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## Clinical course of patients with bronchiolitis obliterans following hematopoietic stem cell transplantation☆

### *Evolución de los pacientes con bronquiolitis obliterante secundario a trasplante de progenitores hematopoyéticos*

*To the Editor:*

Chronic graft-versus-host disease (cGVHD) is a multisystemic disease with high morbidity and mortality that develops as a complication in 30%–70% of allogeneic hematopoietic stem cell (HSCT) transplants[1]. Bronchiolitis obliterans (BO) is the pulmonary manifestation of cGVHD, and usually presents as fibrosis and scarring of the small distal airway and fixed airflow obstruction[1,2]. Its clinical presentation includes dyspnea, exercise intolerance, and non-productive cough[1,3]. Clinical manifestations are non-specific, and many patients are initially asymptomatic, so this disease can be diagnosed late. The incidence in patients receiving allogeneic HSCT is estimated to be 2%–5% and 6% in patients already diagnosed with cGVHD[1,4,5], but recent publications suggest that the incidence is on the rise. Thus, the study by Chien et al. showed a prevalence of BO of 5.5% in general, 10% in patients who survived at least one year, and 16% in patients already diagnosed with cGVHD[6,7].

The aim of this study was to describe the prevalence, clinical and spirometric characteristics, and survival of patients with GVHD who developed BO in the previous 10 years. The Hematology and Respiratory Medicine Departments of the Hospital de la Princesa have been collaborating for years in the joint follow-up of these patients. We conducted a retrospective observational study of the 289 HSCTs performed at the Hospital de la Princesa between January 2009 and June 2018, and finally selected 42 patients who were diagnosed with BO. The following variables were collected: age at the time of transplantation, sex, baseline hematological disease, lung function at diagnosis of BO and pre- and post-transplant, microbiological isolates, radiological findings, clinical course, involvement of other organs, and mean survival. Differences in survival by sex, microbiological isolates, or involvement of the lung only or of the lung and other organs were evaluated.

Of the 42 patients with BO, 23 were men and 19 were women. The prevalence of BO was 14.8%. The mean age of the patients at transplantation was 48.39 ± 12.74 years. The HSCT was performed mainly for acute myeloblastic leukemia (34.8%), myelodysplastic syndrome (28.3%), and acute lymphoblastic leukemia (13%). In total, 52.4% of the patients were former smokers with a pack/year index of 22.26 ± 13.52. Mean $FEV_1$% was 96.28% ± 11.55 before transplantation; 64.6% ± 24.43 at diagnosis of BO; 66.86% ± 31.08 at 6 months; and 69.37% ± 25.94 at 12 months. Sputum culture was carried out in 19 patients: 10 cases were positive for *Aspergillus fumigatus*, 7 for *Pseudomonas aeruginosa* and 2 for *Haemophilus influenzae* and *Stenotrophomonas maltophilia.* The findings on chest computed tomography (CT) were: ground glass and bronchiectasis in 56.4%; alveolar infiltrates in 30.8%; air trapping in 15.4%, and peribronchial thickening and peribronchial nodules in 12.8%. No patient showed images consistent with pleuropulmonary fibroelastosis.

In 11 patients, cGVHD was exclusively pulmonary, while involvement of both the lungs and other organs was observed in the remaining patients (74.4%). The most frequently affected organ was the skin, in 24 cases, followed by ocular (20 cases), oral (17 cases), and hepatic (17 cases) manifestations.

Seventeen patients died, 4 were lost to follow-up, and 24 were still alive at the time of the study. The causes of death were respiratory in 76.4% of the patients, and neurological and digestive in 11.7% each. Fig. 1 shows that the median survival of these patients was 175 months. There were no differences in survival according to sex, microbiological isolates or organ involvement.

In this study, we analyzed the prevalence and clinical characteristics of BO in HSCT. The prevalence of BO in our hospital was 14.8%, which is slightly higher than described in other studies, perhaps due to earlier diagnosis. In previous studies, $FEV_1$% at diagnosis ranged from 40% to 59%, whereas in ours it was 64.6%, suggesting that we may be diagnosing and treating patients with milder involvement. However, mortality was high, and median survival was 175 months. Limitations of our study include particularly the number of patients and the patient inclusion timeline, so it was difficult to analyze all factors that could influence mortality.

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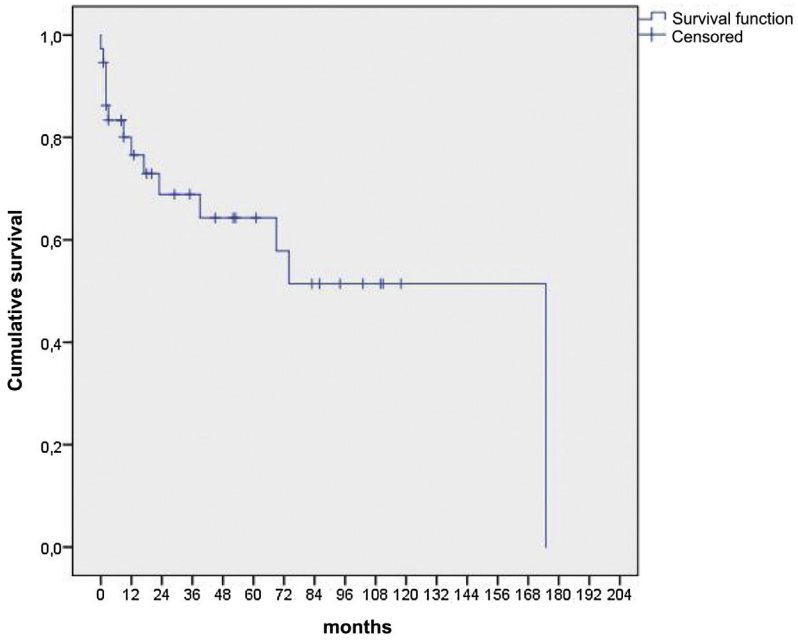


**Fig. 1.** Overall survival of patients diagnosed with bronchiolitis obliterans due to allogeneic hematopoietic stem cell transplantation.

In 2015, the National Institutes of Health (NIH) modified their earlier 2009 criteria, specifying that in the presence of any sign of cGVHD, a clinical diagnosis of BO syndrome would be given if all of the following criteria were met: $FEV_1/FVC < 70\%$ and $FEV_1 < 75\%$ predicted with decline in $FEV_1 \geq 10\%$ in less than 2 years, absence of evidence of active respiratory tract infection at diagnosis from symptoms, chest X-ray or chest CT and microbiological studies (culture of sputum, bronchial aspiration, or bronchoalveolar lavage), and one of the following: presence of air trapping on expiratory acquisition slices, small airway thickening, or bronchiectasis on high-resolution CT of the chest or evidence of air trapping in lung function tests, residual volume (RV) > 120% predicted, or RV/total lung capacity (TLC) > 90%. If the patient already had a diagnosis of GVHD involving any organ, then only the first of the 3 criteria was necessary for the diagnosis of BO. If BO was the only clinical manifestation, a lung biopsy would be required to establish the diagnosis.

The detection of BO requires lung function tests and chest CT tests with expiratory acquisition. Some studies propose performing lung function tests every 3 months in the first 2 years after HSCT. If BO is diagnosed during that period, 3-monthly follow-ups are recommended. In contrast, in patients without BO after 2 years, spirometric monitoring is only proposed in the case of respiratory symptoms[1,8].

Recently, the European Society for Blood and Marrow Transplantation published a consensus document containing recommendations for prophylaxis and treatment of GVHD[9]. FAM therapy is recommended for the management of BO, as follows: inhaled fluticasone 440 μg/2 times daily, azithromycin 250 mg/3 times weekly, and montelukast 10 mg/once daily. The guidelines also recommend discontinuing azithromycin once BO control has been achieved, since the possibility of recurrence of underlying hematological disease associated with prolonged treatments has been described[9].

In this study, we conclude that BO is a complication of cGVHD that affects around 15% of patients with allogeneic HSCT and has a mortality rate of up to 45%. It may appear alone or with the involvement of other organs, so management must be multidisciplinary. The role of pulmonologists in the follow-up of these patients is of the utmost importance, and regular functional tests are necessary after the HSCT, along with radiological and microbiological studies in the case of respiratory symptoms, in order to facilitate the early diagnosis and treatment of BO.

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## Non-Invasive Ventilation for Acute Respiratory Failure in Duchenne Muscular Dystrophy Patients

## *Ventilación no invasiva para la insuficiencia respiratoria aguda en pacientes con distrofia muscular de Duchenne*

*Dear Editor:*

Duchenne Muscular Dystrophy (DMD) is the most common inherited muscle disease in children, with a prevalence ranging between 1.3 and 2.1 per 10,000 live male births.[1] Acute Respiratory Failure (ARF) is a common complication in individuals with DMD and a primary cause of mortality, both in the teenage and adult years.[2]

Non-Invasive Ventilation (NIV) is a ventilatory technique for delivering pressurized gas to the lungs through a sealed mask that can be placed over the mouth, nose or the whole face; its utilization is recommended for the management of ARF across a variety of aetiologies. However, NIV application in exacerbated DMD patients is still controversial and not indicated by major guidelines.[3,] The aim of our study was to evaluate clinical status and outcomes in DMD patients being administered NIV for ARF.

We collected and reviewed all of the medical records of the DMD patients with ARF who were admitted to our adult 4 bed Respiratory ICU (RICU) at the University of Padua Medical Center between January 1, 2005 and December 31, 2019. Ethical approval was waived by the local Ethics Committee in view of the fact that the study was retrospective and not prepared according to a research project.

At the time of admission to the RICU, the clinical and physiologic parameters of these patients were consistent with ARF. In particular, each of them presented at least one of the following: (1) respiratory distress; (2) hypoxemia and/or hypercapnia; (3) acute respiratory acidosis.[4] Patients who had received NIV as first-line ventilatory treatment were included in the study; those who had a tracheostomy tube in place or showed an immediate need for Endotracheal Intubation (ETI)[5] were excluded.

All hospital charts were reviewed for patients' baseline clinical, demographic and pulmonary function data after informed consent release forms were obtained. Clinical, laboratory and blood gas data at RICU admission were also recorded and analyzed.

Causes of ARF were classified as: upper respiratory tract infection (URTI); acute decompensated heart failure (ADHF); pneumonia; and other (e.g., pneumothorax, pulmonary thromboembolism, dysphagia with aspiration, gastroparesis/malnutrition, acute gastrointestinal distension, abuse of sedatives). The diagnosis of URTI was based on the presence of one or more of the following symptoms or signs: fever, throat irritation or sore throat, hoarseness[6]; the diagnoses of pneumonia and/or ADHF were based on major guidelines.[7,8]

The decision to begin NIV was usually made by the attending physician, according to the hospital internal protocol.[9] NIV was usually delivered using a portable ventilator set in assisted pressure-control ventilation (APCV) mode. A commercial full-face mask was used when NIV was initiated and in some cases it was substituted by a nasal mask after the first hours of ventilation. In the event of NIV failure, the patients were shifted from NIV to Invasive Mechanical Ventilation (IMV) by ETI unless they had previously declared that they did not wish to be intubated. Mechanical In-Exsufflation (MI-E) was usually administered to those patients showing bronchial mucous encumbrance and oxyhemoglobin desaturation secondary to secretion retention, according to the hospital internal protocol.[6] The patients were divided into 2 groups depending on their NIV response. "NIV success group" was made up of those individuals who avoided ETI, were discharged from RICU and survived for at least 48 h after being transferred to the respiratory ward. "NIV failure group" was made up of those subjects who required ETI or died while on NIV support.

During the study period, 51 patients were admitted to our RICU for ARF with a primary diagnosis of DMD. Seven (13.7%) had a tracheostomy tube in place and were administered IMV via tracheal cannula, 2 (3.9%) were intubated at admission, while all the remaining 42 (82.3%), received NIV as the first-line ventilatory intervention and were considered eligible to participate in our retrospective study. No patient experienced repeated episodes of ARF. Of notice, RICU admissions were evenly distributed during the study period. Baseline demographic, clinical, pulmonary and cardiac function, of the patients are outlined in Table 1. Conditions associated with the onset of ARF in the patients studied included URTI (19 cases); ADHF (5 cases); pneumonia (4 cases); and other conditions (14 cases). The patients were administered NIV in APCV. The initial inspiratory pressure above PEEP was 12 (8–25) $cmH_2O$. All subjects were fully cooperative during NIV and did not require any sedation. NIV was successful in 36 patients (85.7%), while unsuccessful in the remaining 6 (14.3%). The median time from NIV initiation to intubation was 3.5 (1–11) days. Among patients who failed NIV, the cause of ARF was dysphagia with aspiration in 3 cases; ADHF in 2 cases; and pneumonia in 1 case. Causes of NIV failure were failure to adequately correct hypercapnia and exhaustion (3 cases), persistent accumulation of bronchial secretions (2 cases), and severe hemodynamic instability (1 case). Two patients died following intubation while on IMV support; the remaining four required tracheostomy due to difficult weaning and underwent long-term invasive ventilation. No major NIV complication was observed, while minor complications occurred in 4 patients (nasal skin lesions in 3 cases and acute bowel distension in 1 case). All 36 patients successfully treated and 4 out of 6 who failed NIV were discharged alive from hospital. Patients' characteristics at RICU admission are outlined in Table 1. The median survival of the 42 NIV patients after RICU admission was 67.1 (95%CI, 15.0 to 125.4) days. Survival was significantly reduced for patients who failed NIV, compared to those who succeeded [median survival time: 11.7 (95%CI, 0.0 to 131.0) vs 85.9 (95%CI, 24.9 to 125.4) days], with an HR of dying of 3.91 (95%CI, 1.10 to 13.93; $p = 0.0351$). None of the covariates had a significant effect on NIV failure. However, patients who did not respond to NIV were younger than those who succeeded [15 (14–30) vs. 24.5 (14–41) yrs; $p = 0.0201$]; moreover, patients' characteristics at RICU admission showed greater HR values [123.0 (120.0–134.0) vs. 104.0 (45.0–112.0) b/min; $p = 0.0095$], total WBC count [13.2 (11.06–17.80) vs. 8.65 (2.06–18.02); $p = 0.0113$] and $SaO_2$ [98 (94.8–99.2) vs. 95.1 (88.9–99); $p = 0.011$] for failures, as opposed to successes (Table 1).