

Decreased lung function in one year survivors of allogeneic bone marrow transplantation conditioned with high-dose busulphan and cyclophosphamide

M.B. Lund*, J. Kongerud*, L. Brinch**, S.A. Evensen**, J. Boe*

Decreased lung function in one year survivors of allogeneic bone marrow transplantation conditioned with high-dose busulphan and cyclophosphamide. M.B. Lund, J. Kongerud, L. Brinch, S.A. Evensen, J. Boe. ©ERS Journals Ltd 1995.

ABSTRACT: Conditioning with busulphan (BU) and cyclophosphamide (CY) prior to allogeneic bone marrow transplantation (BMT) is an alternative to regimens that include total body irradiation (TBI). The aim of the study was to assess the occurrence and degree of lung function impairment after this treatment.

Prospectively, 43 consecutive patients, aged 17–51 (median 31) yrs, were examined by lung function measurements and clinical and radiographic evaluation, prior to BMT and at 3 month intervals up to 1 yr after BMT.

All patients had normal chest radiographs before BMT and at the 12 month follow-up. Mean baseline values were above 100% of predicted normal for lung volumes and above 90% for gas transfer. Excluded from the lung function follow-up analyses were nine patients who had suffered infectious pneumonia and/or developed obliterative bronchiolitis. For the remaining patients (n=34), mean alveolar volume (VA), forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) had dropped by nearly 10% compared with baseline 3 months after BMT, but were restored within 1 yr. FEV1/FVC×100 (FEV1%) was increased, reflecting the restrictive pattern. Hb-adjusted transfer factor of the lungs for carbon monoxide (TLCO) had dropped by 20% after 3 months, and remained reduced by 15% after 1 year. Prior to BMT the smokers had significantly lower TLCO than the nonsmokers, and after BMT the difference was accentuated. Reductions in lung function were independent of sex, age and type of haematological disorder.

We conclude that BMT with BU/CY is associated with transient declines in lung volumes and a persistent reduction in gas transfer 1 yr after therapy. The decline in gas transfer is especially marked in smokers.

Eur Respir J., 1995, 8, 1269–1274.

*Dept of Thoracic Medicine and **Medical Dept A, The National Hospital, University of Oslo, Norway.

Correspondence: M.B. Lund
Dept of Thoracic Medicine
The National Hospital
University of Oslo
N-0027 Oslo
Norway

Keywords: Bone marrow transplantation
busulphan
cyclophosphamide
lung function tests

Received: November 21 1994
Accepted after revision March 27 1995

Allogeneic bone marrow transplantation (BMT) following high dose chemotherapy is a potentially curative treatment for selected patients with various severe haematological disorders [1, 2]. Cyto-reductive therapy with busulphan (BU) and cyclophosphamide (CY) prior to BMT is an alternative to the conditioning regimens that include total body irradiation (TBI) [3]. However, the risk of adverse effects and serious complications remains a problem of major concern [4].

BU and CY are both potential lung-toxic agents that may induce interstitial pneumonitis and subsequent pulmonary fibrosis [5, 6]. There is also evidence that obliterative bronchiolitis (OB) may develop in bone marrow recipients, usually associated with chronic graft *versus* host disease [7, 8].

Studies on pulmonary function within 1 yr after BMT have demonstrated varying degrees of reduction in lung volumes and gas transfer [9–15]. Some of these studies comprised inhomogeneous patient groups with various haematological disorders [10, 12, 13]. Other studies

included both allogeneic and autologous marrow transplants [13, 15]. Many patients had received thoracic irradiation or multidrug chemotherapy including bleomycin, as conventional treatment prior to BMT [14, 15]. The conditioning regimens all included TBI, and various prophylactic regimens against graft *versus* host disease were applied [9, 13, 15].

In Norway, all BMTs are performed in one single hospital. The patient population is recruited from the entire country, referred and selected according to uniform criteria and subjected to standardized treatment procedures. From 1989, conditioning with TBI prior to BMT was replaced by high-dose BU and CY as standard cyto-reductive treatment for malignant blood disorders.

To our knowledge, there is no previous large, prospective, single centre clinical study on pulmonary function after BMT with high dose BU and CY. The aims of the present study were, thus, to assess the occurrence and degree of lung function impairment during the first year after BMT with BU and CY.

Material and methods

Study subjects

Between February 1989 and October 1993, 53 adult patients underwent BMT and were consecutively enrolled in the study. Within the first 1–7 months after treatment, six patients died. Four patients were transplanted for nonmalignant blood disorders (one for paroxysmal nocturnal haemoglobinuria, and three for severe aplasmal anaemia) and were given conditioning regimens without BU. One patient was conditioned with TBI and CY. The remaining patients (n=43) were included in the study. All were followed until the end of the first year.

The study population was divided in two groups. Group A consisted of patients who did not experience serious lung complications during the first year (n=34). Group B consisted of patients who suffered such complications (n=9). Serious lung complications were defined as infectious pneumonia, idiopathic interstitial pneumonitis and OB.

The patients' characteristics at inclusion are outlined in table 1. Three patients had a history of mild asthma, otherwise there were no cases of chronic lung disease prior to BMT. None of the patients had ever been treated with thoracotomy, chest irradiation or bleomycin.

Table 1. – Clinical characteristics at inclusion of 43 consecutive patients with BMT and BU/CY conditioning

	Group A (n=34)	Group B (n=9)	Total (n=43)
Sex M/F	19/15	6/3	25/18
Age yrs*	29 (18–51)	33 (17–43)	31 (17–51)
Diagnosis			
CML	15	6	21
AML	12	1	13
ALL	5	2	7
MDS	2	0	2
Donor			
Sibling	26	7	33
Unrelated	8	2	10
Smoking			
Nonsmoker	21	8	29
Ex-smoker	1	0	1
Current smoker	12	1	13
Asthma	3	0	3
Lung function			
FVC % pred [#]	108±14	107±15	108±14
FEV ₁ % pred [#]	103±13	104±12	104±13
T _{L,CO} -Hb % pred [#]	89±13	97±11	91±13

*: median and range; #: mean±SD. BMT: bone marrow transplantation; BU: busulphan; CY: cyclophosphamide; Group A: no lung complications; Group B: lung complications; M: male; F: female; CML: chronic myeloid leukaemia; AML: acute myeloid leukaemia; ALL: acute lymphocytic leukaemia; MDS: myelodysplastic syndrome; % pred: percentage of predicted value; FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; T_{L,CO}-Hb: transfer factor of the lungs for carbon monoxide corrected for haemoglobin level.

Transplantation procedures

Conditioning prior to BMT consisted of BU orally at a dose of 1 mg·kg⁻¹ of ideal body weight four times daily for four consecutive days, followed by CY at a daily dose of 60 mg·kg⁻¹ administered intravenously (*i.v.*) over a 30 min period for two consecutive days [3]. Bone marrow was infused 2 days after the final dose of CY. Graft *versus* host disease prophylaxis consisted of methotrexate (*i.v.* on day 1, 3, 6 and 11) and cyclosporin A. After stable engraftment, trimethoprim-sulphamethoxazole was given as prophylactic against *Pneumocystis carinii* infection.

Clinical and radiographic evaluation

All patients underwent clinical examination and had chest radiographs taken at the time of inclusion and at each of the four follow-up consultations. Special attention was paid to symptoms and signs of OB, lower respiratory tract infections, and infiltrative lung disease. Lung complications occurring between the regular 3 month follow-up examinations were also recorded. All chest radiographs were evaluated by two radiologists.

Lung function measurements

Lung function tests included dynamic spirometry and gas transfer factor. Spirometry was performed with a water-sealed spirometer. Gas transfer was measured by the single-breath technique. Alveolar volume was measured during the same manoeuvre by the helium dilution method. All measurements were performed with the Gould automated system 2400 (Sensormedics BV, Biltoven, Netherlands) and according to the guidelines recommended by the American Thoracic Society [16, 17]. Lung volume variables were alveolar volume (V_A), forced vital capacity (FVC), forced expiratory volume in one second (FEV₁) and FEV₁/FVC×100 (FEV%). Gas transfer variables were the transfer factor of the lungs for carbon monoxide (T_{L,CO}) and T_{L,CO} divided by V_A (carbon monoxide transfer coefficient (K_{CO})). T_{L,CO} and K_{CO} values were adjusted for haemoglobin (Hb) concentration by using the correction of COTES *et al.* [18]. The Hb levels were obtained on the same day as the pulmonary function testing for all patients. The patients were instructed to refrain from smoking on the day of the test. No correction was made for carbon monoxide back pressure (COHb).

The lung function variables were expressed in absolute values and as percentage of predicted normal values. Reference values were those of the European Coal and Steel Community (ECSC) [19].

Each patient was examined on five occasions; prior to BMT, and at approximately 3, 6, 9 and 12 months post-BMT. Tests were not performed during episodes of lung infection.

Statistics

All calculations were performed with the SPSS/PC statistical computing package [20]. Categorical data were

compared by the Chi-squared test. Group mean data were compared with the unpaired Student's t-test (two-tailed). The t-test was used for paired data to compare lung function values pre-BMT with post-BMT at the time of maximum reduction, and at 1 yr follow-up. Bonferroni's correction was applied for multiple comparisons. Patients who experienced serious lung complications (n=9) were analysed separately from the main study group. Multiple linear regression was used to detect relationships between pulmonary function and relevant covariates. Variables with more than two categories were transformed into binary variables. Chronic myeloid leukaemia (CML) and myelodysplastic syndrome (MDS) were tested *versus* the acute leukaemias (CML+MSD=1 and otherwise=0). The one ex-smoker was excluded from the statistical analysis, smokers were tested *versus* nonsmokers (smokers=1 and otherwise=0). The independent variables entered into the regression models were those found to be significant at 20% level by previous univariate analysis.

Results

All patients had normal chest radiographs at inclusion. For the entire study group, baseline ventilatory function

was above 100% and gas transfer (Hb-corrected) above 90% of predicted normal values (table 1). The smokers had lower baseline $T_{L,CO-Hb}$ than the nonsmokers (83 vs 94% of predicted; $p=0.004$). The three patients with asthma had normal baseline lung function, comparable with the total study group.

Group A

Tables 2 and 3 show pulmonary function before BMT, and at the four examinations post-BMT for the patients without serious lung complications (n=34). They had normal chest radiographs at all four follow-up examinations.

V_A and FVC dropped to minimum values after 3 months, and FEV₁ after 9 months. The corresponding increase in FEV₁% reflected the restrictive ventilatory pattern. $T_{L,CO}$ reached its lowest value after 3 months, with 20 and 18% declines in $T_{L,CO-Hb}$ and Kco-Hb, respectively, compared with the initial values.

After 12 months, V_A , FVC, FEV₁ and FEV₁% no longer differed significantly from baseline values. Gas transfer had improved from the 3 month low, but remained significantly decreased after 12 months, with $T_{L,CO-Hb}$ and Kco-Hb both reduced by 15% compared with their baseline values.

Table 2. – Group A, subjects who did not experience serious lung complications (n=34); prior to and at 3 month intervals after BMT

	Pre-BMT	Time after BMT months			
		3	6	9	12
V_A L	6.5 (5.8–7.0)	6.0*** (5.4–6.7)	6.1 (5.6–6.9)	6.2 (5.6–6.9)	6.3 (5.7–7.0)
FVC L	4.9 (4.5–5.4)	4.5*** (4.0–4.9)	4.6 (4.1–5.0)	4.6 (4.2–5.2)	4.7 (4.3–5.3)
FEV ₁ L	4.0 (3.6–4.3)	3.8 (3.4–4.2)	3.8 (3.4–4.2)	3.7* (3.4–4.1)	3.9 (3.5–4.3)
FEV ₁ %	81 (78–83)	84** (81–86)	84 (80–85)	82 (78–84)	82 (78–83)

Values are presented as mean, and 95% confidence interval in parenthesis. V_A : alveolar volume; FEV%: FEV₁/FVC×100. For further abbreviations and explanations see legend to table 1. Statistical comparisons: values at the time of maximum reduction and values at 12 months after BMT are compared with values pre-BMT. ***: $p<0.001$; **: $p<0.01$; *: $p<0.05$. Bonferroni's correction for multiple comparisons.

Table 3. – Group A, subjects who did not experience serious lung complications (n=34); gas transfer and haemoglobin prior to and at 3 months intervals after BMT

	Pre-BMT	Time after BMT months			
		3	6	9	12
$T_{L,CO}$ %	82 (75–87)	58*** (51–63)	60 (56–66)	63 (59–69)	69*** (64–75)
$T_{L,CO-Hb}$ %	89 (84–94)	69*** (62–76)	70 (64–75)	70 (65–76)	74*** (69–82)
Kco-Hb %	76 (69–83)	58*** (55–66)	61 (53–62)	60 (55–64)	61** (57–66)
Hb g·100 mL ⁻¹	12.2 (11.4–12.9)	10.2*** (9.5–10.5)	11.2 (10.6–11.6)	11.7 (11.2–12.1)	12.5 (11.8–12.7)

Values are presented as mean, and 95% confidence interval in parenthesis. $T_{L,CO}$ %: transfer factor of the lungs for carbon monoxide expressed as % predicted; Hb: haemoglobin; $T_{L,CO-Hb}$: $T_{L,CO-Hb}$ corrected; Kco: $T_{L,CO}/V_A$ (carbon dioxide transfer coefficient); Kco-Hb %: Kco Hb-corrected expressed as % predicted. For further abbreviations and explanations see legends to tables 1 and 2.

Table 4. – Group B, patients who experienced serious lung complications (n=9); clinical characteristics and lung function within the first year after BMT

Pt No.	Sex	Age yrs	Time months*	Isolated agents	OB	FVC Pre	% pred Post	FEV ₁ Pre	% pred Post	TL _{CO} Pre	% pred Post
1	M	32	1, 8	<i>S. pneumoniae</i> Nsp	-	106	100	104	97	92	112
2	F	24	3	<i>Aspergillus sp.</i>	-	96	89	102	87	104	67
3	M	38	8, 10	<i>P. carinii</i> <i>S. pneumoniae</i>	-	113	102	112	92	94	81
4	M	30	10	<i>S. pneumoniae</i>	-	88	76	97	71	97	68
5	M	17	10	<i>P. carinii</i>	-	106	66	112	61	92	56
6	F	17	2	Nsp	+	112	76	105	40	98	54
7	M	36	7, 8	<i>P. carinii</i> <i>S. pneumoniae</i>	+	104	59	102	51	100	57
8	F	39	-	-	+	132	93	127	34	80	84
9	M	43	-	-	+	89	88	83	62	90	54

*: months from BMT to infection; OB: obliterative bronchiolitis; Nsp: nonspecific. For further abbreviations see legend to table 1.

Compared with baseline values, no subgroup of patients had nonsignificant changes in their lung function tests after BMT.

Multiple regression analysis of the effects of prior asthma, smoking, Hb-level and type of haematological disorder on pulmonary function, showed that smoking was the only significant variable of influence. Prior to BMT, smoking was associated with a reduced TL_{CO}-Hb (beta coefficient -8.3; SE 3.7; p=0.03). Three months after BMT, this association was accentuated (beta coefficient -16.9; SE 5.1; p=0.003). After 12 months, this accentuated association persisted (beta coefficient -12.9; SE 3.8, p=0.002), and a significant association with KCO also appeared (beta coefficient -8.5; SE 3.6; p=0.02).

Group B

Nine patients (21%) experienced serious lung complications within the first year (table 4). Their baseline lung function values did not differ significantly from those of the other patients. In seven patients, nine episodes of pneumonia were recorded. All cases were radiologically verified and infective agents were isolated from bronchoalveolar fluid in seven of them. Two of the patients (Nos. 6 and 7) developed OB at a later stage within the first year. Out of eight patients with diagnosed chronic graft *versus* host disease within the first year, four developed persistent moderate/severe airflow obstruction consistent with OB. They were nonsmokers with no history of asthma. Airflow obstruction was diagnosed after 9 months in three patients and after 6 months in one. At the 12 month follow-up, the nine patients with lung complications all had normal chest radiographs. Only those with OB differed significantly in lung function (FVC, FEV₁ and FEV₁%) from the main study group (p<0.01).

There were no cases of cytomegalovirus pneumonia or idiopathic interstitial pneumonia.

Discussion

The major finding of this study was that allogeneic BMT with BU/CY conditioning was associated with a

substantial decline in gas transfer, especially in the smokers.

In several studies, TL_{CO} has proved to be a sensitive indicator for drug-induced pulmonary toxicity [21, 22]. Both BU and CY are known to induce parenchymal lung injury [23, 24]. BU-induced lung damage is not thought to be directly dose-dependent, but there appears to be a critical cumulative dose (500 mg) above which toxicity may occur [6]. This assumed threshold dose is exceeded in all adult patients conditioned according to our standard BU/CY protocol [3]. CY-induced lung toxicity has been documented in numerous case reports [25, 26]. No definite relationship seems to exist between dosage and the severity of lung toxicity [6].

A decline in TL_{CO}, comparable to that which we observed one year after BMT, has been reported in four series which all applied TBI conditioning in combination with various chemotherapy regimens [9, 11, 14, 15]. In contrast, one other study that also involved TBI could not document a significant reduction in TL_{CO} one year after BMT [12]. The latter study, however, comprised a small number of patients (n=12). In a study that involved three different conditioning regimens, including BU/CY, a progressive 12% annual decline in percentage predicted TL_{CO} over a mean follow-up period of 2 yrs was reported [13]. The patients who had received BU/CY did not differ significantly from the rest in rate of change in TL_{CO}. However, the BU/CY group included only seven patients, and an effect may have been missed due to the small numbers.

We found that smoking was the only significant predictor for gas transfer impairment, both prior to and after BMT. It is known that smoking is associated with a substantial reduction in gas transfer [27]. Although our patients were young and their histories of smoking correspondingly short, the initially observed 11% difference in percentage predicted TL_{CO} between smokers and nonsmokers may be explained by smoking *per se* [27]. As we did not measure the COHb levels of each patient, the TL_{CO} values were not corrected for any degree of anaemia induced by COHb [28]. The patients were, however, instructed to refrain from smoking on the days of lung function testing in order to reduce CO back pressure, as recommended in the recent ECSC guidelines

[19]. Furthermore, since smoking habits were unchanged during the study and each patient served as his own control, the accentuated difference in $T_{L,CO}$ and K_{CO} between smokers and nonsmokers after BMT can hardly be explained by COHb-induced anaemia. It may be hypothesized that smoking sensitizes the lung for cytotoxic injury or that high-dose chemotherapy makes the lung more susceptible to smoking-induced damage.

SUDETJA *et al.* [11], RODRIGUEZ-ROISIN *et al.* [12] and BADIER *et al.* [15] reported that smoking did not influence lung function in their patients. Their various conditioning regimens did not include BU. Their results were, furthermore, compromised by small patient numbers or heterogenous materials. Three other studies failed to provide any data on smoking [9, 10, 14].

A negative effect of smoking on $T_{L,CO}$ has been demonstrated after multidrug therapy, including bleomycin, for germ cell cancers [29]. It is possible that smoking and high-dose BU/CY may have a similar effect.

We found that the changes in ventilatory function after BU/CY conditioning were comparable to those reported in studies where regimens including TBI have been applied [11–13]. A restrictive impairment was observed after 3 months, followed by gradual recovery. The reduced lung volumes at 3 months may, in part be explained by extrapulmonary factors, as many of the patients still suffered from general debility and muscular weakness at this early point after BMT.

Contrary to LINK *et al.* [10], but in agreement with other reports [11, 13], we did not find a trend toward progressive airway obstruction in our patients once the four cases of OB were excluded.

The frequency of infiltrative lung disease in our study was lower than that reported in some previous studies [15, 30, 31]. In a survey of 932 TBI-conditioned BMTs reported to the International Bone Marrow Transplant Registry, the 2 year actuarial incidence of interstitial pneumonia was 35% [30]. The disease was considered to be idiopathic in 50% of the cases, and cytomegalovirus associated in 37%. Neither idiopathic nor cytomegalovirus-induced interstitial pneumonia occurred in our patients, suggesting that these complications may primarily be associated with TBI. This hypothesis has been supported by CARLSON *et al.* [32], who in a recent follow-up study of 102 patients with autologous BMT found that idiopathic, interstitial pneumonia occurred predominantly in patients conditioned with TBI, whereas infectious pneumonia occurred with the same frequency in TBI and non-TBI treated patients.

Four patients developed moderate/severe airflow obstruction suggesting obliterative bronchiolitis. This was, in all cases associated with chronic graft *versus* host disease. The association between OB and graft *versus* host disease has been well-documented [7, 8, 33]. Graft *versus* host disease prophylaxis with cyclosporin A has proved to be protective against the development of OB [34]. All of our patients received cyclosporin A. The role of different cytoreductive regimens, with regard to development of OB, is not known, since TBI-conditioning has been the principal technique in all previous studies [8, 33, 34]. Our material is too small (n=4) to tell

whether BU/CY conditioning is preferable to TBI-containing regimens in order to reduce OB.

We conclude that allogeneic BMT with BU/CY conditioning is associated with transient decreases in lung volumes and with a persistent reduction in gas transfer one year after therapy. Smoking is a significant risk factor for reduced gas transfer prior to BMT, and the association is accentuated after BMT.

References

1. Appelbaum FR. Marrow transplantation for hematologic malignancies: a brief review of current status and future prospects. *Semin Hematol* 1988; 25: 16–22.
2. Bortin MM, Horowitz MM, Rimm AA. Increasing utilization of allogeneic bone marrow transplantation. *Ann Intern Med* 1992; 116: 505–512.
3. Tutschka PJ, Copelan EA, Klein JP. Bone marrow transplantation for leukemia following a new busulfan and cyclophosphamide regimen. *Blood* 1987; 70: 1382–1388.
4. Bandini G, Belardinelli A, Rosti G, *et al.* Toxicity of high-dose busulfan and cyclophosphamide as conditioning therapy for allogeneic bone marrow transplantation in adults with haematological malignancies. *Bone Marrow Transplant* 1994; 13: 577–581.
5. Ginsberg SJ, Comis RL. The pulmonary toxicity of anti-neoplastic agents. *Semin Oncol* 1982; 9: 34–51.
6. Cooper JAD, White DA, Matthay RA. Drug-induced pulmonary disease: cytotoxic drugs. *Am Rev Respir Dis* 1986; 133: 321–340.
7. Chan CK, Hyland RH, Hutcheon MA, *et al.* Small-airways disease in recipients of allogeneic bone marrow transplants. *Medicine* 1987; 66: 327–340.
8. Schwazer AP, Hughes JMB, Trotman-Dickenson B, Krausz T, Goldman JM. A chronic pulmonary syndrome associated with graft-*versus*-host disease after allogeneic marrow transplantation. *Transplantation* 1992; 54: 1002–1008.
9. Sørensen PG, Ernst P, Panduro J, Møller J. Reduced lung function in leukaemia patients undergoing bone marrow transplantation. *Scand J Haematol* 1984; 32: 253–257.
10. Link H, Reinhard U, Blaurock M, Ostendorf P. Lung function changes after allogeneic bone marrow transplantation. *Thorax* 1986; 41: 508–512.
11. Sutedja TG, Apperley JF, Hughes JM, *et al.* Pulmonary function after bone marrow transplantation for chronic myeloid leukaemia. *Thorax* 1988; 43: 163–169.
12. Rodriguez-Roisin R, Roca J, Granena A, Agusti AGN, Rozman MC. Lung function in allogeneic bone marrow transplantation recipients. *Eur Respir J* 1989; 2: 359–365.
13. Prince DS, Wingard JR, Saral R, Santos GW, Wise RA. Longitudinal changes in pulmonary function following bone marrow transplantation. *Chest* 1989; 96: 301–306.
14. Gandola L, Siena S, Bregni M, *et al.* Prospective evaluation of pulmonary function in cancer patients treated with total body irradiation, high-dose melphalan and autologous hematopoietic stem cell transplantation. *Int J Radiat Oncol Biol Phys* 1990; 19: 743–749.
15. Badier M, Guillot C, Delpierre S, Vanuxem P, Blaise D, Maraninchi D. Pulmonary function changes 100 days and one year after bone marrow transplantation. *Bone Marrow Transplant* 1993; 12: 457–461.

16. American Thoracic Society. Standardization of spirometry: 1987 update. *Am Rev Respir Dis* 1987; 136: 1285–1298.
17. American Thoracic Society. Single-breath carbon monoxide diffusing capacity (transfer factor): recommendations for a standard technique. *Am Rev Respir Dis* 1987; 136: 1299–1307.
18. Cotes JE, Dabbs JM, Elwood PC, Hall AM, McDonald A, Saunders MJ. Iron deficiency anaemia: its effect on transfer factor for the lung (diffusing capacity) and ventilation and cardiac frequency during submaximal exercise. *Clin Sci* 1972; 42: 325–335.
19. Quanjer PhH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Standardized lung function testing. *Eur Respir J* 1993; 6 (Suppl. 16): 5–52.
20. SPSS Inc. Version 3.0. 444 N. Michigan Ave. Chicago, IL.
21. Luursema PB, Star-Kroesen MA, van der Mark TW, Sleyfer DT, Koops SH, Peset R. Bleomycin-induced changes in the carbon monoxide transfer factor of the lung and its components. *Am Rev Respir Dis* 1983; 128: 880–883.
22. Sørensen PG, Rossing N, Rørth M. Carbon monoxide diffusing capacity: a reliable indicator of bleomycin-induced pulmonary toxicity. *Eur J Respir Dis* 1985; 66: 333–340.
23. Burns WA, McFarland W, Matthews MJ. Busulfan-induced pulmonary disease. *Am Rev Respir Dis* 1970; 101: 408–413.
24. Mark GJ, Lehimgar-Zadeh A, Ragsdale BD. Cyclophosphamide pneumonitis. *Thorax* 1978; 33: 89–93.
25. Spector JJ, Zimble H, Ross JS. Cyclophosphamide and interstitial pneumonitis. *J Am Med Assoc* 1980; 243: 1133.
26. Burke DA, Stoddart JC, Ward MK, Simpson CGB. Fatal pulmonary fibrosis occurring during treatment with cyclophosphamide. *Br Med J* 1982; 285: 696.
27. Knudson RJ, Kaltborn WT, Burrows B. The effects of cigarette smoking and smoking cessation on the carbon monoxide diffusing capacity of the lung in asymptomatic subjects. *Am Rev Respir Dis* 1989; 140: 645–651.
28. Frans A, Stanescu DC, Veriter C, Clerbaux T, Brasseur L. Smoking and pulmonary diffusing capacity. *Scand J Respir Dis* 1975; 56: 165–183.
29. Hansen SW, Groth S, Sørensen PG, Rossing N, Rørth M. Enhanced pulmonary toxicity in smokers with germ-cell cancer treated with cis-platinum, vinblastine and bleomycin: a long-term follow-up. *Eur J Cancer Clin Oncol* 1989; 25: 733–736.
30. Weiner RS, Bortin MM, Gale RP, *et al.* Interstitial pneumonitis after bone marrow transplantation. *Ann Intern Med* 1986; 104: 168–175.
31. 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: 359–365.
32. Carlson K, Bäcklund L, Smedmyr B, Öberg G, Simonsson B. Pulmonary function and complications subsequent to autologous bone marrow transplantation. *Bone Marrow Transplant* 1994; 14: 805–811.
33. 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: 648–656.
34. Payne L, Chan CK, Fyles G, *et al.* Cyclosporine as possible prophylaxis for obstructive airways disease after allogeneic bone marrow transplantation. *Chest* 1993; 104: 114–118.