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ORIGINAL ARTICLE

Impact of cumulative anthracycline dose, preparative regimen and chronic graft-versus-host disease on pulmonary and cardiac function in children 5 years after allogeneic hematopoietic stem cell transplantation: a prospective evaluation on behalf of the EBMT Pediatric Diseases and Late Effects Working Parties

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This prospective study focused on risk factors and clinical outcome of pulmonary and cardiac late effects after allogeneic hematopoietic stem cell transplantation (allo-HSCT). We prospectively evaluated 162 children by pulmonary function tests (PFTs) and cardiac shortening fraction (SF) before allo-HSCT and yearly up to the 5th year of follow-up. The 5-year cumulative incidence of lung and cardiac impairment was 35 (hazard rate = 0.03) and 26% (hazard rate = 0.06), respectively. Patients presenting abnormal PFTs and SF at last follow-up were 19 and 13%, respectively, with a median Lansky performance status of 90% (70–100). Chronic graft-versus-host disease (c-GVHD) was the major risk factor for reduced lung function in univariate ($P = 0.02$) and multivariate analysis ($P = 0.02$). Total body irradiation (TBI) alone and TBI together with pre-transplant anthracycline administration were significant risk factors for reduced cardiac function in univariate analysis, only ($P = 0.04$ and 0.004, respectively). In conclusion, our prospective study demonstrates an asymptomatic post-allo-HSCT deterioration of pulmonary and cardiac function in some long-term survivors, who had been transplanted in childhood, and thus emphasizes the need for lifelong cardiopulmonary monitoring and the development of new strategies both to reduce pre-transplant cardiotoxic regimens and to treat more efficiently c-GVHD.
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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been recognized as one of the most important treatment options in some hemato–oncological disorders unresponsive to conventional therapy. It is well known that pulmonary and cardiac impairment due to chemo–radiotherapy in children is particularly relevant, given that the heart and lung parenchyma are still growing in children.[1]

One of the most frequent causes of pulmonary late effects seems to be acute and chronic graft-versus-host disease (c-GVHD), even if the precise relationship with lung complications remains unclear.[2] Although data in animal models support a role of alloreactive donor T cells in determining lung damage following c-GVHD, the precise mechanism by which this complication can affect lung interstitium remains unsolved.[3,4] In adult patients, late pulmonary function abnormalities have been shown to be responsible for higher non-relapse mortality, mostly because of c-GVHD.[4,5] This prospective study aimed to demonstrate both the incidence and the risk factors of post-allo-HSCT pulmonary and cardiac late effects, including a

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large number of children with a longer follow-up than described in the past.[6–14]

Patients and methods

This multicenter prospective study enrolled 162 consecutive pediatric patients who underwent allo-HSCT from January 1994 to December 1997, for malignant and non-malignant diseases, in nine European Group for Blood and Bone Marrow Transplantation (EBMT) centers, which agreed to participate in the study. An informed consent from each patient's parents or guardians was obtained before starting the study. The EBMT investigators set up a simple form which registered patients' demographics and clinical characteristics, including information on severe lung and heart abnormalities, acute and c-GVHD as well as every cause of death after allo-HSCT.

Data on cytomegalovirus (CMV) antigenemia were collected for every patient. In the case of severe lung pathologies, lung biopsies were considered optional for the study.

Patients 0–18 years old at the time of allo-HSCT were requested to perform standardized pulmonary function tests (PFTs) and echocardiography (Echo) before allo-HSCT and at yearly intervals up to the 5th year after allo-HSCT. More sophisticated functional tests, such as exercise tests, were not taken into consideration, given that they were not performed by all participating centers. The information on Echo was reported on the form, whereas all PFTs features were reviewed by a single pneumologist in order to give a more homogeneous interpretation of the data. Because of its well-known cardiac toxicity, the total dose of anthracyclines only was requested in the form.

PFTs

PFTs were generally performed in patients older than 6 years. The following parameters were considered for the study: (a) slow vital capacity (=VC%), measured during a maximal slow inspiration; (b) forced vital capacity (=FVC%); (c) forced expiratory volume in the first second (=FEV1%); (d) ratio between FEV1 and FVC% (FEV1%/FVC%). PFTs were performed according to the American Thoracic Society's criteria.[15,16]

Diffusion capacity for carbon monoxide was not mandatory because of the well-known difficulty to perform this test in pediatric patients. Total lung capacity (TLC) was calculated as the sum of VC and residual volume.

Patients were considered to have normal PTFs when the percentage of VC and FEV1 was >80 or when VC was >80, FEV1 >70 and FEV1%/FVC% was >90.

'Restrictive syndrome' was defined when VC% was <80 and FEV1%/FVC% >90 and 'obstructive syndrome' when VC% was >80, FEV1% <80, FEV1%/FVC% <90 or VC%>80, FEV1% >80 and FEV1%/FVC% <90. In case of VC% <80 and FEV1%/FVC% <90, it was not possible, in absence of TLC, to differentiate between a mixed pattern and an obstructive pattern associated with hyperinflation.

Cardiac evaluation

Two-dimensional directed M-Mode Echo was performed in order to obtain information regarding dimensions, volumes, ventricular systolic function and cardiac mass. Left ventricular-end diastolic and systolic diameters were measured and cardiac function was considered normal in presence of shortening fraction (SF) >30%.[6]

Statistical analysis

Data were updated until December 2005 and then analysed.

The probability of PFTs or SF abnormalities and annual time units hazard rate were calculated using the cumulative incidence-life table method based on data collected annually.[17]

Variables to determine risk factors for reduced cardiopulmonary function included gender, age at HSCT, diagnosis, pre-HSCT anthracycline dose, total body irradiation (TBI), donor type, status at HSCT, acute and c-GVHD. The data were analysed in univariate analysis using χ^2 or Fisher exact tests, including only patients with normal test at baseline assessment and the variables with a *P*-value <0.3 entered in the multivariate logistic regression model.[18] The events were considered PFTs or SF abnormal values according to the criteria described in the Patients and methods section, for pulmonary or cardiac function respectively.

The *t*-test was used to compare test values (VC, FEV1 or SF) at each year of follow-up with the baseline pre-transplant pulmonary and cardiac values. A *P*-value less than 0.05 was considered statistically significant.[19]

The probability of 5-year overall survival (OS) after allo-HSCT to the date of death or to the date of the last follow-up was calculated using the Kaplan–Meier estimator.[20]

The cumulative incidence of non-relapse mortality was calculated using the cumulative incidence–function method, considering relapse as an alternative cause of death.[17]

The statistical analysis was performed using the SAS statistical program (SAS Institute, Cary, NC, USA; Version 8.2) and NCSS (Number Cruncher Statistical Systems; Kaysville, UT (J Hintze, 2001)).

Results

General features of all patients

Patients' characteristics are listed in Table 1. The patients enrolled in the study were affected by malignant (130/162) or non-malignant diseases (32/162). At the time of allo-HSCT, 89 patients with malignant diseases were in first or second complete remission, whereas 41 patients were in a more advanced disease stage. One hundred and five patients received an allo-HSCT from an HLA-matched sibling donor, whereas the remaining 57 patients underwent allo-HSCT from an unrelated or alternative HLA-matched donor.

In 107 of 130 patients the pre-transplant first or second-line chemotherapy included anthracyclines with a median cumulative dose of 270 mg/m^2 (range 30–690). Forty-four out of 107 patients received more than 300 mg/m^2 of anthracyclines cumulative dose.

Table 1 Patient characteristics

		No. of patients
Gender	M/F	102/60
Median age in years (range) at HSCT		8.9 (0.5–17.9)
Diagnosis	Malignant	130
	Acute lymphoblastic leukemia	76
	Acute myeloid leukemia	31
	Chronic myelogeneous leukemia	8
	Non-Hodgkin lymphoma	6
	Myelodysplastic syndrome	9
	Non-malignant	32
	Severe aplastic anemia	17
	Thalassemia	3
	Fanconi's anemia	6
	Langerhans cells histiocytosis	1
	Familiar eritrophagocytic lymphohistiocytosis	4
	Severe combinated immunodeficiency	1
Anthracyclines	Yes/no	108/54
TBI	Yes/no	94/68
Status at HSCT for malignant disease	1st or 2nd CR/other	89/41
Type of HSCT	HLA-matched sibling donors	105
	HLA-matched unrelated donors	33
	Alternative related or unrelated donors	24
aGVHD	No	60
	Yes	102
	Grade	
	1	8
	2	69
	3	21
	4	4
cGVHD	Absent	115
	Present	42
	Limited	25
	Extensive	17
	Not applicable	5

Abbreviations: aGVHD = acute graft-versus-host disease; cGVHD = chronic graft-versus-host disease; CR = complete remission; F = female; HLA = human leucocyte antigen; HSCT = hematopoietic stem cell transplantation; M = male; TBI = total body irradiation.

Ninety-four out of 162 patients received TBI for conditioning (fractionated TBI with 12 Gy as maximum dosage in 92 of them; single-dose TBI with 10 Gy in two patients only) together with high-dose chemotherapy, mostly including standard dose of cyclophosphamide with or without VP-16. The remaining patients received high dose combined chemotherapy based mostly on cyclophosphamide- and busulphan-containing regimens. The majority of patients with allo-HSCT from a sibling donor received cyclosporin-A (CSA) and patients with allo-HSCT from an unrelated or alternative donor received CSA combined with other immunosuppressive drugs (mainly methotrexate and/or antithymocyte globulin).

The OS at 5 years was 77% (confidence interval 95%: 70–84).

At last observation time, 126 out of 162 patients were alive and well (median Lansky score = 90%, range 70–100), whereas 36 patients died at a median time of 1 year post-allo-HSCT (range 24 days–4.7 years). Nineteen patients died from persistent or recurrent disease and 17 patients from transplant-related causes, most of them (71%) within the 1st year after allo-HSCT. The causes of transplant-related mortality were multiorgan failure in 10 cases, acute respiratory distress syndrome (ARDS) in three cases, systemic infectious diseases (none CMV-induced) in three and non-viral acute pneumonia in one case. The c-GVHD alone did not cause any death and no patient suffered or died from severe bronchiolitis obliterans throughout the study period. The cumulative incidence of non-relapse mortality was 10.8%, whereas relapse mortality was 12%.

PFTs evaluation

Partial information regarding VC or FEV1 tests was collected at allo-HSCT time for 136 out of 162 patients, whereas complete data able to define the normality of PFTs, according to the above-mentioned criteria, were available for 99/136. At baseline assessment, 21 out of 99 patients (21%) had pathological PFTs values. The yearly cumulative incidence and hazard rate of PFTs abnormalities of the 78 patients with normal basal values are shown in Figure 1a. Hazard rate was remarkable at the 1st year,

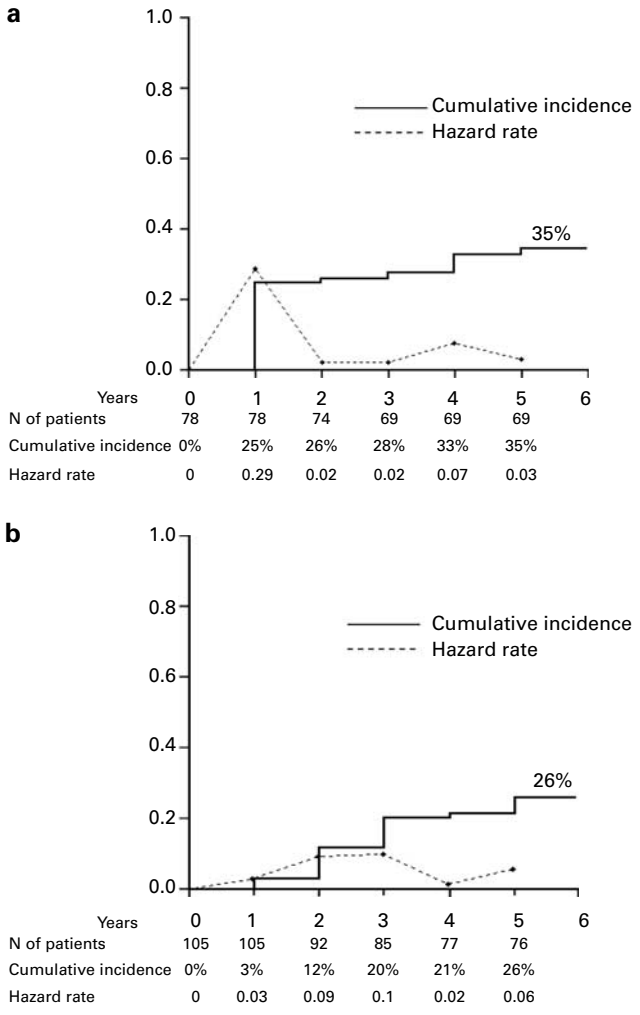

Figure 1 (**a**) The annual cumulative incidence and hazard rate of PFTs abnormalities were calculated on 78 patients with normal values at pre-HSCT phase. Every pattern different from VC > 80% or FEV1 > 70% or FEV1%/FVC% > 90% was considered an event. (**b**) The annual cumulative incidence and hazard rate of cardiac abnormalities were calculated on 105 patients with normal values of SF at pre-HSCT phase. A SF value < 30% was considered an event.

being 0.29, and decreasing to 0.03 at the 5th year. The 5th year cumulative incidence of respiratory function abnormalities was 35%. The number of patients decreased from 78 to 69 owing to allo-HSCT-related death (three patients) or lack of PFTs information during the follow-up (six patients).

Table 2 summarizes the results of univariate and multivariate analyses for risk factors performed at 5th year of follow-up. c-GVHD was the only statistically significant risk factor for deterioration of lung function at both univariate ($P = 0.02$) and multivariate analysis ($P = 0.02$), with odds ratio of 7.9.

Overall, 7/69 (10%) and 6/69 (9%) patients at 5th year of follow-up presented asymptomatic pulmonary restrictive and obstructive abnormalities, respectively (Table 3). These patients did not present a clinical history of CMV lung disease or bronchiolitis obliterans and had a normal quality of life with a median Lansky score of 90%. The yearly mean values and standard errors of VC for 90 patients and FEV1 for 89 patients are shown in Figure 2a1 and b1, respectively. For both tests, there was a statistically significant decrease (*t*-test $P < 0.001$).

In Figure 2a2 and b2, the scatter plots show the distribution of the pre-allo-HSCT test values versus the corresponding 5th year post-allo-HSCT test values.

Cardiac function test evaluation

Information regarding SF tests was available for 119 out of 162 patients. Before allo-HSCT, 14/119 (12%) of patients had abnormal and 105 patients had normal basal SF *t* tests (Figure 1b). The 5th year cumulative incidence of SF abnormalities was 26% with a hazard rate value increasing from 0.06 to 0.1 during the 1st, 2nd and 3rd year, then decreasing during the last 2 years.

At 5th year, 76 out of 105 patients were alive, nine patients have died (none of them due to late cardiac dysfunction), and 20 patients were lacking SF evaluation during the follow-up (20 cases).

In this cohort of patients, TBI alone and TBI together with anthracyclines had a statistically significant negative impact on cardiac function at the 5th year. At 3rd year follow-up, there was a significant difference by univariate analysis ($P = 0.04$ and 0.004, respectively), but not by multivariate analysis (Table 2). In particular, at last follow-up, 26% of patients who received TBI and anthracyclines had abnormal SF values, as compared with only 2% of patients without TBI and anthracyclines. No patients with acute GVHD III°–IV° or c-GVHD had abnormal cardiac function test, thus it was not possible to calculate odds ratio for these variables.

Overall, 10 out of 76 (13%) patients at 5th year presented asymptomatic cardiac abnormalities, with a median Lansky score of 90% (Table 3).

The paired *t*-test analysis was applied to 81 patients (Figure 2c1) showing a statistically significant decrease of SF test-values from the baseline evaluation to the 5th year follow-up ($P = 0.03$).

The SF scatter plot of the distribution of the pre-allo-HSCT test values versus the corresponding 5th year post-allo-HSCT test values is represented in Figure 2c2.

Discussion

The heart and lungs are considered target organs for late complications after allo-HSCT because of a number of iatrogenic factors including pre-transplant cytotoxic chemotherapy, thoracic radiation and acute or c-GVHD.[2,3,7,8,21–28]

In a systematic review focusing on late lung function abnormalities, 11 of 20 studies included 1305 patients transplanted before 1990.[24] Nine more recent studies (up to 481 patients) included patients transplanted between 1995 and 2003.[24,28] Cardiac function studies on children undergoing HSCT are still scarce[6,8,11–14] and often did not evaluate risk factors associated with late impairment of cardiac function.

Table 2 Univariate and multivariate analysis for risk factors performed at the 5th year of follow-up in patients with normal PFTs and cardiac tests at pre-allo-HSCT

Variables	*+5 years*				
	% Events		P – *univariate*	P – *multivariate*	*Odds ratio*
PFTs					
Gender M/F	23% (10/44)	12% (3/25)	0.3	NS	0.5
Non-malignant/malignant	15% (2/13)	20% (11/56)	1		
TBI alone (yes/no)	16% (7/45)	25% (6/24)	0.4		
TBI plus anthracyclines (yes/no)	12% (4/34)	26% (9/35)	0.2	NS	2.6
Status at HSCT 1st–2nd CR/other	15% (6/41)	33% (5/15)	0.1	NS	2.9
Donor type (sibling vs MUD)	16% (7/45)	25% (6/24)	0.4		
aGVHD grade 0–2/3–4	18% (10/57)	25% (3/12)	0.7		
cGVHD no or limited/extensive	15% (9/62)	57% (4/7)	0.02	0.02	7.9
Age at HSCT< >8.9 years	13% (4/32)	24% (9/37)	0.2	NS	2.3
SF					
Gender M/F	14% (7/51)	12% (3/25)	1		
Non-malignant/malignant	5% (1/20)	16% (9/56)	0.3	NS	3.6
Anthracyclines (yes/no)	19% (9/48)	4% (1/28)	0.08	NS	6.2
TBI alone (yes/no)	21% (9/43)	3% (1/33)	0.04	NS	8.5
TBI plus anthracyclines (yes/no)	26% (9/34)	2% (1/42)	0.004	NS	14.8
Status at HSCT 1st–2nd CR/other	15% (7/48)	25% (2/8)	0.6		
Donor type (sibling vs MUD)	13% (7/55)	14% (3/21)	1		
aGVHD grade 0–2/3–4	15% (10/66)	0% (0/10)	0.3	NS	—
cGVHD no or limited/extensive	14% (10/74)	0% (0/2)	1		—
Age at HSCT< >9.5 years	10% (4/42)	18% (6/34)	0.3	NS	2.0

Abbreviations: aGVHD = acute graft-versus-host disease; cGVHD = chronic graft-versus-host disease; CR = complete remission; F = female; allo-HSCT = allogeneic hematopoietic stem cell transplantation; M = male; MUD = matched unrelated donor; PFT = pulmonary function test; SF = shortening fraction; TBI = total body irradiation.
Multivariate analysis was perfomed including the variables with a univariate *P*-value <0.3.
cGVHD was the only negative prognostic factor in multivariate analysis at the 5th year for PFTs tests.
TBI alone and TBI together with anthracyclines resulted in the only statistically significant variables in univariate analysis at the 5th year for cardiac abnormalities.

Table 3 General features of patients with lung and cardiac function abnormalities at the last follow-up

	Restrictive abnormalities	*Obstructive abnormalities*	*SF<30%*
No. of patients (%)	7/69 (10)	6/69 (9)	10/76 (13)
Gender (M/F)	5/2	5/1	7/3
Age (median, range)	16 (8–20)	14 (12–17)	15 (9–21)
Anthracyclines (yes/no)	5	3	9/1
Anthracyclines (median dose, range)	350 (120–500)	270 (51–360)	300 (210–410)
Malignant disease (yes/no)	6/1	5/1	9/1
Fractionated TBI (12 Gy)	4/3	3/3	9/1
cGVHD (yes/no)	4/3	3/3	2/8
Lansky	90 (70–100)	90 (70–100)	90 (90–100)

Abbreviations: cGVHD = chronic graft-versus-host disease; F = female; M = male; SF = shortening fraction; TBI = total body irradiation.

To our knowledge, this is the only study designed to prospectively assess cardio–pulmonary function over an extended period of time after allo-HSCT performed in childhood. Noteworthy, this study includes a large number of allo-HSCT long-term survivors (77% of OS), with a substantial number of HSCT with an alternative donor and therefore at higher risk for GVHD and transplant-related mortality. To evaluate better the impact of some risk factors on pulmonary and cardiac function late effects, we chose to perform the statistical analysis on cumulative incidence and hazard rate in patients who had normal functional tests at the beginning of the study and to consider the pre-transplant procedures as principal factors in determining a future negative impact. Because of the strong association between active c-GVHD and adverse health outcome as recently stated,[29] we further focused on the role of this complication, reported in 27% of our patients, with regard to pulmonary and cardiac function late sequelae. Very little information regarding viral infections, except for CMV, was available for this analysis. This fact was because of the paucity of the specific tests available from 1995 until the end of the study in most participating centers.

With the limitation of unavailable data on factors responsible for pre-allo-HSCT pulmonary and cardiac toxicity (except for anthracyclines), it is remarkable that

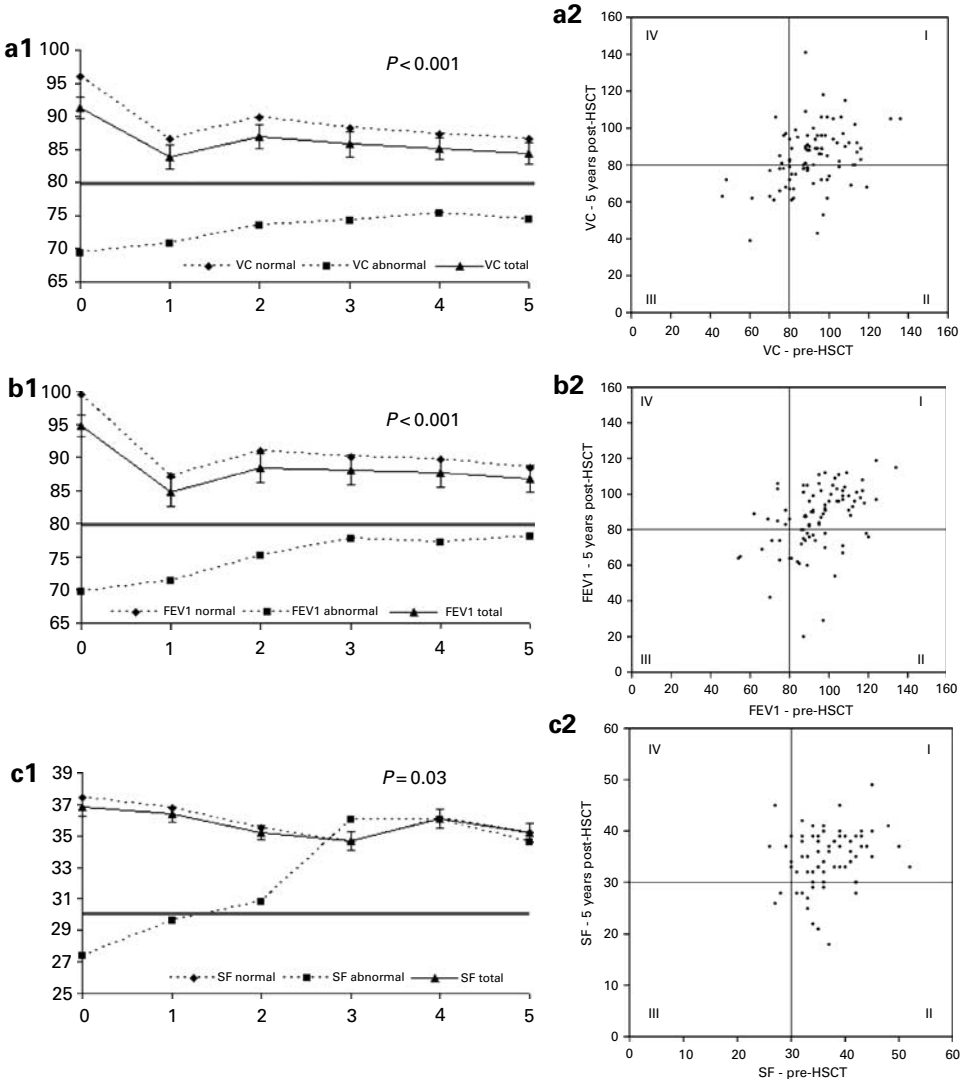

Figure 2 (**a1**) Ninety patients (74 with normal and 16 with abnormal VC tests at HSCT) are described with available data on VC tests. The values of the VC tests show a statistically significant decrease ($P<0.001$) at the 5th year. (**b1**) Eighty-nine patients (75 with normal and 14 with abnormal FEV1 tests at HSCT) are described with available data on FEV1 tests. The values of the FEV1 tests show a statistically significant decrease ($P<0.001$) at the 5th year. (**c1**) Eighty-one patients (76 with normal and five with abnormal SF tests at HSCT) are described with available data on SF tests. The values of the SF tests show a statistically significant decrease ($P=0.03$) at the 5th year. (**a2**) The scatter plots show the pre-HSCT versus the corresponding 5th year post-HSCT values, for VC tests. The majority of patients (58%) are plotted in the 1st quadrant, revealing normal tests at the 1st and the 5th year post-HSCT as well. A small group of patients with abnormal tests at HSCT became normal at the 5th year (12%), as represented in the 4th quadrant. (**b2**) The scatter plots show the pre-HSCT versus the corresponding 5th year post-HSCT values for FEV1 tests. The majority of patients (61%) are plotted in the 1st quadrant, revealing normal tests at the 1st and the 5th year post-HSCT as well. A small group of patients with abnormal tests at HSCT became normal at the 5th year (8%), as represented in the 4th quadrant. (**c2**) The scatter plots show the pre-HSCT versus the corresponding 5th year post-HSCT values, for SF tests. The majority of patients (81%) are plotted in the 1st quadrant, revealing normal tests at the 1st and the 5th year post-HSCT as well. A small group of patients with abnormal tests at HSCT became normal at the 5th year (4%), as represented in the 4th quadrant.

21 and 12% of our patients had pathological PFTs and SF respectively, at the pre-allo-HSCT baseline assessment. Our hypothesis is that increasing use of high-dose chemotherapy before HSCT also in pediatric patients may explain that both cardiac and lung dysfunction was already present in pre-transplant phase. In fact, since 1995, most of our patients, treated for malignant or non-malignant diseases at European hematology and oncology centers have received anthracyclines and high-dose methotrexate,[30,31] historically considered toxic for cardiac and lung function.[32–35]

Despite the relatively high cumulative incidence of pulmonary function late sequelae in our patients (35%), there was a continuous decline of hazard rate for PFTs abnormalities from the 1st to the 5th year of follow-up. It is worth noting that at the end of the study, 10 and 9% of patients presented only asymptomatic pulmonary restrictive and pure obstructive abnormalities, respectively.

As expected but not well demonstrated in past studies, both the univariate and multivariate analyses confirmed the negative role of c-GVHD on pulmonary function at 5th year after allo-HSCT ($P=0.02$). A small subset of patients

was at high risk to have abnormal PTFs (odds ratio = 7.9), but even then none of our adolescent patients suffered from severe air flow obstruction or obliterans bronchiolitis. This is quite different to what has been described in adults, where a severe air flow obstruction was responsible for up to 18% of mortality at 10 years after HSCT.[28–36] In our series of patients, there is no association between PFTs abnormality and the non-relapse mortality rate.

Cardiac activity, monitored by SF, likewise showed a continuous decline of the hazard rate at the end of the study. We have registered a relatively low incidence (13%) of only asymptomatic late cardiac dysfunction in patients who received a median dose of 300 mg/m^2 of anthracyclines. We are aware that SF studied by M-mode Echo is an index of global systolic function of the left ventricle in resting patients only. More comprehensive information could be obtained by exercise tolerance tests including those performed after inotropic drug infusion, as impaired myocardial performance significantly affects exercise performance.

Regarding cardiac function risk factors, univariate analysis showed that TBI alone ($P = 0.04$) and TBI in combination with pre-transplant anthracyclines ($P = 0.004$) played a negative role on SF. This finding suggests the impact that both anthracyclines and TBI have on inducing an anatomic deterioration of the cardiac muscle,[37–39] resulting in a progressive decrease of the left ventricular mass as the children grow. Based on this result, one could speculate that in adolescents, where there is an increased after load because of growth as well as increased cardiac activity, an altered SF value might be synonymous with decreased cardiac reserve. With this in mind, one could harbor concerns about the results of a Dutch study involving 607 non-transplanted children treated with anthracyclines (300 mg/m^2 as median dosage) for malignancies. In this study, the cumulative incidence of early and late cardiac insufficiency was 2.8% at 6.3 years after therapy withdrawal.[40]

With regard to the pulmonary function over the years, despite the fact that there was a significant mild worsening of PFTs between baseline and the 5th year post-HSCT, most of our patients who had normal values at the beginning of the study remained functionally normal even at the last follow-up. Our patients, although normal from the clinical point of view, presented mean VC basal values below those expected, indicating a probable restrictive pulmonary involvement. A mild VC worsening was also evident, especially within the 1st year after HSCT, in the majority of so-called normal patients, probably owing to GVHD. We have no valid explanation for the few patients with PFTs basal abnormalities (Figure 2a1 and b1) showing some improvement, especially after the 1st year from the HSCT. However, we could assume that a pre- and post-HSCT obstructive lung pattern could have benefited from corticosteroid treatment for GVHD, whereas the restrictive pattern, owing to a loss of lung volume at the pre-HSCT phase, was more likely linked to an insufficient thorax size, which thereafter tends to improve during childhood, rather than linked to interstitial damage.

Moreover, a statistically significant decrease in cardiac function tested by Echo was found at 5th year of follow-up ($P = 0.03$). In those few patients with abnormal SF at the pre-transplant phase, a post-transplant recovery of SF was observed. This finding could encourage an allo-HSCT even in patients with asymptomatic cardiac dysfunction before transplantation.

In conclusion, those children who undergo HSCT for malignant or non-malignant diseases seem to be prone to developing cardiac and respiratory late effects (even if subclinical), as compared with a healthy matched population. Factors such as the age at HSCT, the diagnosis of malignant versus non-malignant disease or non-TBI-containing regimens did not play a major role in the development of cardiopulmonary late effects.

Fortunately, our study underlines that most cured patients (now adolescents) have a good performance score (90% Lansky) and transplant-related mortality owing to severe pulmonary and cardiac function abnormalities has not been observed.

The significant impact of some pre-transplant risk factors, such as anthracycline and TBI treatment or post-transplant complications such as c-GVHD, should encourage clinicians to pay more attention to pre-allo-HSCT treatment, which can itself damage the cardiac somatic growth[41] and to the choice of the conditioning regimen (with or without TBI) or to the improvement of the c-GVHD therapy. With regard to rescuing the cardiac function, recent data are in favor of the use of dexrazoxane in leukemic children who are likely to have myocardial anthracycline-associated injury.[42]

Finally, asymptomatic patients should be monitored lifelong, including use of more sophisticated tools capable of evaluating cardiopulmonary exercise performance after allo-HSCT.[43–46] This could be particularly advisable in the routine follow-up of HSCT survivors in the event of heavy manual labor or anaerobic sport activities, which could possibly trigger cardiac pulmonary insufficiency during post-adolescent age.

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