



Early View

Research letter

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Home spirometry in bronchiolitis obliterans post allogeneic haematopoietic cell transplant

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Take home message: Long-term outcome of patients with BOS post HSCT with home spirometry is encouraging despite suboptimal adherence

To the Editor:

Bronchiolitis obliterans syndrome (BOS) is a well-characterised late-onset noninfectious pulmonary complication of allogeneic haematopoietic stem cell transplantation (HSCT), occurring in 2% to 26% of recipients[1]. It is considered to be a pulmonary manifestation of graft *versus* host disease (GVHD)[2] and is associated with a mortality rate varying from 14 to 100 % in historical series[3, 4]. Although immunosuppressive drugs are modestly effective, early diagnosis and treatment could improve its outcome[5]. After lung transplantation, home spirometry (HS) monitoring of pulmonary function allows early detection of BOS[6]; it is associated with a better response to steroids[7] and consequently is considered as a standard of care[8]. Our group was the first to report the use of HS in 37 HSCT recipients[9]. More recently, Cheng et al. showed a good correlation between HS and classical laboratory spirometry in this population[10]. We present here the incidence and long-term outcome of BOS occurring after HSCT in an extended cohort of 110 patients monitored with HS.

This single-centre study was conducted in 110 patients who received an allogeneic HSCT for haematological malignancy from June 2001 to November 2008. Inclusion criteria were: a) living in the Paris area, b) having a landline telephone and c) consenting to the study. BOS was defined as a persistent non-reversible obstructive ventilatory impairment, with a drop of forced expiratory volume in one second (FEV₁) above 20% compared to baseline value before the graft, after exclusion of other causes, using the international society of heart and lung transplantation criteria[11]. No histological confirmation was required due to the high risk of the procedure in this population.

Before HSCT, complete pulmonary functional tests (PFT) were performed and patients were trained to perform flow-volume curves twice a week with HS (individual portable spirometer, Spirotel[®], M-Elect, France, and its modem). HS monitoring was scheduled to start three months after transplantation for 18 months. HS results were centrally transmitted in real time using a landline telephone for analysis and monitoring. For each patient, correlation between data from HS and from classical laboratory spirometry was checked before transplant. When HS deterioration was detected,

with a FEV₁ drop superior to 20%, patients were referred to pulmonologists for BOS diagnosis by PFT confirmation and performance of a high resolution thoracic computed-tomography scan with expiratory phases and an infectious workup including a fiberoptic bronchoscopy with bronchoalveolar lavage to rule out a pulmonary infection. The trial was conducted in accordance with the declaration of Helsinki.

Main characteristics of the patients are described in Table 1. The median time from transplant to HS monitoring onset was 4.4 months (IQR 3 – 7.1) and the monitoring was continued for a median time of 16.2 months (IQR 7.2 – 21.2). According to the criteria published by Kugler et al.[12], good adherence (>80% scheduled HS effectively performed) was observed in 35.5% patients, moderate adherence (50 – 80% HS performed) in 31.8% and poor adherence (<50% HS performed) in 32.7%. During the follow-up time, 49 drops \geq 20% in FEV₁ in HS were reported in 34 patients, and 34/49 (69%) in 26 patients were confirmed by standard spirometry. Seventeen drops were related to BOS diagnosis (N=13) or worsening (N=4), but HS anomalies also allowed the detection of other pulmonary complications: infections (N=6), pulmonary embolism (N=1), cardiac failure (N=3) or others (N=7).

Twenty-six BOS were diagnosed at a median time of 14 months (IQR 10.5 – 21.1) post HSCT, leading to a 5-year cumulative incidence of 27.7% (95% CI 19.9 – 38.8%). In 13 of the cases, BOS detection was made by HS. Reasons for lack of BOS diagnosis by HS were non-adherence (N=6), BOS occurring before (N=2) or after (N=4) monitoring or non-specified (N=1). Finally, HS detected 13/20 (65%) BOS occurring during the effective period of equipment: 9/11 (82%) in good/moderate adherers *versus* 4/9 (44%) in poor adherers. Thus, HS was a useful tool for BOS detection in good adherers.

At BOS diagnosis, three patients were asymptomatic. The median initial drop in FEV₁, compared with pre-transplant data, was 39.9% (IQR 27.3 – 45.8). All patients with BOS except one presented extra pulmonary manifestations of chronic GVHD. The 5-year cumulative incidence of BOS was 36.9% (95% CI 25.2 – 48.5%) in patients with chronic GVHD, compared to 2.4% (95% CI 0 – 7%) in those who did

not ($p=0.006$ Fine and Gray test). This confirmed that patients with extrapulmonary chronic GVHD have the highest risk of developing BOS, and could represent a group of patients that could benefit from HS.

BOS features were followed for a median of 9.4 years (IQR 7.4 – 10.7). The median maximal drop in FEV₁, compared with pre-transplant data, was 45.8% (IQR 36.4 – 58.5). Treatment of BOS consisted in systemic steroids less than 1 mg/kg/day in 65.4% patients, associated with other immunosuppressive therapies depending on those previously administered and on GVHD extrapulmonary organ involvement and specific pulmonary treatment (inhaled corticosteroids and bronchodilators, and azithromycin) as well as infectious prophylaxis. At last evaluation, worsening of FEV₁ (decrease >15% compared to diagnosis) was observed in seven (26.9%) patients whereas improvement (increase >15%) occurred in eight (30.8%) and stabilisation (variation ≤15%) in 11 (42.3%). From the 26 patients with BOS, two died of evolution of BOS associated with respiratory infection leading to an 8-year mortality due to BOS of 8.1% (95% CI 0 – 19.1%).

Aiming to indirectly evaluate the HS efficacy, we compared BOS outcome in good/moderate or poor adherers and failed to detect any difference between these patients (Table 1). Although this could argue against the HS utility after HSCT, no definitive conclusions can be drawn and only a randomised trial would definitely conclude about the HS usefulness.

We report here with a long follow-up time the features of BOS in a population of HSCT recipients monitored by HS, remarkable by the absence of pejorative effect of BOS occurrence. Indeed, only two of the 26 BOS patients died from respiratory failure, while 73% patients showed a favourable evolution (FEV₁ stable or improved) which has been correlated to a better outcome in post HSCT BOS[13]. It is noteworthy that BOS incidence, 27.7%, was similar to other studies[14] and FEV₁ drop at diagnosis was close to that reported in the NIH series[15] making unlikely the good outcome of BOS patients being related to a lower gravity of BOS.

We showed in this large cohort that HS was feasible in HSCT patients. However, adherence rate was 35.5%, which is lower than the 68% observed after pulmonary transplantation[12]. This low adherence rate could be a limiting factor for HS use in HSCT patients. In further studies, specific interventions are warranted to improve adherence of these patients less aware of the severity of pulmonary complications than lung transplant patients. These include a) a better education of patients with dedicated consultations, requiring a close collaboration between haematologists, pulmonologists and patients, b) development of systems with internet based transmission of HS data and c) providing reminders to patients through an automated reminding system.

Our study shows that HS allows BOS detection in most adherer patients and raises the issue of a potential favourable impact of HS on post HSCT BOS outcome. A randomized trial, comparing HS versus absence of HS monitoring in HSCT patients, with specific interventions to improve adherence, would definitively address the interest of this non-invasive procedure on BOS outcome.

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HAEMATOLOGICAL CHARACTERISTICS OF THE POPULATION		N= 110 (%)
Gender	Male	59 (53.6)
Age at transplant, years		46.3 (40.1 – 54.7)
Diagnosis	Acute Leukaemia	28 (25.5)
	Non Hodgkin Lymphoma	34 (30.9)
	Myeloma	16(14.5)
	Chronic Lymphocytic Leukaemia	10 (9.1)
	Other ¹	22 (20)
Previous HSCT	Autologous	45 (40.9)
	Allogeneic	3 (2.7)
Conditioning regimen	Myeloablative / Reduced Intensity	57 (51.8) / 54 (49.1)
	With anti thymocyte globulin	29 (26.4)
	Total Body Irradiation	
	> 6 Gray	38 (34.5)
	≤ 6 Gray	12 (10.9)
Stem cell source	Peripheral Blood Stem Cells	59 (53.6)
	Bone Marrow	50 (45.5)
	Cord Blood	1 (0.9)
Donor / Recipient sex Mismatch		55 (50)
Type of Donor	Matched related	58 (52.7)
	Matched unrelated	46 (41.8)
	Mismatched	6 (5.5)
GvHD prophylaxis²	Cyclosporine + methotrexate	65 (59.1)
	Cyclosporine + mycophenolate mofetil	22 (20)
	Other	11 (10)
5-year overall survival		71,4% (95% CI 62.8 – 80.1 %)
5-year non relapse mortality		15,1% (95% CI 6.5 – 23.7%)
CHARACTERISTICS AND EVOLUTION OF THE BOS POPULATION		N= 26(%)
Time from transplant to BOS, months (range)		14 (10.5 – 21.1)
Pulmonary symptoms at BOS diagnosis		23 (88.5)
Chronic Graft versus Host Disease at diagnosis		
	No	1 (3.8)
	Limited	7 (26.9)
	Extensive	18 (69.2)
Immunosuppression therapy at diagnosis		
	Yes	19 (73.1)
	No	7 (26.9)
Drop in FEV₁³ at diagnosis, % baseline		39.9 (27.3 – 45.8)
Predicted FEV₁ at diagnosis, % theoretic		59 (51 - 74)
Maximal Drop in FEV₁, % baseline		45.8 (36.4 – 58.5)
Drop in FEV₁ at last follow-up, % baseline		31.2 (23.5 – 49.1)
FEV1 evolution at last follow up (compared to BOS diagnosis)		
	Improving	8 (30.8)
	Stable	11 (42.3)
	Worsening	7 (26.9)
Oxygenotherapy requirement		2 (7.7)
Death of respiratory failure without haematological relapse		2 (7.7)
EFFECT OF ADHERENCE IN FEV₁ EVOLUTION IN THE BOS POPULATION		N= 26
Drop in FEV₁ at diagnosis, % baseline		
	Good/moderate adherers	37.1 (25.3 – 50.7)
	Poor adherers	39.9 (34.9 – 41.8)
		p=0.84
Maximal Drop in FEV₁, % baseline		
	Good/moderate adherers	46 (38.4 – 58.6)
	Poor adherers	42.7 (36.5 – 52.8)
		p=0.62
Drop in FEV₁ at last follow-up, % baseline		
	Good/moderate adherers	31.2 (24.3 – 55.1)
	Poor adherers	29 (23.2 – 36.6)
		p=0.60

Table 1: Characteristics of the population. Data are expressed as median (interquartile range) or number (percent). **Upper part:** haematological characteristics. ¹ Others include: Myelodysplastic syndromes, chronic myelogenous leukemia, Hodgkin lymphoma, bone marrow failure, myeloproliferative syndromes, chronic myelomonocytic leukemia, hemoglobin disorders. ² 12 missing data. **Middle part:** Characteristics and evolution of the BOS population. ³ expressed in percentage of pre transplant values. **Lower part:** Evolution of FEV₁ according to adherence group in the BOS population. Good/Moderate adherers N=15, Poor adherers N=11 (p, unpaired t test).