Lung function after allogeneic bone marrow transplantation for leukaemia or lymphoma

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Abstract

Longitudinal data were analysed on the lung function of 25 of 29 survivors of childhood leukaemia or lymphoma, who had been conditioned with cyclophosphamide and total body irradiation before allogeneic bone marrow transplantation, to test whether children are particularly vulnerable to pulmonary damage after transplantation. None developed chronic graft-versus-host disease. Transfer factor and lung volumes were reduced immediately after bone marrow transplantation, but increased during the following years. However, at the last follow up, 4-13 years (median 8) after transplantation, patients had significantly reduced transfer factor, total lung capacity, and forced vital capacity (-1.0 , -1.2 , and -0.8 SD score, respectively), and increased ratio of forced expiratory volume in one second to forced vital capacity ($+0.9$ SD score). None of the patients had pulmonary symptoms, and changes were unrelated to their age at bone marrow transplantation. In conclusion, patients had subclinical restrictive pulmonary disease at a median of eight years after total body irradiation and allogeneic bone marrow transplantation.

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During the last two decades, allogeneic bone marrow transplantation has been used to treat children with relapsed or very high risk leukaemia and lymphoma. Many of these children become long term survivors,¹ so the late effects of bone marrow transplantation have become increasingly important. Pulmonary complications are a major cause of post-transplant morbidity and mortality.²⁻⁶ There have been only a few reports of lung function in children after allogeneic⁷⁻⁹ or autologous bone marrow transplantation,^{10 11} while several large studies have been published for adults.^{3-5 12-14} The studies in adults have identified the dose, dose rate, and fractionation of total body irradiation as risk factors for restrictive lung disease. Chronic graft-versus-host disease (GVHD), greater age of the patient at bone marrow transplantation, and prolonged use of methotrexate for GVHD prophylaxis are risk factors for developing obstructive lung disease in adults. Since the lungs of children should grow after the bone marrow transplantation, conclusions for

children cannot be drawn directly from studies on adults. One paediatric study confirmed chronic GVHD as a risk factor for obstructive lung disease,⁹ while four other studies, with a relatively short follow up, did not identify any risk factors.^{7 8 10 11} Thus, information about pulmonary function in children after bone marrow transplantation is sparse. We therefore analysed longitudinal data on lung function in a population based cohort treated with total body irradiation and allogeneic bone marrow transplantation for childhood leukaemia or lymphoma, to describe the changes over time and the outcome four to 13 years after bone marrow transplantation.

Methods

PATIENTS

Before 31 December 1990, 43 patients had been treated with allogeneic bone marrow transplantation for haematological malignancies diagnosed before the age of 15 while residing in East Denmark (population 2.4 million). Twenty five (86%) of the 29 patients who were alive in January 1992 (survival 67%) gave their informed consent to participate in the present study and are described in table 1. Twenty one participants had acute lymphoblastic leukaemia, two had acute myeloblastic leukaemia, one had chronic myelocytic leukaemia, and one had T cell non-Hodgkin's lymphoma. None received radiotherapy of the lungs before conditioning for bone marrow transplantation, but patients 4, 18, and 23 received spinal irradiation in midline doses of 20, 10, and 12 Gy, respectively, with the risk of scatter to the lungs.¹⁵ Seventeen participants received marrow from an HLA identical sibling, while the rest received marrow from other family donors. The median age at diagnosis, at bone marrow transplantation, and at the follow up pulmonary function test was 6.9 years (range 1.9 to 15.0), 11.3 years (5.7 to 17.6), and 17.2 years (11.6 to 26.5) respectively, and the median follow up time after bone marrow transplantation was 7.5 years (4.0 to 12.6). Twelve of the 25 participants developed acute GVHD of grade 2 or more, which means a rash on more than 25% of the body surface, or GVHD of the liver or gut.¹⁶ Cases 15 and 20 had interstitial pneumonia after bone marrow transplantation. At the follow up test, none had respiratory symptoms and the mean height standard deviation score [(observed value - predicted value) ÷ residual standard deviation] of the participants was normal compared with Danish reference values.¹⁷ Patients 1, 3, 10, and 11 were smokers and had consumed 1.5 to 7.5 pack-years of tobacco, one pack-year being 20

Table 1 Basic characteristics of the 25 participants

Patient No	Sex	Diagnosis	Age at diagnosis (years)	Chemotherapy before BMT conditioning	Stage at BMT†	Age at BMT (years)	Bone marrow donor‡	Acute GVHD grade	Age at follow up test (years)
1	M	ALL	3	CYC 219*, DAU 202, PRD, VCR, ASP, MTX, 6MP	CR3	13	IS	0	26
2	F	ALL	10	CYC 2501, DAU 146, DOX 178, PRD, VCR, ASP, MTX, 6MP, 6TG, ARA	CR2	12	Father	1	23
3	F	CML	14	BUS 158, ARA, MTX	CP1	14	IS	0	25
4	M	ALL	4	CYC 3541, DOX 207, PRD, VCR, ASP, MTX, 6MP, 6TG, ARA	CR1	5	Father	2	15
5	F	ALL	9	DOX 120, PRD, VCR, ASP, MTX, 6MP, 6TG, ARA	CR2	11	IS	1	20
6	F	NHL	11	CYC 3885, DOX 241, PRD, VCR, ASP, MTX, 6MP, ARA	CR2	12	IS	4	22
7	M	ALL	8	CYC 33 791, DAU 411, PRD, VCR, ASP, MTX, 6MP, ARA	CR3	17	IS	1	26
8	M	ALL	7	BCNU 119, CYC 2041, DOX 120, PRD, VCR, ASP, MTX, 6TG, ARA	CR1	7	SIB	3	17
9	F	ALL	11	CYC 3976, DOX 194, PRD, VCR, ASP, MTX, 6MP, 6TG, ARA	CR1	13	IS	1	21
10	F	AML	14	DAU 146, DOX 142, PRD, VCR, MTX, ARA	CR1	15	IS	1	23
11	F	ALL	12	PRD, VCR, ASP, MTX, 6MP	CR2	17	IS	1	25
12	M	ALL	3	PRD, VCR, ASP, MTX, 6MP, ARA, VMN	CR2	6	IS	1	13
13	F	AML	12	DAU 229, DOX 218, PRD, VCR, MTX, 6TG, ARA	CR2	13	IS	0	21
14	F	ALL	6	DOX 75, PRD, VCR, ASP, MTX, 6MP, 6TG, ARA	CR2	8	SIB	1	15
15	M	ALL	6	CYC 1014, DOX 80, PRD, VCR, ASP, MTX, 6MP, 6TG, ARA	CR3	12	SIB	3	19
16	F	ALL	2	CYC 2077, DOX 191, PRD, VCR, ASP, MTX, 6MP, ARA	CR2	6	IS	1	13
17§	M	ALL	2	CYC 1005, DOX 317, PRD, VCR, ASP, MTX, 6MP, ARA	CR2	6	IS	2	13
18	M	ALL	1	DOX 248, PRD, VCR, ASP, MTX, 6MP, ARA	CR2	6	SIB	0	12
19	F	ALL	2	CYC 2165, DAU 118, PRD, VCR, ASP, MTX, 6MP, ARA	CR2	6	IS	3	11
20	M	ALL	12	CYC 1989, DAU 118, MIT 44, PRD, VCR, ASP, MTX, 6MP, ARA	CR1	13	SIB	3	17
21	M	ALL	6	CYC 2934, DAU 116, PRD, VCR, ASP, MTX, 6MP, ARA, VMN	CR1	7	IS	2	12
22	M	ALL	10	CYC 2022, DAU 118, PRD, VCR, ASP, MTX, ARA	CR1	11	IS	2	16
23	M	ALL	4	CYC 949, DOX 240, PRD, VCR, ASP, MTX, 6MP, 6TG, ARA	CR2	8	¶	3	13
24	F	ALL	6	CYC 1108, DAU 133, PRD, VCR, ASP, MTX, 6MP, ARA	CR2	11	IS	2	15
25	M	ALL	3	CYC 4852, DAU 124, DOX 117, PRD, VCR, ASP, MTX, 6MP, ARA, VMN	CR2	7	IS	2	11

ALL=acute lymphoblastic leukaemia; AML=acute myeloblastic leukaemia; ARA=cytarabine; ASP=*L*-asparaginase; BCNU=carmustine; BMT=bone marrow transplantation; BUS=busulfan; CML=chronic myeloid leukaemia; CYC=cyclophosphamide; DAU=daunorubicin; DOX=doxorubicin; GVHD=graft-versus-host disease; MIT=mitoxantron; MTX=methotrexate; NHL=non-Hodgkin lymphoma; PRD=prednisone; VCR=vincristine; VMN=teniposide; 6MP=6-mercaptopurine; 6TG=6-thioguanine. *Doses are given as cumulated mg/m² for anthracyclines and alkylating agents. †CR1/CR2/CR3 1st/2nd/3rd complete remission; CP1=1st chronic phase. ‡IS=HLA identical sibling; SIB=sibling. §This patient had an isolated testicular relapse 1 year after BMT. He was treated with orchiectomy and chemotherapy and is now in CR3. ¶Mother's mother.

cigarettes a day for 1 year. None were ex-smokers.

All four non-participants had acute lymphoblastic leukaemia. They did not differ significantly from the participants for age at diagnosis, age at bone marrow transplantation, type of marrow donor, or frequency of acute GVHD of grade 2 or more, but three of the non-participants had severe chronic GVHD and one of these recently died of lung insufficiency. The 14 patients who died before 1992 did not differ from those still alive with respect to age at diagnosis, age at bone marrow transplantation, or type of marrow donor. Seven died of relapse, one of graft rejection, three of interstitial pneumonia during the first year after bone marrow transplantation, and three of other infections during the first year after transplantation while suffering from acute or chronic GVHD.

CONDITIONING REGIMEN, BONE MARROW TRANSPLANTATION AND SUPPORTIVE CARE

All participants were conditioned for the bone marrow transplantation with 120 mg/kg of cyclophosphamide and total body irradiation. Patients 1–4 received 8.5 Gy (8.0 to 8.5) and patients 5 and 6 received 10 Gy, both in one fraction at a dose rate of 0.060 Gy/min; all other participants received 11.3 Gy (10.9 to 11.7) in three fractions at a dose rate of 0.088 Gy/min. Total dose was measured by *in vivo* dosimetry, and the lungs were shielded to receive a maximal dose of 9.0 Gy. Patients with an HLA identical sibling donor received cyclosporin A for GVHD prophylaxis routinely for six months. The other patients received three doses of intravenous methotrexate in addition. Patient No 1 received seven doses of intravenous methotrexate but no cyclosporin A. The donor marrow was not T cell depleted. Glucocorticoids and, in some cases, anti-

thymocyte globulin were used to treat GVHD. Supportive treatment during bone marrow transplantation included skin and gastrointestinal decontamination, laminar air flow isolation, and prophylactic sulphamethoxazole and trimethoprim for six months.

CONTROLS

Control subjects took part in a prospective population study of asthma, allergy, and bronchial hyperresponsiveness initiated in 1986.¹⁸ A random sample of 983 children and adolescents living in the area surrounding the National University Hospital Rigshospitalet in Copenhagen was drawn from the civil registration list; all subjects were born in the first week of each month in the years 1969 to 1979, and the first examination of the sample was conducted in 1986. The sample was invited by letter to a second examination in 1992 and a total of 662 participated (67% of those invited). All data used in the present analysis were taken from the second examination. From the total sample of 662 subjects we excluded 260 people who had smoked at any time, 52 who had never smoked but who reported present or past symptoms indicating a diagnosis of asthma,¹⁹ one subject with Turner's syndrome, and one with Down's syndrome; the final sample therefore comprised 348 controls, of whom 167 were females. Controls were 13.1 to 23.8 years old (median 17.9) at time of the study.

PULMONARY FUNCTION TESTING

Pulmonary function tests, scheduled to be done before bone marrow transplantation and six, 12, 24, and 36 months after bone marrow transplantation, were often lacking or incomplete because the child could not cooperate or for technical reasons. During 1992 and 1993 all

Development of transfer factor (T_{LCO}), total lung capacity (TLC), forced vital capacity (FVC), and ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC) after bone marrow transplantation (BMT). Lines connect serial test results in individual patients and each measurement is marked by a point. Values are given as standard deviation scores ($SDS = [observed\ value - predicted\ value] \div residual\ standard\ deviation$), calculated from paediatric^{21, 22} or adult²⁰ reference values.

participating patients were tested again, and we call these measurements the follow up tests. All the follow up tests, as well as the tests of controls, were done in one laboratory, while some of the previous tests were done in another laboratory. Both laboratories had the same type of equipment (Jaeger, Germany) and followed the European recommendations.²⁰ Testing included measurement of forced vital capacity (FVC), forced expiratory volume in one second to FVC ratio (FEV_1/FVC), total lung capacity (TLC), and transfer factor of carbon monoxide. The transfer factor of the patients was corrected to a haemoglobin concentration of 9 mmol/l.²⁰ In some of the previous tests, where FVC had not been measured, the vital capacity was used as a substitute for FVC. Flow-volume curves, which were obtained at the follow up test, were evaluated by one of us (BH). TLC was measured with the single breath helium dilution technique and transfer factor with the carbon monoxide single breath technique. In small children who could cooperate, the steady state technique was used.

Pulmonary function test results were compared with paediatric reference values^{21, 22} for patients younger than 18 years and with adult reference values²⁰ for those over 18. To make data comparable, they were analysed as standard deviation scores (SDS).²⁰⁻²² Pulmonary function test results of 348 healthy people from the same region of Denmark who had never smoked (the controls) were analysed in the same way, to test the fit of the reference values chosen. At the follow up test, the predicted transfer factor for patients who were smokers was corrected according to the

equations of Knudson *et al.*²³ Predicted lung volumes were not corrected, as lung volumes are unchanged after a few years of smoking.²³ Pulmonary function test results for some patients in this study have been reported earlier.²⁴

STATISTICS

The distribution of the follow up test results was not significantly different from normal (Shapiro-Wilk test), so these results as given as mean values, 95% confidence intervals of mean, and ranges. All other data are reported as median values with ranges unless otherwise stated. Student's *t* test was used for comparing height and pulmonary function test results with 0 SDS, and for comparing the follow up test results for groups of patients. Simple linear regression was used to test for a relation between the follow up test results and the age of the patients at bone marrow transplantation. The χ^2 test, Fisher's exact test, and Mann-Whitney's unpaired test were used for comparing groups of patients. We considered pulmonary function test results abnormal if they were more than 1.645 residual standard deviations from the predicted mean value.²⁰ If raised as well as reduced values of a variable are considered abnormal (TLC, FEV_1/FVC) this corresponds to two sided 90% prediction limits for reference data. If only reduced values are considered abnormal (transfer factor, FVC) this corresponds to one sided 95% limits. We considered probabilities below 0.05 statistically significant and analysed data with the SAS computer software package (SAS Institute).

Table 2 Results of the follow up pulmonary function tests for the 25 participants and for 348 healthy Danes 13 to 23 years old. Values are given as standard deviation scores (SDS, [observed value – predicted value] ÷ residual standard deviation) calculated from the reference values of Rosenthal et al^{21,22} for those younger than 18, and from the European reference values²⁰ for those older than 18

Variable	25 BMT patients				Patients with abnormal values* (Pt No)	348 Healthy Danes	
	Mean	95% Confidence interval of mean	p For mean different from 0 SDS	Range		Mean	p For difference between means of patients and controls
Transfer factor	-1.0	-1.4 to -0.5	0.0001	-2.6 to 1.3	↓ 2, 3, 5, 11, 21	0.5	<0.0001
Total lung capacity	-1.2	-1.7 to -0.7	0.0001	-3.8 to 1.1	↓ 2, 3, 5, 8, 12, 15, 16, 17, 19, 21	-0.3	<0.0001
Forced vital capacity	-0.8	-1.3 to -0.3	0.003	-3.0 to 1.8	↓ 2, 6, 8, 12, 15, 21	0.2	<0.0001
FEV ₁ /FVC†	0.9	0.6 to 1.2	0.0001	-0.4 to 1.9	↑ 4, 8, 12, 21	0.5	0.01
Flow-volume curves	—	—	—	—	Restr: 2, 3, 5, 6, 8, 15, 16, 17, 19, 21	—	—

*↓/↑=reduced/increased value; Restr=mildly restrictive; †FEV₁/FVC=ratio of forced expiratory volume in one second to forced vital capacity.

ETHICS

All participants, and the parents of children younger than 18, gave their written, informed consent. The study was in accordance with the Helsinki II declaration and was approved by the local ethics committee of Copenhagen, Denmark (Approval No (KF) V92-097).

Results

The figure shows the development in the pulmonary function test variables for each patient, plotted against years of follow up after bone marrow transplantation. During the first two years after their transplant, 13 of 14 patients tested had one or more reduced transfer factor values. For nine of these, the transfer factor gradually increased to values in the lower normal range during the following years. Lung volumes (TLC, FVC) were generally reduced during the first year after transplantation, then increased a little. There was then either a further slow increase (n=5) or else the values remained largely unchanged during the following years. The FEV₁ to FVC ratio was reduced in only three patients during the first year after transplantation. In only four patients was there a reduction in the later measurements.

Table 2 gives the results of the follow up tests and, for comparison, the lung function of the 348 controls. On average, the transfer factor and lung volumes (TLC, FVC) of the patients were significantly reduced and the FEV₁/FVC was significantly increased, both compared with the reference values and compared with the 348 controls. Ten of 25 patients had an abnormally low TLC and four to six patients had abnormal transfer factor, FVC, and FEV₁/FVC at the follow up test (table 2). At follow up, females had a significantly lower transfer factor than males (p=0.04); the mean values differed 0.8 standard deviation scores (95% confidence interval 0.0 to 1.6). Results of the follow up tests were not significantly different for patients with an identical sibling marrow donor (n=17) compared to other donors, for patients with more (≥grade 2, n=12) v less acute GVHD,¹⁶ or for different stages of disease at bone marrow transplantation. At the follow up test, three patients who received spinal irradiation, and two who had interstitial pneumonia after bone marrow transplantation, did not have particularly low values compared with the other patients. We found no relation between the follow up test results and the patients' age at bone marrow transplant (data not shown). We classified 10

of 25 flow-volume curves as mildly restrictive (table 2). The other curves had no signs of restriction, and none of the curves had signs of obstruction. Nine of 10 restrictive curves were from patients with an abnormally low TLC (table 2). All patients were asymptomatic at the time of the follow up test.

Discussion

In this study we describe pulmonary function in a population based cohort of childhood cancer and bone marrow transplant survivors with the longest follow up reported to date. The transfer factor and the lung volumes were reduced, and the FEV₁/FVC was increased at the follow up test, suggesting subclinical and moderately restrictive lung disease in patients without chronic GVHD, four to 13 years after total body irradiation and allogeneic bone marrow transplantation. One in four patients had abnormally low transfer factor, TLC, and FVC values at the follow up test, whereas this would be expected in only one in 20 normal subjects. Most pulmonary function tests shortly after bone marrow transplantation showed reduced lung function, and in many patients lung function improved more than three years after bone marrow transplantation.

Restrictive changes in pulmonary function after bone marrow transplants and late increases in lung volumes and transfer factor have been found previously in studies of children and adults,^{8 10 24 25} but these studies all had a shorter follow up time than ours. Our study is the first to show that the restrictive pulmonary changes persist for a median of eight years after bone marrow transplantation. A recent study of children¹¹ found lung volumes around or above normal from before bone marrow transplantation until four years after it, with a slow but significant decrease in lung volumes with time.

Several sequelae of cancer treatment are worse in children treated at a young age,²⁶⁻²⁹ but we found no relation between the patients' age at bone marrow transplantation and the transfer factor or lung volumes (TLC, FVC) at follow up. Hence the lungs of younger children do not seem to be more sensitive to damage from this type of cancer treatment than the lungs of teenagers. A previous study of patients treated for Wilms's tumour did not find a relation between the age at lung irradiation and the severity of reduced lung function either.³⁰

The significance of correct reference values is obvious, but the choice from published

reports is difficult: continuous reference values are few and incomplete,³¹ and adult reference values²⁰ predict higher results for an 18 year old than most paediatric reference values,^{21 22 32} resulting in artificial decreases in relative pulmonary function test values (for example, SDS) for persons passing their 18th birthday. The disagreement at age 18 can be avoided by relating pulmonary function test results of young adults to extrapolated paediatric reference values, but they predict too low values for our young adult controls (data not shown). Since the reference values chosen did not quite fit with our 348 controls (table 2), we might have slightly underestimated our patients' reduction in transfer factor and FVC, and overestimated their reduction in TLC and the increase in FEV₁/FVC, but taking this into account did not change our conclusions (table 2).

Our participants were so homogeneous that we could not test for any influence of interstitial pneumonia, chronic GVHD, type of malignancy, tobacco smoking, or type of GVHD prophylaxis on long term lung function. We could not relate changes in lung function to either the bone marrow transplantation procedure and its complications or to the malignancy and the pre-bone marrow transplantation treatment because we lacked pulmonary function tests before transplantation in most of the patients.

In conclusion, survivors of childhood leukaemia or lymphoma were asymptomatic but had a moderately restrictive pulmonary deficiency at a median of eight years (range four to 13) after total body irradiation and allogeneic bone marrow transplantation. The degree of restrictive pulmonary deficiency was not related to the age of the patient at transplantation. Lung function in some patients changed considerably several years after their transplants, so it will be of clinical importance to follow lung function in these patients long term.

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