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RESEARCH ARTICLE

Obstructive and Restrictive Lung Disease After Hematopoietic Stem Cell Transplantation

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ABSTRACT
Pulmonary complications are frequently encountered by clinicians in patients who have undergone hematopoietic stem cell transplantation and are associated with increased morbidity and mortality in these patients. Complications involving the lung are caused by both infectious and non-infectious etiologies, with non-infectious complications associated with significant long-term effect on the quality of life and can occur several years after transplantation. One manifestation of non-infectious post-transplant complication is a change in pulmonary function testing compared to pre-transplant testing. These changes can either be of an obstructive or restrictive pattern with each being associated with specific post-transplant complications. An improved understanding of obstructive and restrictive lung disease after hematopoietic stem cell transplant is necessary for both primary care physicians and specialists to recognize these diseases early in their course in order to facilitate work-up, treatment, and necessary follow-up. This review will provide an overview of obstructive and restrictive lung disease after hematopoietic stem cell transplant focusing on the etiologies, diagnosis, treatment, and outcomes. We will highlight bronchiolitis obliterans syndrome as an example of obstructive disease after transplant and will discuss pleuroparenchymal fibroelastosis as a cause for restrictive findings on pulmonary function testing. Improvements in the knowledge of the underlying etiologies and pathophysiology of obstructive and restrictive lung disease after hematopoietic stem cell transplant will allow for the identification of novel biomarkers to facilitate the diagnosis of these patients and will assist in the design of future targeted therapies to improve treatment and prognosis.

Keywords: pulmonary complications, hematopoietic stem cell transplantation, obstructive lung disease, BOS, restrictive lung disease, serositis, PPFE

Introduction

Hematopoietic stem cell transplantation (HSCT) is increasingly being used to treat both hematological and some non-hematological malignancies, as well as select genetic disorders with over 150,000 HSCT performed yearly worldwide.[1,2] Although HSCT is a lifesaving treatment, patients can develop post-transplant complications after the HSCT, especially those undergoing allogeneic transplantation. These complications can involve any organ but the most frequent organ involved is the lung wherein 30-60% of patients will develop lung complications.[1,3-6] These complications in the lung can be either infectious or non-infectious in etiology with the non-infectious lung complications having long term effects on both the quality of life as well as the prognosis after transplant.[3-5]

The onset of infectious complications is highest shortly after HSCT, when immunosuppression is at its greatest, whereas the non-infectious complications occur within the first 100 days after HSCT or much later, including several years after transplant.[7-10] These non-infectious pulmonary complications include post-transplant engraftment syndrome, idiopathic pneumonia syndrome, pulmonary veno-occlusive disease, bronchiolitis obliterans with organizing pneumonia/cryptogenic organizing pneumonia, serositis, eosinophilic pneumonia, bronchiolitis obliterans syndrome (BOS), other forms of obstructive disease, and restrictive lung disease.[11,12] Specifically for the etiologies of BOS, restrictive lung disease, eosinophilic pneumonia, and serositis these occur much later after HSCT and are associated with chronic graft versus host disease (cGvHD).

Pulmonary disease after HSCT is evaluated using clinical signs and symptoms, radiologic imaging studies (chest x-ray and computed tomography (CT) images), pulmonary physiology as assessed by pulmonary function testing, laboratory studies, and frequently bronchoscopy with bronchoalveolar lavage and occasionally lung biopsy. In regards to assessment of pulmonary physiology, results from pulmonary function testing can be broadly divided into two disease processes, obstruction and restriction. During the first year after HSCT, slow vital capacity and total lung capacity decrease by 10-20% reaching a nadir but then return to pre-transplant levels by 10 months after transplant.[13] On long-term follow-up of patients after HSCT, findings of either obstruction or restriction on PFT's occur in over 25% of patients over a 10 year time period.[14] Specifically for obstructive findings, the incidence was 7.1% at 2 years post transplant and increased to 15.7% at 10 years with a median time to the onset of obstruction being 2.5 years.[14] For restrictive findings on PFT's these values were 7.4% at 2 years and up to 19.5% at 10 years with a median time to presentation of 2.6 years.[14] These findings, however, do not necessarily indicate the development of a long-term pulmonary complication after transplant as less than 50% of those in the study by Kishida, et al that developed abnormalities on pulmonary function testing went on to develop a diagnosed obstructive or restrictive lung disease as the observed changes on PFT's were transient.[14] Taken together, this suggests that changes in PFT's seen after HSCT are reversible and require close clinical monitoring as well as serial PFT's before establishing a diagnosis of a lung complication.

Due to the frequency of pulmonary function abnormalities seen after transplant, and the associated significant morbidity and mortality with obstructive and restrictive lung disease after HSCT, it has been recommended that patients undergo screening PFT's, at least spirometry, after HSCT.[15,16] The recommended timing for these screening PFT's has been variable. The consensus conference from the NIH recommended screening by spirometry every 3 months in high risk patients for the first two years after transplant[15] whereas an international multi-society panel recommended screening PFTs to be completed 6 and 12 months after HSCT and then yearly thereafter.[16] The overarching goal of regular screening is to facilitate the earlier detection of late-onset non-infectious pulmonary complications, thereby allowing for earlier intervention and treatment. Concerns have been raised that the lack of response to treatment for obstructive lung disease (OLD) and restrictive lung disease (RLD) after HSCT is due to a delay in their diagnosis.[15,16] Although regular PFT screening after HSCT is recommended, studies have shown that these recommendations are not strictly followed. In the study by Sheshadri, et al only 40% of post-HSCT patients underwent screening PFT's during the first year after transplant wherein another study only 65% of patients received yearly or at least twice yearly PFTs after HSCT during the first two years after transplantation.[17,18] The lack of stringent follow-up described in these studies has been suggested to reflect the lack of consistent evidence that screening PFT's identify OLD and RLD earlier in their course, modify treatment response, and improve patient outcomes.[17,19] Additional large randomized, multicenter studies are necessary to address the question if serial screening PFT's after HSCT improve outcomes and patient's quality of life

In this review we will focus on the obstructive and restrictive lung diseases seen after HSCT with a

particular focus on the best described and most important obstructive lung disease after HSCT, bronchiolitis obliterans syndrome (BOS). Both obstructive, particularly BOS, and restrictive lung disease after HSCT are relatively rare complications after HSCT and are poorly understood due to a lack of large clinical trials or case series describing their clinical course, underlying pathophysiology, and treatment. As such we will discuss the diagnosis and implications of obstructive and restrictive lung disease after HSCT with a focus on potential etiologies, establishment of a diagnosis, available biomarkers, current treatment options, and outcomes.

Obstructive lung disease

As described above, finding of obstructive on PFTs after HSCT is frequent (up to 15.7% at 10 years) however only ~50% of these patients develop definable obstructive lung disease with spirometry testing returning to normal in the other 50%.[14] Accordingly, obstructive lung disease (OLD) is a rare occurrence after HSCT. Transient findings of obstruction on lung function testing is commonly caused by respiratory infections, particularly those caused by respiratory viruses.[14] As such, patients that present with newly found obstruction on PFT's need to evaluated for the presence of infection, particularly respiratory viruses, by laboratory testing and sometimes by bronchoscopy with bronchoalveolar lavage. In such cases we typically repeat spirometry 1 month after an acute respiratory illness to assess for resolution of obstruction. Persistent obstruction on repeat spirometry suggests a diagnosis of OLD, and in the setting of cGvHD, a potential diagnosis of BOS. However, findings of persistent obstruction on post-HSCT PFT's does not necessarily confirm a diagnosis of BOS, as other OLD can occur after HSCT. For example, cases of new onset asthma and/or allergies have been described in post-HSCT patients, depending on their donor source and medical history of the donor.[20] This new onset asthma reported in post-HSCT patients is thought to be due to donor lymphocytes from a donor with a pre-existing history of asthma or allergies.[20] Accordingly, a patient and donor history are necessary as well as additional testing (e.g. methacholine challenge and allergy testing) to confirm a new diagnosis of asthma or allergies after HSCT. Treatment for these cases follows established asthma therapy protocols in non-HSCT patients with the rarity of this condition preventing clinical trials for this unique population. Finally, a diagnosis of COPD needs to be considered in those with new findings, or worsening, of obstructive on PFT's after HSCT. A smoking and occupational history needs to be obtained as well as review of pre-transplant PFT's (generally performed in >90% of patients) to exclude a pre-existing history of COPD.

Bronchiolitis obliterans syndrome

The most feared non-infectious pulmonary complication after HSCT is cGvHD of the lung, also known as the bronchiolitis obliterans syndrome (BOS). This is a late stage OLD complication after allogeneic HSCT, occurring after day 100, and occurs in 5-10% of allogeneic transplant recipients.[21-23] As currently defined, BOS occurs in the setting of established non-pulmonary cGVHD, although it has been suggested to be the initial manifestation of cGvHD in a small number of patients.[23] In addition, rare cases have also been described in those undergoing autologous transplants,[24,25] At present BOS is defined using guidelines established by the National Institutes of Health (NIH) consensus conference that were recently updated.[26] These guidelines define BOS as airflow obstruction found on pulmonary function testing, with a decrease in the ratio of the forced expiratory volume in one second (FEV-1) over the forced vital capacity (FVC)(FEV-1/FVC ratio) of < 70%, a decrease in FEV-1 < 75% of predicted, a 10% decline in the FEV-1 over 2 years, or by the presence of air trapping as determined by a residual volume (RV) > 120% of predicted or as seen on expiratory CT images of the lung with the presence of lung mosaicism.[22,25,26] To increase the sensitivity of testing, and allow for the earlier detection of BOS, some groups have advocated for a 10% decline in FEV-1 as a risk for the later development of BOS and patients who need closer monitoring. As above, other causes for airflow obstruction, such as new onset asthma, COPD, or the presence of a respiratory infection need to be excluded prior to establishing a diagnosis of BOS.

Etiology and pathophysiology

The etiology of BOS is not well understood but is thought to be an alloimmune response of donor cells against host lung antigens. The involvement of T cells, B cells, NK cells, and an increase in TNF-α and interleukin 17 levels have been linked to cGvHD and BOS.[27] Other risk factors for the development of BOS have been described including use of peripheral blood as the stem cell source, undergoing total body irradiation with the conditioning regimen, an unmatched donor source, and low total immunoglobulin G (IgG) levels post-transplant.[28] Finally, respiratory infections, particularly viruses, have also been thought to play a role with the development of BOS but no study has directly confirmed this association.[23,29-31] Ongoing studies are needed to better identify the underlying etiology and pathophysiology for the development of post-HSCT BOS. The lack of an

established animal model limits the advancement in the understanding of BOS after HSCT.[32] A similar process occurs in lung transplant recipients as one form of chronic lung allograft dysfunction (CLAD) with presumed similar pathophysiology.[33] Extensions from studies of BOS in lung transplant recipients may allow for the design of novel diagnostic tools or algorithms to improve the understanding of BOS after HSCT. However, due to the unique factors with HSCT, including the hematologic malignancy and exposure to chemotherapy and radiotherapy during treatment and the conditioning regimen, there are likely unique differences between BOS that occurs after lung transplant and that which occurs after HSCT.

Diagnosis of Bronchiolitis obliterans syndrome

As mentioned above, the diagnosis of BOS is currently established by a consistent decrease in airflow on pulmonary function testing (PFT) or the presence of airflow trapping on PFT's on expiratory chest CT utilizing guidelines established by the NIH consensus conference[26]. A lung biopsy to confirm the presence of bronchiolitis obliterans is rarely performed due to the risks involved both during and after the procedure. As such, the diagnosis of bronchiolitis obliterans syndrome is used in place of bronchiolitis obliterans due to this lack of histologic confirmation and accordingly is a clinical diagnosis. In our experience, as well as that by others, the decrease in the FEV-1 and the FEV-1/FVC ratio at the time of diagnosis in patients with post-HSCT BOS is profound (average of 40-60% reduction compared to pre-transplant PFT's[19,34] and Unpublished observations. Based on the profound decrease in airflows at the time of BOS diagnosis, findings of a lesser decrease in the FEV-1/FVC ratio, in our opinion, suggest the possibility of another etiology causing the decrease in airflows. This is particularly true if no serial post-HSCT testing of lung function was undertaken. As above, the other etiologies that need to be excluded include post- infectious bronchiolitis (common after viral infections), exposure to environmental toxins/medications, or new onset asthma or reactive airway disease. With regards to chest CT imaging in post-HSCT BOS, apart from the presence of air trapping, no other chest CT findings are present in BOS. Findings on chest CT of ground glass opacities or nodular infiltrates are suggestive of a potential infectious or other non-infectious inflammatory condition (i.e. cryptogenic organizing pneumonia (COP)//bronchiolitis obliterans with organizing pneumonia (BOOP)) as the cause for the observed airway obstruction and not BOS. Importantly findings of COP or BOOP imply a completely separate disease entity and one that is generally steroid responsive, in contrast to BOS, as will be discussed below, which is generally steroid resistant. Further diagnostic testing by bronchoscopy or lung biopsy may be necessary to exclude other possibilities for the observed airflow obstruction, particularly viral infections.

Although at present BOS is diagnosed by a decline in the FEV-1/FVC ratio on spirometry or air trapping on exhalation CT imaging, at the time of BOS diagnosis the decrease in the FEV-1 and FEV-1/FVC ratio is profound (40-60% of predicted). Patients may have a profound decrease in lung function (i.e. FEV-1/FVC ratio) prior to the onset of symptoms.[35] Interestingly, changes in the NIH respiratory symptom score correlated with non-relapse survival whereas changes in the FEV-1/FVC ratio did not.[36] One reason proposed for the observation of a significant decrease in the FEV-1/FVC ratio prior to the diagnosis of BOS is the delay in detection due to the lack of consistent performance of screening spirometry after HSCT. As discussed earlier, although screening spirometry after HSCT has been proposed, recommendations are not strictly followed.[17,18] Furthermore, other studies have questioned the utility of post-HSCT screening spirometry for the earlier detection of BOS. In a study by Yadev, et al a decline in the FEV-1 at day + 80 after HSCT did not correlate to the later development of BOS.[37] Similarly, in a study of pediatric HSCT patients that underwent post-HSCT spirometry screening for one year, screening was only able to identify 2 of the 5 patients who were later diagnosed with BOS.[19] One criticism of these studies is that the onset of BOS may have occurred outside of the window of screening used in these studies as BOS typically occurs during years 1 and 2 after HSCT and that early post-HSCT PFT's have a low sensitivity for the later determination of BOS. As such, additional studies are necessary to determine if screening PFT's can detect BOS earlier and change prognosis. The use of home spirometry, via handheld spirometers, has been shown to correlate with formal pulmonary function testing and is useful in the screening of post-HSCT patients.[36,38] Use of such testing will simplify serial screening by facilitating more frequent testing, avoidance of patient travel, and a decrease in resource utilization.

Another concern that has been raised for the potential delay in diagnosis is that a decreases in the FEV-1/FVC ratio lack sensitivity for the early diagnosis of BOS.[39,40] The pathologic finding of BOS is involvement of the small airways with either constrictive bronchiolitis (CB) or lymphocytic bronchiolitis (LB) that lead to fibrotic changes and narrowing of the airways with resultant airflow

obstruction.[41] As these small airways only contribute to less than 20% of the FEV-1/FVC ratio and therefore decreases in the FEV-1/FVC ratio is only observed when most of the small airways are involved.[41] This observation is consistent with the findings of Holbro, et al where less than 60% of their patients with biopsy proven CB or LB, and therefore changes in small airway caliber, had a decrease in the FEV-1/FVC ratio fitting the NIH diagnosis of BOS.[26,41] Several researchers have examined the use of other diagnostic tests for the diagnosis of BOS including exhaled nitric oxide, a decline in the forced expiratory force over 25-75% lung volume (FEF25-75%), multi-breath washout test with calculation of the lung clearance index (LCI), and lung oscillatory testing.[28,39,42] Several of these tests were initially examined for the diagnosis of BOS in lung transplant recipients with their potential use then extended into the post-HSCT population as described in several small studies.

The fractional exhaled nitric oxide (FeNO) levels have been suggested to be useful in the diagnosis of BOS in post-HSCT patients. In contrast to patients with asthma or patients with BOS after lung transplantation, wherein FeNO levels are high[43,44], levels in post- HSCT BOS were reportedly to be low, with levels of <15 ppm thought to be diagnostic of post-HSCT BOS.[42] The above was a small study with FeNO levels measured only at the time of diagnosis thereby limiting their findings. Additional confirmatory studies, and in particular the use of serial FeNO levels to determine disease onset and progression, are necessary prior to using FeNO as a diagnostic or prognostic tool in post-HSCT BOS.

As measurement of mid expiratory flows, as detected by the FEF25-75%, is thought to better assess small airway obstruction, measurement of FEF25-75% has been proposed as a better diagnostic tool for the earlier diagnosis of BOS. A small study in pediatric lung transplant patients examined if a 20% decline in the FEF25-75% would detect BOS earlier than a 20% decrease in the FEV-1/FVC ratio.[45] Results from this study showed that the drop in FEF25-75% occurred significantly earlier, by 168.65 days, compared to the decline in the FEV-1/FVC ratio in those diagnosed with BOS. Similar findings were seen by Patterson, et al wherein the decrease in FEF25-75% in those with BOS occurred on average 112 days earlier than the FEV-1 decline.[46] These findings of the potential use of the FEF25-75% for the diagnosis of BOS in lung transplant recipients were then extended to post-HSCT patients with the exploration if a decline in FEF25-75% versus a decrease in the FEV-1 at day +80 could predict a diagnosis of BOS in the future.[28] Results showed that a decrease in the FEF25-75% was a better predictor of the diagnosis of BOS and also added to the diagnostic capability of an FEV-1decline.[28] In contrast, in the study described above by Yoon, et al, a decrease in FEF25-75% was observed in 5 patients with only one of these patients eventually going on to develop BOS.[19] This suggests that a decline in FEF25-75% may be too sensitive for the later diagnosis of BOS after HSCT.[19] Further studies on the use of FEF25-75% as a diagnostic tool for the earlier diagnosis of BOS after HSCT, as well as its use for clinical follow-up, need to be undertaken.

Airway oscillometry is another technique that has been explored for the diagnosis and screening of BOS. Advantages of oscillometry are that it is effort independent, therefore more useful in pediatric patients, frail adults, or patients with chronic chest pain from surgery, is economical, and is easy to perform.[47,48] Oscillometry measures airway resistance via use of multifrequency pulse waves (5 and 19 Hz) with the lower frequency penetrating into small airways.[47] Important measurements obtained include R5, the difference between 5 and 19 Hz (R5-R19), and Ax which is the area under the curve for the reactance at all frequencies.[39] Previously, oscillometry has been shown to be useful in the diagnosis of obstructive lung disease in patients with asthma, cystic fibrosis, COPD, inhalational toxin exposure, and other obstructive airway diseases.[39,49,50] In regards to its use as a screening tool for BOS after lung transplant, oscillometry was initially explored for the diagnosis and management of acute cellular rejection and chronic lung allograft dysfunction (CLAD).[48,51] In the study by Cho, et al changes in oscillometry correlated with the findings of grade 2 acute cellular rejection as determined by lung biopsy in 94% of their patients whereas their spirometry remained normal.[48] Furthermore, oscillometry values returned to normal after treatment for the acute cellular rejection. These findings were then extended specifically to post-transplant BOS. In a small study by Lee, et al findings from oscillometry showed good correlation to PFT results (FEV-1, FEF25-75%, and total lung capacity) in patients with BOS compared to results from a healthy cohort.[39] Importantly for this discussion, over 75% of the BOS patients included in that study had undergone HSCT, suggesting its potential use for this specific group in the diagnosis of BOS.[39] Similar results were seen by Kuint, et al showing a good correlation of R5 and R5-R19 and the spirometric parameters of FEV-1, FEV-1/FVC, and FEF25-75% in patients with BOS after undergoing HSCT.[52] In contrast, a recent study in lung transplant patients with BOS did not find any correlation between

oscillometry and PFT parameters.[53] Although oscillometry changes appear to correlate with the decline in FEV-1 and FEF25-75% in most studies, the ability of this test to detect BOS earlier than the decline in the FEV-1 and FEV-1/FVC ratio remains to be determined. Changes in oscillometry, done every 3 months for up to 41 months after transplant, although correlative with changes in spirometry, did not appear to diagnose BOS earlier than changes in FEV-1 alone in lung transplant recipients.[51] Similar findings were seen after HSCT[54]. Further studies are necessary to determine the role of oscillometry in the diagnosis and management of BOS after HSCT.

Another technique examined to improve the diagnostic sensitivity and earlier detection of BOS after HSCT is inert gas washout (either single or multi-breath) which assess for ventilation distribution. Changes in inert gas distribution indicates ventilation inhomogeneity and therefore small airway disease.[55-57] Typical gases used for these experiments include nitrogen, helium, and sulfur hexafluoride.[58-60] These techniques have been previously established for the diagnosis and follow-up of airflow obstruction in asthma, COPD, and cystic fibrosis.[59,60] Studies examining the use of single or multi-breath washout techniques for the diagnosis of BOS initiated in lung transplant patients with an extension of these studies into post-HSCT patients. In the study by Reynaud-Gaubert, et al described above utilizing FEF25-75%, these investigators examined the use of nitrogen washout for the diagnosis of BOS.[61] Similar to their findings using FEF25-75%, an increase in the nitrogen washout slope was able to diagnose BOS 150 days earlier than an FEV-1 decline.[61] Similar findings were observed by others using single breath washout for helium (He), nitrogen, and sulfur hexafluoride (SF6) with both He and SF6 able to diagnose BOS earlier (median > 350 days) than a 20% decrease in the FEV-1 in over 85% of the patients examined.[58] In contrast, changes in FEF25-75% only identified two thirds of the patients diagnosed with BOS in that study with a much shorter lead time to diagnosis (median 102 days) compared to He and SF6 washout. An extension of the studies exploring the use of nitrogen multibreath gas washout in the diagnosis of BOS directly examined ventilation heterogeneity at the acinar entrance (Sacin) and found that Sacin was higher in patients with BOS compared to non-BOS patients with levels increasing based on the severity of the disease.[62] Furthermore, changes in Sacin correlated with the decline in FEV-1. These results were confirmed by a later study from the same group.[63] In examining long-term survivors of HSCT in pediatric patients, significant changes in Sacin and the lung clearance index (LCI), a global measure of ventilation distribution inhomogeneity, were identified in the post-HSCT group compared to controls.[64] Over half of these patients had an abnormal Sacin with one third an abnormal LCI, whereas only 9% of these patients had a significant decrease in the FEV-1. Positive correlations were seen between the Sacin and LCI and the FEV-1. Overall, this suggests that changes in the Sacin or LCI may be more sensitive than a decrease in the FEV-1 in the diagnosis of BOS with similar specificity. Strengthening a role for the measurement of Sacin and LCI for the diagnosis of BOS was the study in patients with biopsy confirmed bronchiolitis obliterans (BO) that showed changes in LCI and Sacin were observed in 95.5% and 82% of these patients[65]. Overall, this suggests a high sensitivity for the measurement of Sacin and LCI in the detection of lung associated cGvHD in these patients This is in contrast to changes in the FEV-1/FVC ratio that was found to be abnormal in only 56% of patients with biopsy confirmed BO.[65] The LCI was also shown to correlate with BOS grade in patients who have undergone lung transplant in the study by Driskel, et al,[60] suggesting it may be a useful tool in the clinical follow-up and prognosis of BOS. Finally, 47% of patients with an abnormal LCI were in the setting of a normal FEV-1/FVC ratio, thereby questioning the usefulness of spirometric changes in the detection of small airway disease.

Treatment for Bronchiolitis obliterans syndrome

Unlike other forms of cGvHD after HSCT, BOS has been difficult to treat. Standard treatments include the use of corticosteroids and augmentation of other immunosuppresants. With use of these agents the response rate is reported to be ~50%, although the experience at our institution suggests a much lower response rate 31 and Unpublished observations. During this time patients' symptoms do not significantly improve and can worsen with a corresponding decrease in the FEV-1 and FEV-1/FVC ratio.[2,21,31,66] The estimated survival after a diagnosis of BOS is < 50% at 5 years after the initial diagnosis of BOS.[2,23,6,68] These outcomes in patients with post-HSCT associated BOS, however, appear to be better than those of post-lung transplant patients with BOS with the latter group having a progressive decline in FEV-1 with a median survival of 3 years after the initial diagnosis of BOS.[33] This suggests that the inciting event or underlying pathophysiology of BOS in these two patient groups may be distinctly different. In addition to the progression of the underlying disease, patients with BOS can also have clinically worsening during times of respiratory infection, particularly viral infections, and need to be closely monitored

during these illnesses. In regards to treatment, the lack of an animal model that accurately mimics post-HSCT BOS, as well as the lack of biomarkers, limits advancement in the understanding of the underlying pathophysiology of post-HSCT BOS and therefore the discovery of new effective agents to be used in its treatment.[32,33] To date no randomized controlled studies have shown a survival benefit with any treatment modality in post-HSCT BOS patients. As BOS is thought to be the lung manifestation of cGvHD, treatment for BOS has focused on treatment of the underlying cGvHD with the augmentation in immunosuppression. Specifically, treatment for cGvHD, and in particular for HSCT associated BOS, has targeted the inflammatory cells and cytokines thought to be driving the disease. As mentioned above, the etiology of BOS is not well understood but is thought to be an alloimmune response of donor cells against host lung antigens with involvement of T cells (particularly T-regs), B cells, dendritic cells, and NK cells as well as increased levels of TNF-α and transforming growth factor beta levels.[27] Accordingly, treatment has focused on modifying these pathways. Initial treatment in all patients consists of a burst of glucocorticoids in attempt for symptom control and well as stabilization of pulmonary function testing. Typically, only a small fraction of the patients respond to an initiation or increase in steroids with several adverse effects related to steroids.[33] For this reason, second line immunosuppressive agents are also commonly introduced, or dosages increased, early in the course after the diagnosis of BOS. Second line agents that have been examined include cyclosporine, azathioprine, tacrolimus, sirolimus, and mycophenolate mofetil.[69,70] Again, success rates with the addition of second- or third-line agents have been poor with no regimen shown to reduce the further decline in lung function, patient symptoms, or mortality. Other novel pathways have been recently targeted including antibodies against CD-20 (rituximab[71] or TNF-α[2], and tyrosine kinase inhibitors (imatinib,[72] again with limited success. In addition, non-pharmacologic treatment with extracorporeal photophoresis has been tried in post-HSCT BOS, although it was not shown to be overall effective.[73] Recently some success in the treatment of post-HSCT BOS has been seen with the use of the macrolide antibiotic azithromycin, the prostaglandin inhibitor monteleukast, and inhaled corticosteroids both individually and in combination.[66,74-78] At present the standard of care for treatment of BOS after HSCT is a steroid burst and initiation of FAM therapy (fluticasone, azithromycin, and montelukast). Use of FAM has been shown in several studies to improve lung function and improve symptoms scores and quality of life. In an early retrospective study use of FAM allowed for a significant decrease in the daily steroid dose, although its effects on lung function could not be assessed in that study.[76] In a small phase II study, fewer patients had a > 10% decrease in FEV-1 while on FAM treatment compared to a group of historical controls (6% vs 40%).[70] In addition, almost 50% of the patients were able to taper their steroid dose by half. Finally, patients on FAM treatment had an improvement in quality of life, as assessed by short form 36 (SF-36) surveys and symptoms as determined by Lee symptom scores.[70]

Newer agents that have recently been tried in the treatment of post-HSCT BOS include pirfenidone and ruxolitinib.[71,79-83] In the study by Matthaiou, et al the tolerability of pirfenidone over 52 weeks was examined in post-HSCT BOS patients. Results showed that pirfenidone was tolerated in the majority of the patients (59%).[79] In addition, on secondary outcome analysis, there was a small (7%) increase in the FEV-1 and an overall improvement in symptoms scores.[79] Taken together this suggests that pirfenidone may be an effective treatment in post-HSCT BOS in those patients that can tolerate the medication with larger randomized studies necessary to confirm these results. Finally, as BOS is thought to be partially mediated by the release of pro-inflammatory cytokines and regulatory T-cell (Treg) activation, use of a JAK kinase 1/2 inhibitor, ruxolitinib, has been explored in the treatment of post-HSCT BOS.[81-83] Ruxolitinib increases the number of Tregs and decreases interferon gamma and IL-17A release by preventing CD4+ T cell maturation.[81] Support for the use of ruxolitinib for HSCT associated BOS was based on its overall effectiveness in treating patients with cGvHD, showing a higher rate of response than use of conventional immunosuppression regimens, even in the more challenging organ systems of the lung and liver.[84] In a small retrospective study examining the effect of ruxolitinib as a second line agent in addition to FAM in the treatment of BOS, use of ruxolitinib was associated with the ability to decrease steroid dosing and a stability in the FEV-1 within three months of starting therapy.[83] Similar results were seen by Zhao, et al where both symptoms and FEV-1 improved with the use of ruxolitinib as salvage therapy and steroid dosages were able to be reduced.[82] To further these results, the potential use of ruxolitinib as a first line treatment for BOS after HSCT was examined by Zhang, et al wherein all patients included in the study had a least a partial response to rixolitinib, as assessed by symptom scores and FEV-1, with the ability again to significantly decrease steroid dosing.[81] In contrast to the above studies, Bondeelle,

et al examined lung function in patients with sclerodermatous cGvHD with co-existing BOS treated with ruxolitinib.[80] In that study there was no change in the observed decrease in lung function over time in those treated with ruxolitinib versus a standard immunosuppressive regimen.[80] Currently a prospective randomized multicenter study is underway to further explore the use of ruxolitinub in the treatment of HSCT associated BOS.

As stated above, response rates using the current treatment regimens for BOS are poor, with several patients having ongoing decline in the FEV-1, an increase in respiratory symptoms, poor quality of life, and decreased survival. Ongoing attempts to identify novel therapeutic targets and clinical treatment trials are desperately needed to improve outcomes in these patients. At present, for those patients with progressive disease and a lack of response to treatment limited options exist. These patients should undergo evaluation for lung transplantation if otherwise found to be a suitable candidate. Success rate for lung transplantation in this patient population is equivocal to that of the general lung transplant population.[85-90]

Restrictive lung disease after hematopoietic stem cell transplant

In contrast to obstructive lung disease after HSCT, and specifically the diagnosis of BOS, restrictive lung disease (RLD) is less well studied and is poorly understood. This is particularly true for the idiopathic interstitial pneumonias that can occur after HSCT. Findings of restrictive lung disease on PFT's early after HSCT is common when looked for, however the overall prevalence is not fully known, as serial PFT's, and in particular lung volume measurements, are not routinely done at most transplant centers. This lack of screening pulmonary function tests after HSCT makes it difficult to define the true prevalence of restrictive PFT's after HSCT and to determine if early findings of restriction lead to restrictive lung disease in the future. Based on our clinical experience, in the small number of patient who undergo PFT's shortly after transplant, findings of restriction is common (unpublished observations). Supporting this is the study by Dharmagunawardena, et al where 46% of their patients with new PFT abnormalities after HSCT had restrictive disease.[91] Typically restriction on PFT's are found early after HSCT, within 100-300 days after transplant, and are frequently transient in nature[14] and Unpublished observations. Only 2.4% percent of patients with findings of restriction on PFT's go on to develop severe restrictive lung disease.[92] Those with persistent RLD present with non-specific symptoms including shortness of breath, dyspnea on exertion, cough, and a sense of the inability to take a deep breath. On physical exam they may have lung crackles, clubbing, and oxygen desaturation with exertion. Several well defined causes of restrictive lung disease after HSCT have been described including infectious pneumonia, pulmonary edema, diffuse alveolar hemorrhage (DAH), idiopathic pneumonia syndrome (IPS), serositis, pleuroparenchymal fibroelastosis (PPFE), and other forms of interstitial lung disease (COP, usual interstitial pneumonitis, non-specific interstitial pneumonitis). Many of these may be idiopathic or secondary to drugs used in the treatment of the underlying hematological malignancy or the conditioning regimen prior to undergoing HSCT.[11,12] Some of these (infectious pneumonia, DAH, IPS) occur early after HSCT (within the first 100 days) and are quickly identified, diagnosed, and treated. Others, including serositis, PPFE, and other interstitial lung diseases (ILD), are rare and have a more insidious onset with presentations months to years after HSCT and are typically associated with cGvHD.[93-96] In one large series examining the prevalence of ILD after HSCT, the median time to onset was 11.3 months with all cases diagnosed within the first three years following transplant.[96] Seventy percent of these patients had co-existing cGvHD.[96] Pathologic findings included organizing pneumonia, non-specific interstitial pneumonitis, and lymphocytic interstitial pneumonitis.[96] Diagnosis of these ILD's are currently made on review of chest imaging (chest x-ray or CT) with discussion utilizing a multidisciplinary group with lung biopsy generally avoided to prevent complications. Less well understood is the finding of RLD on PFT's in post-HSCT patients without one of the above diagnoses. The possibilities for the restrictive lung volumes in these patients include deconditioning and muscle loss during the time of hospitalization for the HSCT, the use of corticosteroids resulting in muscle loss or weight gain, and generalized deconditioning.[14,97] The prevalence of frailty has been shown to be higher in patients who have undergone HSCT compared to an age matched control, which supports this reasoning.[97] In addition, restrictive PFT's can be associated with the effects of cGvHD, particularly skin associated cGvHD and the development of sclerodermatous like skin lesions that inhibit chest wall excursion.[69,98] The prevalence and long-term effects of the above non-specific causes of restrictive PFT's after HSCT have not been specifically examined. Treatment for these conditions includes a regular exercise program to improve overall physical conditioning and optimal management of steroid dosing.

To illustrate two causes of RLD after HSCT involving separate compartments causing the restriction, we will briefly discuss serositis, with restriction due to

surrounding pleural fluid, and PPFE, with restriction due to interstitial inflammation and fibrosis of the lung. Both of these conditions are rare complications after HSCT and are associated with cGvHD.[99-103] Serositis occurs in 2-4% of patients after HSCT with typical presentation after day 100 and more commonly in the first to second year after transplantation[99,100] and Unpublished observations. Although pleural and pericardial effusions are common during the first 100 days after HSCT, these typically resolve over time and do not return (Unpublished observations). Those that persist are classified as serositis after ruling out congestive heart failure, renal disease, and volume overload as potential causes. The etiology for post-HSCT serositis is unknown but it appears that unrelated or mismatched donor source is a risk factor.[104] In addition, although not conclusively linked, infections, particularly viral, may be a risk factor for the development of serositis after HSCT.[99,100] In regards to treatment, there have been no randomized clinical trials showing an effective treatment regimen for post-HSCT serositis. Augmentation in immunosuppression, typically corticosteroids, has been suggested to be successful in 50% of patients[99] but has been less successful in our experience (Unpublished observations). Other immunosuppressants that have been tried include tacrolimus, sirolimus, and rituximab.[99,100] For long-term clinical management, patients generally undergo repeat thoracentesis to control symptoms. Pleurodesis has been utilized in a few cases with limited success.[105]

Pleuroparenchymal fibroelastosis (PPFE) is a rare RLD after HSCT that involves progressive pleural thickening and lung fibrosis. The etiology is not known and overall, it remains a poorly understood disease. Proposed etiologies have included the effects of chemotherapy, used in the treatment of the hematologic malignancy or in a pre-HSCT conditioning regiment, or infections.[101-103] Patients present with cough, progressive shortness of breath, anorexia, and not uncommonly a pneumothorax.[92,103,106,107]

Pleuroparenchymal fibroelastosis is a late onset complication after HSCT that occurs in 0.25-3.3% of patients with a median time to onset of 6.9 years after transplant but with a wide range of onset (0.25-17.9 years).[93,94,101,102] The diagnosis is established based on clinical criteria only with the above described symptoms, findings of restrictive lung volumes on PFT's, and characteristic findings on imaging with upper lobe predominant pleural thickening with fibrotic bands extending from the pleura to the hilum.[92,107,108] Lung biopsy to confirm a diagnosis is avoided due to the risk for pneumothorax that can be persistent.[101,107] To assist clinicians in this challenging diagnosis, algorithms have been established which utilize involvement of multidisciplinary groups.[109] Patients with PPFE may also have concomitant interstitial lung disease with usual interstitial pneumonia (UIP) or non-specific interstitial pneumonia (NSIP)) patterns most frequently observed on chest CT imaging.[94,102,107,108] Separately, patients who have undergone HSCT may develop UIP or NSIP without concomitant PPFE, as described above.[93-96] The disease course for PPFE is variable but typically involves a slow progression of disease with an estimated 5 year survival rate of 23.3-58.9% and a median life expectancy of 11.8 years.[101,108,110] Treatment for PPFE is mainly supportive as no clinical trial has shown an effective therapeutic agent, including the use corticosteroids.[101,102] The rarity of the disease precludes conducting meaningful clinical trials to identify novel treatments. In those with progressive disease, lung transplant remains an option.[111-113]

Conclusion

Obstructive and restrictive findings on pulmonary function testing after hematopoietic stem cell transplant are common but do not always represent the development of obstructive or restrictive lung disease after transplantation. Follow-up testing is required to confirm the initial findings and to establish a diagnosis of obstructive or restrictive lung disease. Serial screening of lung function by spirometry should be considered after hematopoietic stem cell transplant to identify abnormalities earlier in the course of disease. Detection of obstructive or restrictive lung disease earlier after hematopoietic stem cell transplant may allow for effective treatment which are currently lacking. In addition to screening, newer techniques for evaluating airway obstruction are being evaluated in hematopoietic stem cell transplant patients and may be more effective in detecting obstructive disease compared to current spirometry testing. Bronchiolitis obliterans syndrome and pleuroparenchymal fibroelastosis represent examples of obstructive and restrictive lung diseases, respectively, after hematopoietic stem cell transplant with both of these conditions being rare. Although rare, they both cause significant morbidity and risk for death in hematopoietic stem cell transplant patients without effective treatments being currently available for either of these conditions. Identification of biomarkers and the design of novel effective treatments are urgently needed for each condition to lessen disease burden and improve outcomes.

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