Original Article

Pre-operative and post-operative spirometry in bone marrow transplant patients*

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Abstract

Objective: To analyze the spirometry findings in patients undergoing bone marrow transplant, determining the importance of such findings in predicting postoperative pulmonary complications and looking for correlations with postoperative outcomes. **Methods:** The spirometry findings in 120 male and female patients, all above the age of 12, were evaluated retrospectively and compared in terms of the following parameters: the type of bone marrow transplant; the underlying disease; cytomegalovirus serology; source of the transplanted cells; smoking; pulmonary infection; history of lung disease; duration of the hematological disease; chemotherapy employed; conditioning regimen; acute or chronic rejection of the transplant; and post-operative mortality. **Results:** In the pre-operative spirometry, 16 patients (13.3%) presented alterations: 6 (5%) presented pure obstruction; 7 (5.8%) presented pure restriction; and 3 (2.5%) presented obstruction accompanied by a reduction in vital capacity. In the post-operative spirometry, 29 patients (24.2%) presented alterations. The chance of presenting post-operative spirometric alterations was greater in patients presenting acute transplant rejection ($p = 0.02$), patients older than 30 ($p = 0.02$), female patients ($p = 0.02$) and patients receiving stem cells ($p = 0.01$). Having a history of lung disease was found to be associated with greater mortality, as was suffering from chronic transplant rejection. No relationship was found between pre-operative spirometric alterations and post-operative mortality. **Conclusion:** In bone marrow transplant patients, the alterations found through pre-operative spirometry were not predictive of post-operative pulmonary complications or mortality. Nor were such alterations determinant of whether or not a given patient was a good candidate for bone marrow transplant. Simple spirometry seems to be of little practical importance in the evaluation of such patients.

Keywords: Spirometry; Bone marrow transplantation/adverse effects; Bone marrow transplantation/mortality.

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Submitted: 21/2/06. Accepted, after review: 15/5/06.

Introduction

Pulmonary complications constitute an important cause of morbidity and mortality after bone marrow transplant (BMT).[1] The use of pulmonary function tests (PFTs) in pre-operative evaluation and post-operative monitoring, together with the identification of post-operative non-infectious complications, might allow the adoption of early preventive and therapeutic measures in patients at high risk.[2]

The main pulmonary functional alterations seen after BMT are as follows: obstructive ventilatory defects, which are characterized by reduced forced expiratory volume in the first second (FEV_1) and a lower ratio between FEV_1 and forced vital capacity (FVC), bronchiolitis obliterans being the pulmonary complication that results in the worst post-BMT prognosis; restrictive ventilatory defects, which are defined as a reduction in total lung capacity (TLC) and in vital capacity, with the FEV_1/FVC ratio and the ratio of forced expiratory flow between 25% and 75% of FVC to FVC (FEF_{25-75}/FVC) both being either preserved or elevated, the most common factors associated with this condition after BMT being thoracic irradiation, pulmonary toxic chemotherapy, infections, idiopathic pneumonia, and graft-versus-host disease (GVHD); obstructive ventilatory defects with reduced FVC (in this case, the reduced FVC might be due only to the obstructive process or to associated restrictive process, and TLC measurement is necessary in order to make the diagnosis); mixed ventilatory defects, in which obstruction is accompanied by restriction, as determined by measuring TLC (among BMT patients, we might find some with bronchiolitis obliterans who develop concomitant pulmonary fibrosis); reduction in the diffusing capacity of the lung for carbon monoxide (DLCO), which is the most common functional abnormality, occurring in approximately 50% of the patients, the risk factors being the same as those for restrictive ventilatory defects.[1-8]

Since the implementation of the BMT Clinic at the Hospital das Clínicas da Universidade Federal de Minas Gerais (HC-UFMG, Federal University of Minas Gerais Hospital das Clínicas) in July of 1995, simple spirometry with bronchodilator test is routinely performed in the evaluation of pre-operative pulmonary function and in the monitoring of post-operative patients. Despite having been performed for over ten years, it is not exactly known how important these tests are in the early detection and in the adoption of preventive or therapeutic measures in the treatment of post-BMT pulmonary complications. Therefore, the analysis of the progress of patients submitted to BMT at the HC-UFMG and undergoing pre-operative/post-operative spirometry might be important and could permit the adoption of new protocols for the evaluation of pulmonary function in this population.

Methods

This was a retrospective study in which we analyzed the medical charts of all patients submitted to BMT at the HC-UFMG in the period from July of 1995 to January of 2004. We included all patients over 12 years of age, of either gender, in spirometry results were obtained before and (at least once) following the BMT (after post-transplant day 100).

The spirometry tests were performed in the HC-UFMG Pulmonary Function Laboratory using a Collins spirometer with a universal respiratory valve (DS11a; Warren E. Collins, Inc., Braintree, MA, USA) and a Koko spirometer (92494; Ferraris Respiratory Europe, Hertford, UK). The volume-time and the flow-volume curves were obtained following the norms established in the Brazilian Thoracic Society Pulmonary Function Test Guidelines.[8] All spirometry test curves were reviewed by the authors of this study.

The spirometry findings (vital capacity, FVC, FEV_1/FVC, and the FEF_{25-75}/FVC and FVC) were the variables of principal interest. The test results were classified as normal, obstructive, restrictive, or obstructive with a reduction in vital capacity.[8] For this classification, we used the reference table devised by Pereira et al.[7] for male patients over 24 years of age and female patients over 20 years of age. For the remaining patients, those presenting values below 80% of the normal reference value were considered altered.[9] The independent variables analyzed were as follows: gender; age; the underlying diagnosis; cytomegalovirus serology of the donor and receptor; source of cells for the BMT; smoking; the use of pre-BMT chemotherapy; history of lung disease; pre- and post-BMT lung infection; duration of hematological disease; conditioning regimen used; use of total body irradiation (TBI); acute or chronic GVHD of the skin, mouth, eyes, liver, intestines, or lung; and mortality (defined as death at any time after post-transplant day 100).

The use of at least one of the following medications was considered indicative of a pulmonary

toxic reaction to chemotherapy: hydroxyurea, cytosine arabinoside, daunorubicin, cyclophosphamide, busulfan, bleomycin, methotrexate and cyclosporine.[1,10-13]

The information collected was entered into a database developed using the Epi Info program, version 6.04 (Centers for Disease Control and Prevention – CDC – Atlanta, GA, USA, public domain). The variables presenting $p \leq 0.25$ in the univariate analysis (chi-square test or Fisher's exact test) were included in a logistic regression model, in which it was considered that $p < 0.05$ indicated, in an independent manner, a statistically significant association.

The study design was approved by the UFMG Ethics in Research Committee (Process no. ETIC 43904, 17 November 2004).

Results

Of the 368 patients whose charts were analyzed, 134 did not undergo the post-transplant spirometry, 95 died before post-transplant day 100 and therefore also were not submitted to a second spirometry test, and 19 were excluded for being younger than 12 years of age at the time of the transplant. Therefore, 120 patients met the inclusion criteria and were included in this study. Of those 120, 52 (43%) were below the age of 30. The distribution of the sample was similar for both genders. The mortality rate was 10%. As to the diagnosis of the underlying disease, 50% suffered from chronic myeloid leukemia. There were 24 patients who were smokers (20%), and 89 were submitted to pre-BMT chemotherapy (74%). Pre-BMT pulmonary infection was observed in three patients (2.5%). In 60 patients (50%), the underlying disease had been diagnosed less than a year prior to the BMT. None of the patients were submitted to TBI.

In this study sample, all of the transplants were allogeneic. Approximately one-third of the patients presented acute GVHD (at least one site), and two-thirds presented chronic GVHD. Post-BMT pulmonary infection occurred in 22.5% of the patients. Over 90% of the patients and donors tested positive for cytomegalovirus and had been treated with a conditioning regimen that included busulfan and cyclophosphamide (Table 1). Before the transplant, 16 patients (13.3%) presented spirometric alterations, and this number rose to 29 patients (24%) by post-transplant day 100 (Table 2).

Table 1 - Characteristics of bone marrow transplant and post-operative complications.

Characteristics	n	%
Type of transplant		
Allogeneic	120	100.0
Prophylaxis for GVHD		
Cyclosporine + methotrexate	119	99.2
Other*	1	0.8
Source of cells		
Bone marrow	51	42.5
Stem cells	69	57.5
Conditioning regimen		
Busulfan + cyclophosphamide	108	90.0
Other**	12	10.0
Post-operative complications		
GVHDa		
Lung	0	0.0
One or more sites	44	36.7
GVHDc		
Lung	8	6.7
One or more sites	80	66.7
Post-operative pulmonary infection		
Yes	27	22.5
No	93	77.5

*Cyclosporine; **Cyclophosphamide; GVHD: graft-versus-host disease; GVHDa: acute graft-versus-host disease; GVHDc: chronic graft-versus-host disease.

In the univariate analysis, the patients who had acute GVHD at one or more sites, were ≤ 30 years of age and were female had greater chances of presenting altered spirometry results on post-transplant day 100. Receiving peripheral stem cells also presented a statistical tendency toward an association with altered spirometry results (Table 3). A history of lung disease was statistically associated with higher post-operative mortality, and developing chronic

Table 2 - Results of spirometry before and after bone marrow transplant.

	Pre-transplant		Post-transplant day 100		One year after transplant	
	n	%	n	%	n	%
Normal	104	86.7	88	73.3	20	16.7
Obstruction	6	5.0	10	8.3	8	6.7
Restriction	7	5.8	12	10.0	0	0.0
Obstruction with reduction of FVC	3	2.5	7	5.8	6	5.0
Without tests	0	0.0	3	2.5	86	71.7

FVC: forced vital capacity.

Table 3 - Comparison between post-transplant day 100 spirometry results and independent variables.

	Altered results		Normal results		p	OR	95% CI
	n	%	n	%			
Gender							
Male	9	31.0	51	58.0	0.02	0.33	0.12-0.87
Female	20	69.0	37	42.0		1.0	
Age							
≤ 30 years	20	69.0	37	42.0	0.02	3.06	1.15-8.34
> 30 years	9	31.0	51	58.0		1.0	
Source of cells							
Bone marrow	6	20.7	43	48.9	0.01	0.27	0.09-0.81
Peripheral stem cells	23	79.3	45	51.1		1.0	
GVHDa							
One or more sites	16	55.2	26	29.5	0.02	2.93	1.13-7.69
None	13	44.8	62	70.5		1.0	

GVHDa: acute graft-versus-host disease; OR: odds ratio; 95% CI: 95% confidence interval.

GVHD at one or more sites also presented a statistical tendency toward an association with higher mortality. The remaining independent variables analyzed did not show any statistical significance in relation to mortality (Table 4). In the multivariate analysis, it was determined that the chances of presenting altered spirometry results by post-transplant day 100 were greater for female patients aged 30 years or less, as well as for patients who had acute GVHD, than for the remaining patients. For all patients, a history of lung disease was the only variable associated with post-operative death in such patients (Table 5).

Discussion

In the international literature, as well as in the protocols of various health care facilities at which BMTs are performed, it is recommended that PFTs be conducted before the transplant and during the post-transplant follow-up period[14-20]. The argument for doing these tests is that they are important for the diagnosis of post-operative non-infectious pulmonary complications and for the adoption of therapeutic measures and the consequent increase in patient survival.[1,2,4,10] However, this aspect could not be demonstrated in our study. It is of note, however, that, of the 368 patients submitted to BMT at the HC-UFMG in the period under study, only 120 were analyzed, which might have affected the results of our research. Nevertheless, in a systematic review of the literature, we found that the majority of such studies have had small samples (of less than 100 patients).[14] We should also mention the limitations of our study, which used the retrospective review of patient charts as a source of data and only evaluated spirometry findings, whereas the most important studies registered in the literature evaluated spirometry findings, TLC and the DLCO.[1,4,12-14,19,21]

The pulmonary function disorders seen in BMT patients are classically divided into obstructive defects, restrictive defects, and alterations in the DLCO, the last being the most commonly observed alteration.[1,4] The studies do not mention obstruction accompanied by a reduction in FVC. In our study, we observed that some patients, before and after the transplant, presented obstructive ventilatory defect with reduced FVC. Since the TLC was not routinely measured, it was not possible to analyze whether the reduced FVC observed in these patients was caused by concomitant restriction or by air trapping. The protocol of the BMT Clinic of the HC-UFMG does not include routine measurement of the DLCO, thereby preventing its analysis.

The use of TBI is an important risk factor for PFT alterations before and after BMT.[2,13,15-18] In this study, no patient received TBI before the transplant. This fact might have decreased the chances of pulmonary function alterations before and after the transplant. Some authors also reported post-transplant alterations in DLCO and TLC in patients submitted to TBI.[18,19]

In this series of cases, we determined that the spirometric alterations detected before the transplant persisted on post-transplant day 100. These alterations, however, were not related to the pulmonary complica-

Table 4 - Risk of death among independent variables.

	Death		Survival		p	OR	IC 95%
	n	%	n	%			
Previous chemotherapy							
Yes	10	83.3	81	75.0	0.72	1.67	0.31-11.9
No	2	16.7	27	25.0			
History of lung disease							
Yes	4	33.3	5	4.6	< 0.01	10.3	1.82-59.5
No	8	66.7	103	95.4		1.0	
Pulmonary toxic reaction to chemotherapy							
Did not use	2	16.7	28	25.9		1.0	
Hydroxyurea	5	41.7	56	51.9	1.0	1.25	0.20-10.0
Other*	5	41.7	24	22.2	0.25	2.92	0.44-24.15
GVHDa							
One or more sites	4	33.3	40	37.4	1.0	0.84	0.19-3.38
None	8	66.7	67	62.6		1.0	
Spirometry at admission							
Altered	2	16.7	14	13.0	0.67	1.34	0.00-7.79
Normal	10	83.3	94	87.0		1.0	
Spirometry on post-transplant day 100							
Altered	4	33.3	25	23.8	0.48	1.60	0.36-6.66
Normal	8	66.7	80	76.2		1.0	
GVHDc							
One or more sites	11	91.7	69	63.9	0.06	6.22	0.77-135.9
None	1	8.3	39	36.1		1.0	
Post-BMT pulmonary infection							
Yes	5	41.7	22	20.4	0.14	2.79	0.68-11.27
No	7	58.3	86	79.6		1.0	

*Cytosine arabinoside, daunorubicin; GVHDa: acute graft-versus-host disease; GVHDc: chronic graft-versus-host disease; BMT: bone marrow transplant; OR: odds ratio; 95% CI: 95% confidence interval.

tions most frequently described in the literature, such as bronchiolitis obliterans, severe airflow obstruction, and post-operative infection.[20-25] Two recent studies reported pre-operative pulmonary function alterations related to post-operative complications.[4,24] In those studies, it was observed that an FEV_1/FVC ratio lower than 80% was related to a two-times greater risk of post-operative airflow obstruction. In our study, this aspect was not observed, which is in agreement with the findings of other authors who also found no association between pre-operative functional alterations and post-operative complications.[26]

In the analysis of the risk factors associated with post-operative pulmonary alterations, we identified significant associations between such alterations and acute GVHD. This finding is in accordance with the literature, which shows a higher frequency of interstitial pneumonia in patients with acute GVHD.[13,19] Similarly, other authors reported acute GVHD and chronic GVHD to be risk factors for alterations in post-BMT spirometry. However, those authors reported that this complication occurs predominantly in patients who are over 60 years of age,[24,27] unlike our study, in which being 30 years of age or younger was the variable most frequently related to post-BMT functional alterations. In only one previously published study, age above 8 years was demonstrated as the only risk factor associated with altered post-operative PFT.[28] It should be noted that very young children are not able to perform spirometry in a satisfactory manner. Since we did not include patients below 12 years of age, this variable could not be compared with the findings in the literature.

Female patients presented a greater chance of presenting alterations in post-operative spirometry. Other authors also found an association between PFT alterations and being female.[29] However,

Table 5 - Model of logistic regression for altered post-transplant day 100 spirometry findings and mortality.

	Variables			
	Mortality rate	OR	95% CI	p value
Altered spirometry				
Gender (female)	1.2761	3.58	1.32-9.76	0.013
Age (≤ 30 years)	1.4503	4.26	1.55-11.74	0.005
Source of (peripheral stem)cells	1.0425	2.84	0.97-8.29	0.057
GVHDa	1.2378	3.45	1.29-9.25	0.014
Death				
History of lung disease	2.505	12.25	2.36-63.57	0.003
GVHDc	2.071	7.93	0.89-71.02	0.064

GVHDa: acute graft-versus-host disease; GVHDc: chronic graft-versus-host disease; OR: odds ratio; 95% CI: 95% confidence interval.

those authors found alterations only in the DLCO, a parameter not analyzed in our study.

In our analysis, we observed a tendency toward an association between post-operative spirometry alteration and having received peripheral stem cells for the transplant. Patients who receive stem cells have greater chances of GVHD[30] and, therefore, of PFT alterations. However, to our knowledge, this association has yet to be described in the literature.

Although there are several reports of drug-related pulmonary toxicity and its relationship with PFT alterations,[2,12-13,19,21] we were unable to demonstrate such an association in the present study. It is important to emphasize that many patients evaluated in our study did not undergo the spirometry test on post-transplant day 100, which might have jeopardized the analysis of the results.

Twelve patients (10%) died. We found no significant association between altered spirometry findings (pre- or post-operative) and mortality. This is in accordance with the results obtained by some authors, who also found no increase in fatal pulmonary complications.[3,12] However, in one of those studies, DLCO lower than 80% and alveolar-arterial gradient higher than 20 mmHg were associated with higher mortality. The same authors, in another study, observed that restrictive defects or a reduction greater than 15% in TLC at three months after the transplant were associated with a greater risk of death.[21]

The specific characterization of a history of lung disease can not be defined, since it was not included in the treatment protocol of most patients. The fact that these patients did not present altered spirometry findings can be explained, at least partially, by the absence of measurement of the absolute pulmonary volumes and of the DLCO, which are more sensitive methods for diagnosing pulmonary function alterations. However, a history of lung disease was associated with post-operative mortality. This aspect reinforces the need to thoroughly analyze pulmonary function characteristics in patients who are candidates for BMT, since a significant association between pulmonary problems and higher post-BMT mortality has been reported.[24] In that study, the mortality rate reported for patients with airflow obstruction was 9% in three years, 12% in five years, and 18% in ten years.

Despite the considerable knowledge of pulmonary function alterations and pulmonary complications in patients submitted to BMT, the alterations in pre-BMT spirometry findings were not considered a contraindication to performing the procedure. Altered spirometry findings before BMT was not related to an increase in post-operative pulmonary complications. Despite the increase in post-BMT spirometric alterations, it was not possible to demonstrate that these alterations modified the evolution of the patients. It is noteworthy that, in the present study, altered DLCO, the complication most frequently found in BMT patients, was not analyzed. Therefore, spirometry, accompanied by the measurement of DLCO and TLC, should be evaluated in prospective studies so that these important tests can be effectively incorporated into the pre- and post-BMT evaluation process.

Acknowledgments

We would like to thank the Conselho Nacional para o Desenvolvimento Científico e Tecnológico

do Brasil (CNPq, National Council for Scientific and Technological Development in Brazil) and the Comissão de Aperfeiçoamento Permanente de Ensino Superior (CAPES, Coordination of the Advancement of Higher Education) for providing financial support for this study.

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