Spirometry States the Obvious: Recognizing Bronchiolitis Obliterans Syndrome Early after Hematopoietic Cell Transplantation

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Bronchiolitis obliterans syndrome (BOS), or chronic pulmonary graft versus host disease (GVHD), will affect a fairly small proportion of hematopoietic cell transplant (HCT) recipients; a recent analysis found a prevalence of 5.5% among all HCT recipients, but 14% among patients with GVHD (1). Nevertheless, the effect on those individuals is drastic. Development of airflow obstruction (2) and an official BOS diagnosis significantly increases the risk for death in patients post-HCT (1, 3). Bronchiolitis obliterans demonstrated by lung biopsy confirms the diagnosis, but transbronchial biopsies are low yield in the diagnosis of BOS (4, 5), and surgical lung biopsy comes with real risks. These caveats have led to diagnostic guidelines that omit pathologic proof of the disease.

These criteria, first published in a consensus document in 2005, require airflow obstruction, a depressed FEV₁, hyperinflation or characteristic computed tomography findings, and absence of respiratory infection (6). Despite this consensus definition, the natural history of the disease in HCT recipients has overall been poorly characterized.

In this month's issue of *AnnalsATS*, Cheng and colleagues (pp. 1932–1939) characterize, albeit with limitations of the available clinical data, the natural history of lung function decline in HCT recipients who develop BOS (7). Included in the analysis were two cohorts of HCT recipients: a multicentric cohort of patients enrolled in a trial evaluating fluticasone, azithromycin, and montelukast (FAM) for treatment of BOS in HCT recipients (8),

and patients with BOS treated with usual care at a single center, the Fred Hutchinson Cancer Research Center (1). Lung function trajectories at 6-month time intervals beginning before BOS were evaluated, and the effect of lung physiology on survival was analyzed.

The most dramatic finding in this analysis is the severity of airflow obstruction present at the diagnosis of BOS. Both cohorts of HCT recipients have a FEV_{1%} predicted in the 40–50% range at diagnosis. These values are far below the FEV₁ required to diagnose BOS in this patient population, which is less than 75% predicted (6). FEF_{25–75} was also markedly reduced at BOS diagnosis.

The authors proceed to delineate the time course of FEV₁ decline. Unfortunately, less than 50% of the cohort had pulmonary function test (PFT) data available in the 6 months before BOS diagnosis, a notable limitation. The lack of data for this period may signify that a subset of included patients experienced a more gradual disease onset, thereby not prompting more frequent PFTs. This finding speaks to a main point that Cheng and colleagues make: The lack of routine pulmonary physiologic monitoring post-HCT likely contributes to a late diagnosis of BOS, when intervention is much less likely to be effective. Each center that contributed patients to this cohort had a completely different spirometric monitoring protocol post-HCT (or no protocol at all); the majority did not monitor at specific regular time intervals post-HCT. The available trends vividly underscore the problem: the mean change

in FEV_{1%} predicted per month pre-BOS was nearly 7%.

FVC trends were characterized for the first time in a population of HCT recipients with BOS. A significant decline in FVC at BOS diagnosis predicted mortality more than any other factor. This finding, as the authors point out, parallels what has been recently described in lung transplant populations with chronic rejection. In two separate analyses of lung transplant patients, a concurrent drop in FVC at the time of FEV₁ decline correlated with an increased risk for mortality (9, 10). FVC decline appears to be a much more useful prognostic marker than previously recognized, and deserves further attention. Although the data of Cheng and colleagues suggest low FVC might be a useful finding in an HCT population with BOS, this requires further investigation in a larger cohort. Prognostic markers of survival in this population are also of significant importance to clinicians, as they may trigger more aggressive therapeutic interventions or prompt consideration of referral for lung transplantation evaluation.

The authors again recognize the cardinal problem with our diagnosis of BOS in an HCT population: the diagnosis typically occurs very late. Cheng and colleagues are certainly not the first researchers to call for more frequent PFT monitoring in HCT recipients (1, 11, 12). Why do we make the diagnosis, when FEV₁ has already markedly declined? Are our diagnostic criteria for BOS in an HCT population, published for the first time just 11 years ago, too narrow? Should the

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definition include potential BOS, or “BOS 0p” stage, as is included in the lung transplant BOS stages (13)?

Abedin and colleagues recently described that 85% of HCT recipients who meet BOS 0p criteria will subsequently develop official BOS (12). This finding, together with Cheng and colleagues’ data, calls for consideration of adoption of the BOS 0p stage in BOS grading of HCT recipients. It is also now known that lung transplant recipients with chronic rejection may develop a restrictive PFT pattern and more fibrotic CT features (9, 14, 15). Are we missing HCT patients who may have atypical spirometric patterns or who also have concomitant respiratory infection at spirometric decline,

blurring their presentation, and thereby not allowing for a BOS diagnosis to be made given atypical PFTs or concomitant infection? Should we perform routine monitoring more frequently? Or do we need more formal consensus guidelines describing how to effectively monitor these patients?

A new player in the diagnosis of BOS may be around the corner. Galbán and colleagues recently described a new radiographic biomarker that may pave the way to detect BOS earlier in HCT recipients. Parametric response mapping, a voxel-wise methodology able to quantify small airway obstruction based on CT data, demonstrated increased functional small airways disease in HCT

patients with BOS compared with matched controls (16). This metric will likely become more widely available and may serve as an additional clinical marker of BOS onset.

Cheng and colleagues have once again demonstrated that our current practices are suboptimal in detecting BOS in an HCT population. The time is now to reevaluate clinical monitoring protocols and disease definitions in this arena. Earlier diagnosis may lead to better treatment options, or at least set the stage for trials with therapies directed at BOS when fibrosis is actively occurring. ■

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References

- 1 Au BKC, Au MA, Chien JW. Bronchiolitis obliterans syndrome epidemiology after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2011;17:1072–1078.
- 2 Chien JW, Martin PJ, Gooley TA, Flowers ME, Heckbert SR, Nichols WG, Clark JG. Airflow obstruction after myeloablative allogeneic hematopoietic stem cell transplantation. *Am J Respir Crit Care Med* 2003;168:208–214.
- 3 Chien JW, Duncan S, Williams KM, Pavletic SZ. Bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation—an increasingly recognized manifestation of chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2010;16:S106–S114.
- 4 Kramer MR, Stoeck C, Whang JL, Berry GJ, Sibley R, Marshall SE, Patterson GM, Starnes VA, Theodore J. The diagnosis of obliterative bronchiolitis after heart-lung and lung transplantation: low yield of transbronchial lung biopsy. *J Heart Lung Transplant* 1993;12:675–681.
- 5 Chamberlain D, Maurer J, Chaparro C, Idolor L. Evaluation of transbronchial lung biopsy specimens in the diagnosis of bronchiolitis obliterans after lung transplantation. *J Heart Lung Transplant* 1994;13:963–971.
- 6 Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, Martin P, Chien J, Przepiorka D, Couriel D, Flowers ME, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant* 2005;11:945–956.
- 7 Cheng GS, Storer B, Chien JW, Jagasia M, Hubbard JJ, Burns L, Ho VT, Pidala J, Palmer J, Johnston L, et al. Lung function trajectory in bronchiolitis obliterans syndrome after allogeneic hematopoietic cell transplant. *Ann Am Thorac Soc* 2016;13:1932–1939.
- 8 Williams KM, Cheng GS, Pusic I, Jagasia M, Burns L, Ho VT, Pidala J, Palmer J, Johnston L, Mayer S, et al. Fluticasone, azithromycin, and montelukast treatment for new-onset bronchiolitis obliterans syndrome after hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2016;22:710–716.
- 9 Todd JL, Jain R, Pavlisko EN, Finlen Copeland CA, Reynolds JM, Snyder LD, Palmer SM. Impact of forced vital capacity loss on survival after the onset of chronic lung allograft dysfunction. *Am J Respir Crit Care Med* 2014;189:159–166.
- 10 Belloli EA, Wang X, Murray S, Forrester G, Weyhing A, Lin J, Ojo T, Lama VN. Longitudinal forced vital capacity monitoring as a prognostic adjunct after lung transplantation. *Am J Respir Crit Care Med* 2015;192:209–218.
- 11 Hildebrandt GC, Fazekas T, Lawitschka A, Bertz H, Greinix H, Halter J, Pavletic SZ, Holler E, Wolff D. Diagnosis and treatment of pulmonary chronic GVHD: report from the consensus conference on clinical practice in chronic GVHD. *Bone Marrow Transplant* 2011;46:1283–1295.
- 12 Abedin S, Yanik GA, Braun T, Pawarode A, Magenau J, Goldstein SC, Levine JE, Kitko CL, Couriel DR. Predictive value of bronchiolitis obliterans syndrome stage 0p in chronic graft-versus-host disease of the lung. *Biol Blood Marrow Transplant* 2015;21:1127–1131.
- 13 Meyer KC, Raghu G, Verleden GM, Corris PA, Aurora P, Wilson KC, Brozek J, Glanville AR; ISHLT/ATS/ERS BOS Task Force Committee; ISHLT/ATS/ERS BOS Task Force Committee. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur Respir J* 2014;44:1479–1503.
- 14 Sato M, Waddell TK, Wagnetz U, Roberts HC, Hwang DM, Haroon A, Wagnetz D, Chaparro C, Singer LG, Hutcheon MA, et al. Restrictive allograft syndrome (RAS): a novel form of chronic lung allograft dysfunction. *J Heart Lung Transplant* 2011;30:735–742.
- 15 Verleden SE, de Jong PA, Rutten D, Vandermeulen E, van Raemdonck DE, Verschakelen J, Vanaudenaerde BM, Verleden GM, Vos R. Functional and computed tomographic evolution and survival of restrictive allograft syndrome after lung transplantation. *J Heart Lung Transplant* 2014;33:270–277.
- 16 Galbán CJ, Boes JL, Bule M, Kitko CL, Couriel DR, Johnson TD, Lama V, Telenga ED, van den Berge M, Rehmulla A, et al. Parametric response mapping as an indicator of bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2014;20:1592–1598.