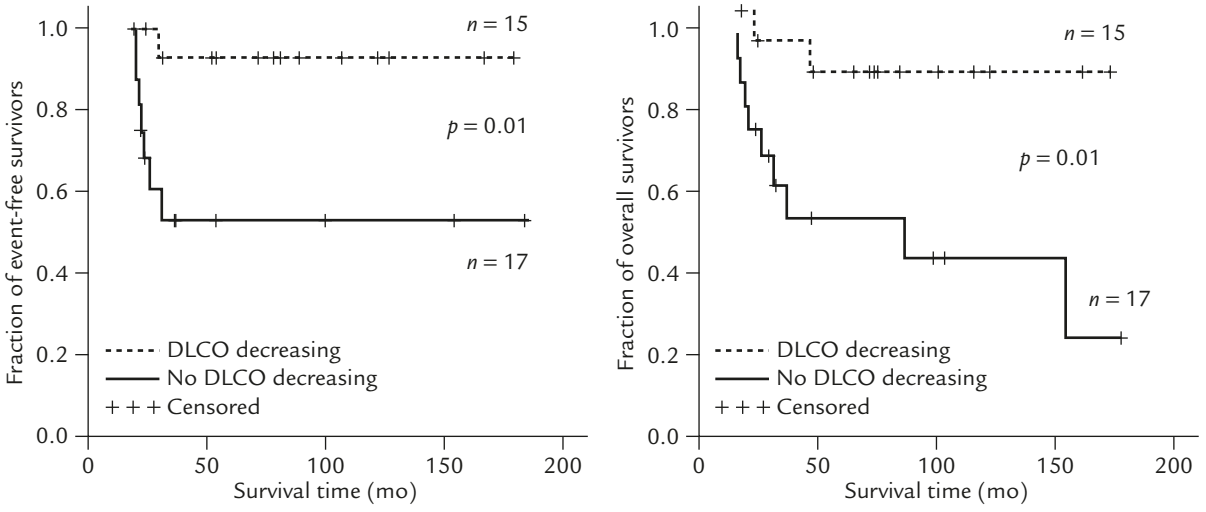

Figure 1. Kaplan-Meier survival curves for acute lymphoblastic leukemia patients in whom diffusion capacity for carbon monoxide (DLCO) did or did not decrease following allogeneic bone marrow transplantation: (A) event-free survival; (B) overall survival.

to this, it is indicated that DLCO decreases occur within the first 3 months post BMT and that subsequent recovery is incomplete.[2,19–23] Such persistent decreases in DLCO may be reflective of permanent damage to the alveolar–endothelial membrane and subclinical pulmonary fibrosis.[6,24,25] In the current study, we also found that decreased DLCO 1 year after BMT was associated with enhanced survival rate. A number of previous studies have failed to find such an association between decreased DLCO and mortality.[2,5,6,26] The mechanism(s) underlying the apparent positive influence of decreased DLCO on survival in this study are unclear. Similar interesting findings were observed in a previous study.[27] In Philadelphia chromosome positive (Ph+) ALL patients after allogeneic stem cell transplantation, those with chronic GVHD had better survival compared to those without chronic GVHD. Although the true mechanism of such a clinical finding is unclear, there may be some correlation between chronic GVHD, enhanced graft-versus-leukemia (GVL)

effect and decreased DLCO in ALL patients, which warrants further investigation.

Several reports have noted an association between diminished FEV_1 due to small airway obstruction and concomitant chronic GVHD and increased frequency of late non-relapse death.[5,26] We did not find any such associations in the present study. However, as already noted, there was an insufficient number of patients who experienced post-BMT decreases in FEV_1 to allow for definitive analysis. We did find that pre-BMT FEV_1 < 70% was associated with an increased mortality risk. There have been reports indicating that there is an association between abnormal FEV_1 values and an increased risk of treatment-related mortality and post-transplantation CMV infection.[28]

A number of studies have indicated that chronic GVHD is a highly significant risk factor for the development of airflow obstruction following BMT.[29,30] Similarly, others have noted that chronic GVHD is a risk factor for airflow obstruction and increased non-relapse mortality and morbidity after allogeneic BMT.[4,18,31] In the current investigation, we found that patients who experienced limited chronic GVHD following allogeneic BMT had better overall survival as compared to patients who did not have GVHD. Yanada and colleagues found that extensive chronic GVHD was associated with increased survival in ALL patients who received allogeneic BMT.[27] The positive impact of limited chronic GVHD on survival might be explained by an associated GVL effect.[27,32]

Crawford and colleagues have previously presented findings demonstrating that decreased DLCO before transplantation is an independent factor for increased risk of death after BMT.[2,33] We did not find this to be the case in the present study. Our finding is in keeping with that of Ghalie et al, who also found no association between pre-transplant DLCO and post-transplant pulmonary complications or outcome.[34] CMV infection was correlated with mortality in our study. This may be related to the high mortality rate of documented CMV infection and poorer general condition and immunity of the patients who got CMV infections.

There are a number of limitations to our study. Due to the relatively small sample size, associations between decreased FEV_1, decreased DLCO, and chronic GVHD could not be determined. Thus, we cannot exclude the possibility that the effects of decreased DLCO and chronic GVHD may overlap. Also related to the small sample size, we were not able to assess the effect of decreased DLCO on more long-term survival (i.e. > 1 year). Another shortcoming is that because the data pertaining to total lung capacity were incomplete and could not be analyzed, its significance as a risk factor could not be evaluated. Previous reports have noted reduced total lung capacity to be associated with an increase in non-relapse mortality following BMT.[2,18] Studies with larger patient groups and/or animal models are warranted to address these unresolved issues.

To our knowledge, this is the first study to examine the relationship between long-term survival and pulmonary function changes in ALL patients after allogeneic BMT. We found that decreased DLCO following allogeneic BMT was associated with better survival in these patients. The relationship between DLCO decrease, chronic GVHD and the GVL effect needs to be further studied. Additional research utilizing the ATS/ERS grading system to separate positive and negative GVL patients may provide further insight.

Acknowledgments

This research was supported by the Taiwan Cancer Clinic Research Foundation.

References

1. Soubani AO, Miller KB, Hassoun PM. Pulmonary complications of bone marrow transplantation. *Chest* 1996;109:1066–77.
2. Crawford SW, Pepe M, Lin D, Benedetti F, Deeg HJ. Abnormalities of pulmonary function tests after marrow transplantation predict nonrelapse mortality. *Am J Respir Crit Care Med* 1995;152:690–5.
3. Clark JG, Schwartz DA, Flournoy N, Sullivan KM, Crawford SW, Thomas ED. Risk factors for airflow obstruction in recipients of bone marrow transplants. *Ann Intern Med* 1987;107:648–56.
4. Chien JW, Martin PJ, Gooley TA, Flowers ME, Heckbert SR, Nichols WG, Clark JG. Airflow obstruction after myeloablative allogeneic hematopoietic stem cell transplantation. *Am J Respir Crit Care Med* 2003;168:208–14.
5. Marras TK, Szalai JP, Chan CK, Lipton JH, Messner HA, Laupacis A. Pulmonary function abnormalities after allogeneic marrow transplantation: a systematic review and assessment of an existing predictive instrument. *Bone Marrow Transplant* 2002;30:599–607.
6. Chiou TJ, Tung SL, Wang WS, Tzeng WF, Yen CC, Fan FS, Liu JH, et al. Pulmonary function changes in long-term survivors of chronic myelogenous leukemia after allogeneic bone marrow transplantation: a Taiwan experience. *Cancer Invest* 2002;20:880–8.
7. Prince DS, Wingard JR, Saral R, Santos GW, Wise RA. Longitudinal changes in pulmonary function following bone marrow transplantation. *Chest* 1989;96:301–6.
8. Ho DL, Chen YC, Kao WY, Chao TY. Acute lymphoblastic leukemia in young adults: two chemotherapeutic protocols for the treatment of 46 patients. *J Chin Med Assoc* 2000;63:45–52.
9. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant* 1995;15:825–8.
10. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, Hackman R, et al. Chronic graft-versus-host

syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med* 1980;69:204–17.
11. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;123:659–64.
12. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948–68.
13. Curtis DJ, Smale A, Thien F, Schwarer AP, Szer J. Chronic airflow obstruction in long-term survivors of allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1995;16:169–73.
14. Socie G, Mary JY, Esperou H, Robert DV, Aractingi S, Ribaud P, Devergie A, et al. Health and functional status of adult recipients 1 year after allogeneic haematopoietic stem cell transplantation. *Br J Haematol* 2001;113:194–201.
15. Cerveri I, Fulgoni P, Giorgiani G, Zoia MC, Beccaria M, Tinelli C, Locatelli F. Lung function abnormalities after bone marrow transplantation in children. Has the trend recently changed? *Chest* 2001;120:1900–6.
16. Gore EM, Lawton CA, Ash RC, Lipchik RJ. Pulmonary function changes in long-term survivors of bone marrow transplantation. *Int J Radiat Oncol Biol Phys* 1996;36:67–75.
17. Beinert T, Dull T, Wolf K, Holler E, Vogelmeier C, Behr J, Kolb H. Late pulmonary impairment following allogeneic bone marrow transplantation. *Eur J Med Res* 1996;1:343–8.
18. Patriarca F, Skert C, Sperotto A, Damiani D, Cerno M, Geromin A, Zaja F, et al. Incidence, outcome, and risk factors of late-onset noninfectious pulmonary complications after unrelated donor stem cell transplantation. *Bone Marrow Transplant* 2004;33:751–8.
19. Fanfulla F, Locatelli F, Zoia MC, Giorgiani G, Bonetti F, Spagnolatti L, Cerveri I. Pulmonary complications and respiratory function changes after bone marrow transplantation in children. *Eur Respir J* 1997;10:2301–6.
20. Quigley PM, Yeager AM, Loughlin GM. The effects of bone marrow transplantation on pulmonary function in children. *Pediatr Pulmonol* 1994;18:361–7.
21. Depledge MH, Barrett A, Powles RL. Lung function after bone marrow grafting. *Int J Radiat Oncol Biol Phys* 1983;9: 145–51.
22. Rodriguez-Roisin R, Roca J, Granena A, Agusti AG, Marin P, Rozman C. Lung function in allogeneic bone marrow transplantation recipients. *Eur Respir J* 1989;2:359–65.
23. Sutedja TG, Apperley JF, Hughes JM, Aber VR, Kennedy HG, Nunn P, Jones L, et al. Pulmonary function after bone marrow transplantation for chronic myeloid leukaemia. *Thorax* 1988; 43:163–9.
24. Schwarer AP, Hughes JM, Trotman-Dickenson B, Krausz T, Goldman JM. A chronic pulmonary syndrome associated with graft-versus-host disease after allogeneic marrow transplantation. *Transplantation* 1992;54:1002–8.
25. Sorensen PG, Ernst P, Panduro J, Moller J. Reduced lung function in leukaemia patients undergoing bone marrow transplantation. *Scand J Haematol* 1984;32:253–7.
26. Marras TK, Chan CK, Lipton JH, Messner HA, Szalai JP, Laupacis A. Long-term pulmonary function abnormalities and survival after allogeneic marrow transplantation. *Bone Marrow Transplant* 2004;33:509–17.
27. Yanada M, Naoe T, Iida H, Sakamaki H, Sakura T, Kanamori H, Kodera Y, et al. Myeloablative allogeneic hematopoietic stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia in adults: significant roles of total body irradiation and chronic graft-versus-host disease. *Bone Marrow Transplant* 2005;36:867–72.
28. Horak DA, Schmidt GM, Zaia JA, Niland JC, Ahn C, Forman SJ. Pretransplant pulmonary function predicts cytomegalovirus-associated interstitial pneumonia following bone marrow transplantation. *Chest* 1992;102:1484–90.
29. Clark JG, Crawford SW, Madtes DK, Sullivan KM. Obstructive lung disease after allogeneic marrow transplantation: clinical presentation and course. *Ann Intern Med* 1989;111:368–76.
30. Bruno B, Souillet G, Bertrand Y, Werck-Gallois MC, So SA, Bellon G. Effects of allogeneic bone marrow transplantation on pulmonary function in 80 children in a single paediatric centre. *Bone Marrow Transplant* 2004;34:143–7.
31. Socie G, Stone JV, Wingard JR, Weisdorf D, Henslee-Downey PJ, Bredeson C, Cahn JY, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. *N Engl J Med* 1999;341:14–21.
32. Passweg JR, Tiberghien P, Cahn JY, Vowels MR, Camitta BM, Gale RP, Herzig RH, et al. Graft-versus-leukemia effects in T lineage and B lineage acute lymphoblastic leukemia. *Bone Marrow Transplant* 1998;21:153–8.
33. Crawford SW, Fisher L. Predictive value of pulmonary function tests before marrow transplantation. *Chest* 1992;101:1257–64.
34. Ghalie R, Szidon JP, Thompson L, Nawas YN, Dolce A, Kaizer H. Evaluation of pulmonary complications after bone marrow transplantation: the role of pretransplant pulmonary function tests. *Bone Marrow Transplant* 1992;10:359–65.