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REVIEW

Lung transplantation for pulmonary chronic graft-versus-host disease: a missed opportunity?

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Chronic graft-versus-host disease is a common complication after allogeneic hematopoietic stem cell transplantation, with pulmonary chronic graft-versus-host disease (PcGvHD) particularly associated with a dismal prognosis. Lung transplantation (LuTx) is a final therapeutic option for well-selected patients affected by this condition. Nevertheless, only a small group of PcGvHD patients are referred for LuTx. This review addresses common concerns regarding referral and listing of PcGvHD patients for LuTx (such as risk of relapse of hematological malignancy, infectious complications and rejection) and survival outcomes of this specific cohort of patients. Importantly, LuTx for PcGvHD has comparable outcomes to other indications. The establishment of specific LuTx indication criteria for PcGvHD patients may improve referral rates and timing of both referral and listing of suitable candidates.
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Abbreviations: ACR, acute cellular rejection; alloHSCT, allogeneic hematopoietic stem cell transplantation; BOS, bronchiolitis obliterans syndrome; cGvHD, chronic graft-versus-host disease; CLAD, chronic lung allograft dysfunction; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; LuTx, lung transplantation; RAS, restrictive allograft syndrome

Take home message (217 char): Lung transplantation is a valuable therapeutic option for selected patients with end-stage pulmonary chronic graft-versus-host disease, with comparable outcomes compared to patients transplanted for other indications.

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Hematopoietic stem cell transplantation and chronic graft-versus-host disease

Hematopoietic stem cell transplantation (HSCT) represents an established, life-saving method for an increasing number of well-selected patients with malignant or non-malignant hematological diseases.[1] Typically, peripheral blood is used as cell source for stem cells, but bone marrow or umbilical cord can also be used.[1] Unlike autologous HSCT where one's own stem cells are used, allogeneic HSCT (alloHSCT) involves transplanting stem cells from a related or unrelated donor, with acute myeloid leukemia and acute lymphocytic leukemia being the most prevalent indications for this procedure.[1] In Europe, almost 20,000 alloHSCT are performed annually.[1] The presence of host antigen-bearing cells may trigger immunocompetent donor lymphocytes to initiate an immune response, resulting in inflammatory and fibrotic changes within host tissues. This manifests clinically as graft-versus-host disease (GvHD), which can be either acute or chronic depending on its clinical presentation (Figure 1A).[2–5]

Chronic graft-versus-host disease (cGvHD) remains the major cause of late post-alloHSCT morbidity and mortality. Affecting 30–50% of alloHSCT recipients, it is the most common cause of non-relapse mortality after alloHSCT.[5–8] Given the ubiquitous presence of host antigens across tissues, cGvHD often presents as a multisystemic disease, manifesting with heterogeneous symptoms, typically involving at least three organs.[4,9,10] Common sites of cGvHD involvement are depicted in Figure 1B. In a study by Arai et al., including 298 cGvHD patients, only 11% of patients had mild cGvHD at enrollment, with moderate and severe disease observed in 59% and 30% of patients, respectively.[9]

Late-onset non-infectious pulmonary complications affect up to 20% of alloHSCT patients, primarily within the first two years post-transplant, of which pulmonary cGvHD (PcGvHD) is a frequent cause.[11] The management of PcGvHD is challenging because of limited therapeutic options and a lack of standardized care. Treatment approaches often include corticosteroids (inhaled and/or systemic) in combination with azithromycin and montelukast, alongside agents used for general cGvHD management.[12] Since PcGvHD typically occurs together with other cGvHD manifestations, patients are frequently already receiving immunosuppressive therapy. Despite the recent approval of several novel treatments (e.g., JAK inhibitors, ROCK inhibitors), there remains little evidence to date to advocate one product over another based on organ involvement. This makes therapeutic choices uncertain.

Pulmonary cGvHD phenotypes resemble CLAD phenotypes

Increasing evidence comparing PcGvHD to chronic lung allograft dysfunction (CLAD) has emerged in recent years.[12] Although the precise immunopathological pathways leading to chronic lung damage in PcGvHD and CLAD are not yet fully understood, striking similarities between these two entities have been observed from the cellular to the macroscopic level.[12–14] Both PcGvHD and CLAD are consequences of alloimmune activation. In terms of HSCT, graft-derived immune cells target non-self antigens of the host (hence *graft* vs host disease), whereas after lung transplantation (LuTx), the allograft is recognized as non-self by the host immune system (*host* vs graft disease).[12] Development of both conditions is driven by numerous risk factors, which may be common to both diagnoses, such as major and minor HLA antigen mismatches, prior acute rejection/GvHD, gastro-esophageal reflux, or infections, or transplant-specific, such as certain myeloablative conditioning regimens used in alloHSCT or use of peripheral blood stem cells.[12,15] At the cellular level, both entities are characterized by the presence of fibrosis with differing distributions: airway-centered in obstructive and interstitium-affecting in restrictive phenotypes.[12,16] In the obstructive phenotypes, obliterative and constrictive bronchiolitis are typical histopathological patterns observed, while various interstitium-centered patterns, such as alveolar fibroelastosis, diffuse alveolar damage, non-specific interstitial pneumonia, or pleuroparenchymal fibroelastosis, and concomitant obliterative bronchiolitis, can be observed in the restrictive phenotypes.[12,16]

A consensus report published in 2019 defined four clinically recognized CLAD phenotypes: bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), mixed, and undefined.[17] In PcGvHD, current National Institutes of Health consensus criteria account for BOS only.[4] Although clear similarities between RAS and restrictive pulmonary cGvHD have been noted,[13,14] the association of cGvHD with restrictive lung impairment remains ill-defined for HSCT survivors.[18] A study by Pang et al. demonstrated that less than half of patients with PcGvHD fitted within the stated criteria for BOS, suggesting a potential for adapting CLAD phenotyping within the PcGvHD population.[19] The similarities and differences between obstructive and restrictive phenotypes of CLAD and PcGvHD were described in detail by Bos et al. in 2022 and a summary is provided in Figure 2 and Table 1.[12]

Lung transplantation

LuTx represents a final therapeutic option for well-selected patients with end-stage pulmonary diseases, with more than 2000 LuTx performed in Europe on an annual basis.[20] Despite significant progress in the field, LuTx recipients still face the shortest median survival among major solid organ transplants, and CLAD (consisting primarily of BOS and RAS) remains the main cause of long-term morbidity and mortality in LuTx.[21] Overall, median post-transplant survival is around seven years and approximately 50% of patients are affected by CLAD five years after transplantation.[22] Nevertheless, there is wide variation in post-transplant outcomes (both CLAD incidence and survival) across LuTx centers. Given the limited therapeutic options, CLAD accounts for up to 5% of indications for LuTx.[22]

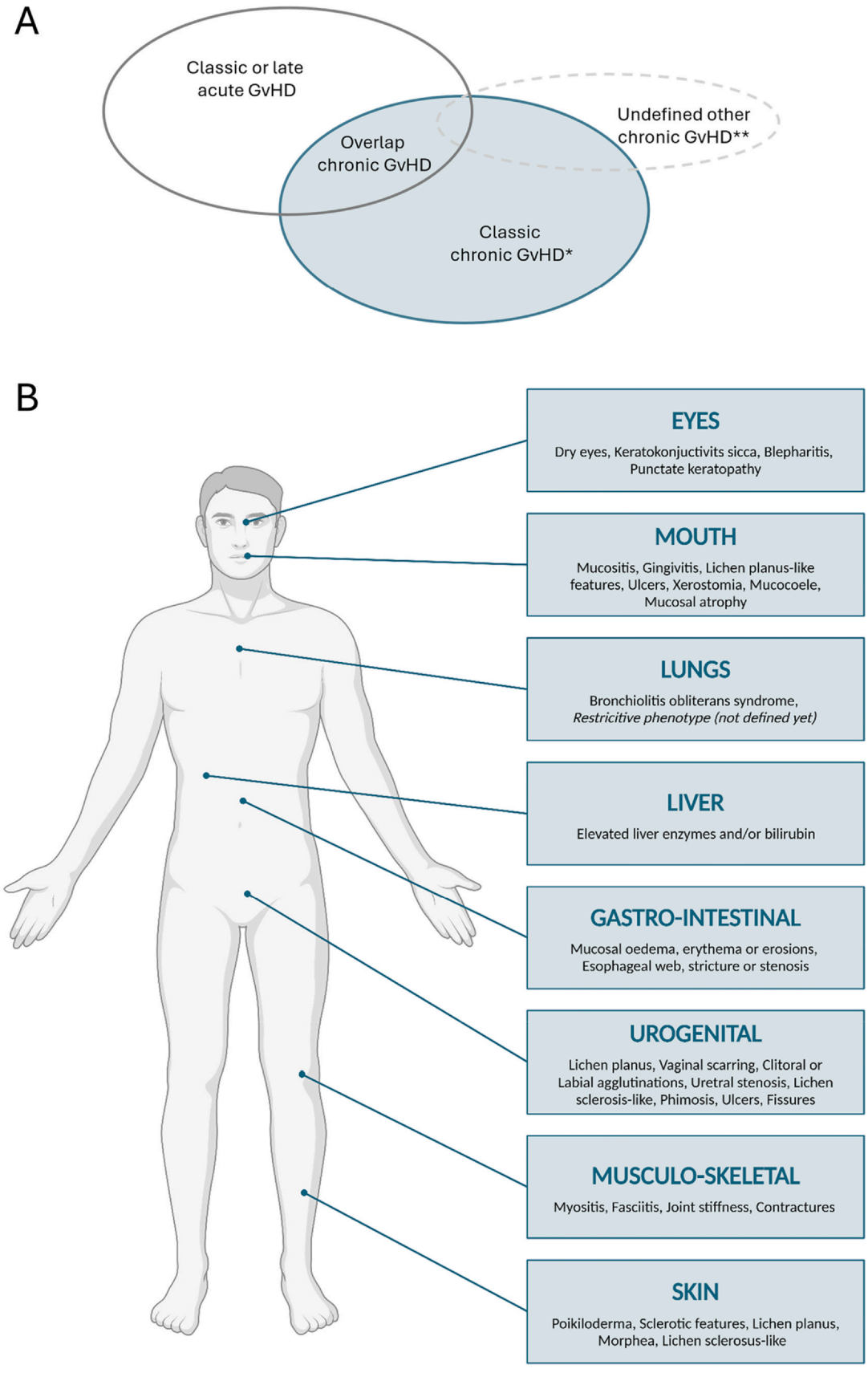

Figure 1 Chronic GvHD: clinical presentation. (**A**) Simplified classification of acute and chronic graft-versus-host disease after hematopoietic stem cell transplantation. ** Atypical signs and symptoms of alloreactivity falling outside the NIH 2014 diagnostic criteria. GvHD: graft-versus-host disease. (**B**) Common sites and clinical manifestations of cGvHD. (A) Adapted from Schoemans et al.[67] * Chronic GvHD manifestations meeting NIH 2014 diagnostic criteria. (B) Adapted from Cuvelier et al.[9].

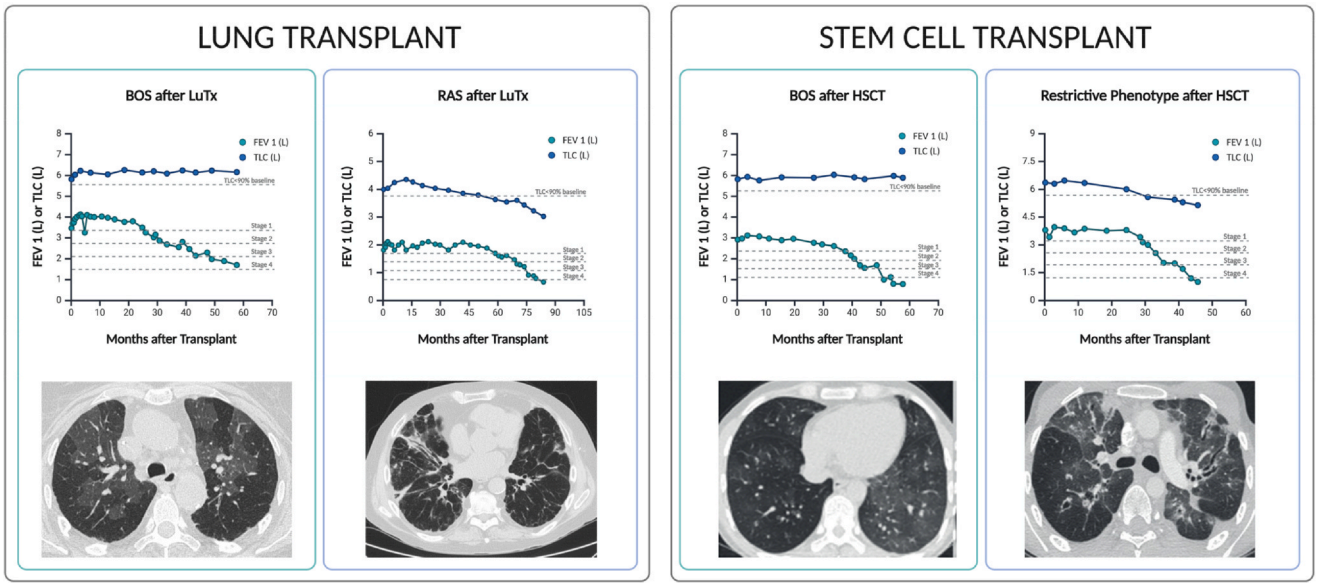

Figure 2 Clinical presentations of CLAD and PcGvHD. Comparison of clinical presentations (spirometry evolution, chest computed tomography scans) of BOS and RAS/restrictive pulmonary chronic graft-versus-host disease after lung and hematopoietic stem cell transplantation. BOS: bronchiolitis obliterans syndrome, FEV1: forced expiratory volume in one second, HSCT: hematopoietic stem cell transplantation, LuTx: lung transplantation, RAS: restrictive allograft syndrome, TLC: total lung capacity.

LuTx for PcGvHD - concerns and evidence

LuTx is also a valuable therapeutic option for carefully selected patients with end-stage PcGvHD.[23] Following disease relapse, cGvHD remains a leading cause of death among HSCT,[24] with lung involvement increasing the risk of cGvHD-related mortality.[8] Yet, PcGvHD remains an infrequent LuTx indication. One reason why patients affected by PcGvHD might not be referred for LuTx is concerns from healthcare providers or patients themselves relating to perceived poor outcomes after LuTx. It is conceivable that clinicians hesitate to refer these patients because of concerns about prior use of immunosuppression, risk of infectious complications or relapse of the underlying hematological disease, comorbidities, or from more systemic factors such as lack of diagnosis, patient refusal and/or lack of access to a LuTx team.

Notably, the ERS/EBMT clinical practice guidelines on treatment of PcGvHD by Bos et al. (published in 2024) recommend lung transplantation in selected cases of PcGvHD as a life-saving therapeutic option.[23] In this review, we aimed to address common concerns regarding indication and listing of PcGvHD patients for LuTx and assess survival outcomes of this specific cohort of patients. The concerns addressed in this review are based on concerns that emerged during the development of the above-mentioned guideline and that are also commonly raised in clinical practice.

Concern: Higher susceptibility to infection in comparison to other LuTx indications

Compared to recipients of other solid organ transplants, LuTx recipients exhibit the highest risk of infectious complications, and infections remain the most common cause of death within the first year of transplant.[22] This heightened susceptibility, caused by administration of potent immunosuppressive therapies following LuTx, impaired airway protective mechanisms, and ongoing environmental exposures, might be further enhanced by prior HSCT and pre-LuTx use of immunosuppressants or pre-existing infections/colonizations.

Patients after HSCT are sometimes more susceptible to infections due to lack of recuperation of components of the immune system, such as impaired humoral and cell-mediated immunity.[25–27] Besides inflammation and tissue injury, dysregulated immunity, seen as activation of effector populations in the adaptive immune system including T cells, B cells, antigen-presenting cells and natural killer cells with compensatory inhibition by regulatory cell populations, is a hallmark of cGvHD.[28] Thymic injury has deleterious effects on pathways of central tolerance and dysregulated donor lymphocyte populations propagate tissue injury and aberrant repair mechanisms. Immune dysfunction in cGvHD patients may manifest as autoimmune-like features with autoantibody production or severe immunodeficiency with functional asplenia, impaired cellular and humoral immunity and increased susceptibility to opportunistic infections. Especially in patients with BOS after alloHSCT, dysgammaglobulinaemia and lack of B cells and their subpopulations were the most pronounced compared with other organ manifestations of cGvHD.[29] Deficiency of memory B cells in patients with cGvHD correlated with severe infections.[30,31] Therefore, patients with PcGvHD may have an increased risk of serious infections.

Another important infection-related concern for this group is prior microbial colonization, influenced by prolonged immunosuppression and antibiotic exposure.[32,33] Recipient-related colonization has been associated with an elevated risk of post-transplant infections, including multidrug-resistant infections that are difficult to treat.[34,35]

Table 1 Summary Table of Similarities and Differences Between Obstructive and Restrictive Phenotypes of CLAD and PcGvHD (adapted from Bos et al.[12])

	Lung Transplantation		Pulmonary Chronic Graft-versus-Host Disease	
Phenotype	BOS	RAS	BOS	Restrictive
Current Definition (year)	2019	2019	2015	Not defined yet
Prevalence	∽ 70% of CLAD patients	20–30% of CLAD patients	∽ 5–15% of alloHSCT patients	Unknown, 12–60% of LONIPCs
Lung function thresholds for diagnosis (after exclusion of other causes)				
FEV1	< 80% of baseline	< 80% of baseline	< 75% of predicted *and* > 10% decline over < 2 years	Not defined yet
TLC	> 90% of baseline	≤90% of baseline	-	Not defined yet
FEV1/FVC	< 0.7	≥0.7	< 0.7	Not defined yet
CT findings	Air trapping, bronchiolitis (tree-in-bud), bronchiectasis	Ground-glass opacities, consolidations, pleural or septal thickening, bronchiectasis, volume loss	Air trapping, bronchiolitis (tree-in-bud), bronchiectasis	Ground-glass opacities, consolidations, and sometimes pleural or septal thickening, bronchiectasis, volume loss
Histological findings	OB/CB	AFE, PPFE, NSIP, AFOP, OP, with concurrent OB/CB	OB/CB	NSIP, LIP, DAD, AFE, PPFE, AFOP, OP and concurrent OB/CB
Median survival after diagnosis	3–5 years	1–2 years	5-year survival 60%, although most likely lower	2-year survival 60%

AFE - alveolar fibroelastosis, AFOP - acute fibrinous and organizing pneumonia, BOS - bronchiolitis obliterans syndrome, CB - constrictive bronchiolitis, CLAD - chronic lung allograft dysfunction, CT - computed tomography, DAD - diffuse alveolar damage, FEV1 - forced expiratory volume in 1 s, FVC - forced vital capacity, LIP: lymphoid interstitial pneumonia, LONIPCs: late-onset non-infectious pulmonary complications, NSIP – non-specific interstitial pneumonia, OB - obliterative bronchiolitis, OP - organizing pneumonia, PcGvHD: pulmonary chronic graft-versus-host disease, PPFE - pleuroparenchymal fibroelastosis, RAS - restrictive allograft syndrome, TLC - total lung capacity.

Evidence: several, mainly small, observational studies have examined infectious complications following LuTx for PcGvHD.[36–51] (Supplemental Table 1) Overall, infections were common, as in the general LuTx population, with cytomegalovirus and fungal infections being common types of infection.[37–41,44] Sepsis was reported as a common cause of death, alongside malignancy and CLAD, again reflecting leading causes of death in the general LuTx population.[36–40,43–46,48,50–52] While the incidence of infection varied across studies from 11% to 100% depending on the definition (colonization/infection/clinically relevant infection) and timeframe used, it was comparable to the incidence in the general LuTx population.[37–45,47] However, one retrospective study of 19 patients identified an increased risk of mortality from infections beyond the first year in the alloHSCT cohort compared to a propensity-matched control group.[49] This raises concerns about long-term susceptibility to infections in this population, potentially due to acquired immunodeficiencies that alter their risk profile. Yet, these findings should be interpreted cautiously due to the study's small sample size and retrospective design.

Regarding risk related to microbial colonization, a large European study analyzing 105 LuTx recipients with PcGvHD did not find evidence supporting an increased infection risk associated with prior colonization.[36]

In conclusion, infections are an important cause of morbidity and mortality after transplantation. The overall risk of post-transplant infections in patients undergoing LuTx for PcGvHD appears comparable to those transplanted for other end-stage lung diseases.

Concern: Increased risk of lung rejection

Given the multi-organ involvement in cGvHD, concerns have been raised about ongoing non-pulmonary rejection, which is inherently linked to immune system activation, resulting in a higher complication rate of lung allograft rejection after LuTx and/or inferior outcomes due to non-pulmonary cGvHD. In addition, many PcGvHD patients receive immunosuppression prior to LuTx, which raises the question of the necessity of induction therapy. Moreover, many HSCT patients have an extensive transfusion history, increasing the likelihood of HLA senitization.[53]

Evidence: several retrospective cohort studies and case series studied acute cellular rejection (ACR) and CLAD outcomes in patients transplanted for PcGvHD. (Supplemental Table 1) Regarding ACR, the incidence ranged between 7–43% depending on the duration of follow-up post-transplant.[37–41,44,49,51,54] This incidence is comparable to the overall ACR incidence after LuTx and was indeed

similar to the incidence in patients transplanted for other indications in the studies by Holm et al. and Riddell et al.[37,49] CLAD reported incidence rates were comparable to the general LuTx registry data.[22] In the largest study by Greer et al., CLAD incidence was 37% in patients who survived the first year (median follow-up was 34 months).[36] Kliman et al. and El Fakih et al. both reported a 5-year CLAD-free survival of 50% in PcGvHD patients.[39,55] In other studies, the incidence varied between 0–33% depending on the duration of follow-up after LuTx.[38,39,41,42,44] Importantly, in the study by Riddell et al., there was no difference in CLAD-free survival compared to matched controls.[49] Most studies reported BOS as the major CLAD phenotype.[37,38,42,44] No significant events of antibody-mediated rejection were reported within any of the cohorts.[36,39,47]

In conclusion, the incidence of ACR and CLAD was comparable to that in patients transplanted for other indications.

Concern: Recurrence of hematological malignancy

Managing immunosuppression after alloHSCT is like walking a tightrope, balancing between desired graft-versus-leukemia effect (in which donor immune cells attack any residual leukemia cells in the recipient's body and reduce the risk of relapse) and the significant morbidity of GvHD (in which donor immune cells mount an immune response against the recipient's tissues).[56] Therefore, escalation of immunosuppression levels after LuTx may raise concerns in terms of hematological disease relapse in patients who received alloHSCT for hematological malignancy.[57]

The 2014 ISHLT Consensus Document for the Selection of Lung Transplant Candidates identified a recent history of malignancy as an absolute contraindication, recommending a minimum disease-free interval of two years in combination with a low predicted risk of recurrence, with a 5-year disease-free interval recommended in most cases.[58] In the updated version of the Consensus Document that was published in 2021, this absolute contraindication was modified to malignancy with high risk of recurrence or cancer-related death.[59] It is important to emphasize that not all neoplastic diseases carry equal risk in the context of LuTx. Several consensus guidelines are available to assist with risk stratification for LuTx candidates with a history of solid organ or hematological malignancy.[60,61]

Evidence: Several small observational studies reported relapse rates after LuTx for PcGvHD. Overall, the risk of hematological relapse was low with incidences ranging between 0% and 11%.[37–47,49–51] Similarly, the incidence of relapse was 4% in the largest European study of 105 patients. Importantly, Greer et al. reported that LuTx within two years after alloHSCT was associated with an increased risk of relapse as well as mortality due to malignancy (including both relapse and secondary malignancy, HR 6.4, 95% confidence interval 1.3–46.0).[36]

In conclusion, the incidence of hematological relapse is low after LuTx and needs to be balanced against the very high mortality of end-stage PcGvHD. The risk of hematological relapse needs to be carefully considered based on the patient profile and initial disease characteristics and the time elapsed since alloHSCT.[62] Waiting at least two years after alloHSCT before undergoing LuTx seems reasonable and is related to improved outcomes.

Concern: Extrapulmonary comorbidities

Another reason that could contribute to concerns for referral and listing for LuTx are extrapulmonary disease manifestations of cGvHD and other comorbidities, such as frailty due to previous alloHSCT and cGvHD, toxicity from prior treatments, such as chemotherapy and radiation, and general comorbidities (renal disease, coronary artery disease, etc.). In addition, the risk of drug toxicity post-transplant may be increased in patients with extrapulmonary cGvHD (e.g., diarrhea in patients with intestinal cGvHD, impaired liver tests in patients with hepatic cGvHD).

Evidence: Not much data are available on the impact of these factors on patient referral, selection and post-transplant outcomes. As with other LuTx candidates, adequate assessment is important to identify and address modifiable risk factors. Additional attention should be paid to optimizing the nutritional and functional status, emphasizing the importance of pre-transplant rehabilitation.[63] Overall, it is preferred that extrapulmonary cGvHD is well controlled at the time of LuTx.[23] A specific factor to consider is sclerotic skin cGvHD, which can cause restriction of the thoracic chest cavity.[64] In addition, there may be technical challenges associated with transplantation, particularly in patients with extensive adhesions or pleuroparenchymal fibroelastosis, which may pose an additional barrier to accessing the transplant list. Therefore, consideration should be given to transplanting these patients in larger-volume centers with adequate experience. Furthermore, close collaboration between the referring hematology team and the transplant team is important, with continued involvement of the hematology team, not only for surveillance of relapse, but also for ongoing management of extrapulmonary complications.

Survival after LuTx for PcGvHD

LuTx recipients transplanted for PcGvHD have been shown to be younger compared with the overall LuTx population.[36–39,41,44,47,51] In the largest published cohort of 105 European PcGvHD patients by Greer et al., median 1-, 3- and 5-year survival rates were 85%, 72% and 67%, respectively.[36] Consequently, these outcomes were very similar to ISHLT registry data (85%, 70% and 59%, respectively, for the most recent era 2010–2017)[22] and also similar to 4075 propensity-matched controls.[36] Similar survival data were reported in other publications, with values ranging between 78–100% for 1-year, 72–100% for 3-year and 63–86% for 5-year survival.[37–39,41,44,51,55]

In conclusion, the majority of the publications demonstrated comparable survival between LuTx recipients with PcGvHD as an indication for LuTx and those with other primary diagnoses.

Future directions

Based on current evidence, LuTx can be considered a life-saving treatment, offering comparable and equally acceptable long-term outcomes in selected adults with end-stage PcGvHD. The risk of post-transplant adverse effects (e.g., infections, malignancy, CLAD) appears comparable to those in patients transplanted for other indications. To improve referral and selection of PcGvHD patients for LuTx, several factors need to be addressed.

The ultimate goal in PcGvHD is to control the disease early in the process with effective preventive and therapeutic regimens, which diminishes the need for LuTx as a therapeutic option for these patients. In this context, frequent monitoring of lung function after alloHSCT and at key moments (such as the diagnosis of cGvHD, treatment changes and/or cGvHD flares) remains the gold standard.[65] When lung function decline is observed, early collaboration between the hematology and respiratory teams may facilitate timely referral for LuTx. Meanwhile, we need to be aware of a striking gap between the absolute number of alloHSCT performed, the number of patients affected by PcGvHD with a high likelihood of under- and delayed diagnosis, and the number of PcGvHD referrals for LuTx. Enhancing awareness among healthcare providers about LuTx as a viable treatment option for this population is pivotal in addressing this gap.

Adequate selection of PcGvHD patients eligible for LuTx and timing of referral and listing

It is known from the CLAD population that survival after retransplantation is lower for RAS than for BOS.[66] Given the similarities between CLAD and PcGvHD,[12] further research on PcGvHD phenotypes (obstructive vs restrictive) and their outcomes after LuTx is essential, along with evaluation of other PcGvHD-specific complications, such as chest wall sclerosis, that could affect post-LuTx outcomes. These and other factors that we believe should be addressed in specific referral and selection criteria for PcGvHD patients are shown in Table 2.

In available publications, median FEV1% and FVC% predicted prior to LuTx were low (around 20% and 35%, respectively, at the time of referral), along with a high number of patients requiring ventilatory support.[36,39,41] This raises the question of whether these patients should have been referred earlier, to allow sufficient time for adequate assessment of possible LuTx candidacy and to identify and address modifiable risk factors before listing.

This emphasizes the need to establish specific LuTx indication, referral and listing criteria for PcGvHD patients, as also suggested in the 2024 ERS/EBMT clinical practice guidelines on treatment of PcGvHD in adults.[23]

Conclusion

Available evidence shows that LuTx is a valuable therapeutic option for well-selected patients with end-stage PcGvHD. Outcomes following LuTx for this diagnosis are favorable and, importantly, comparable to primary LuTx for other diagnoses. As with other transplant candidates, comorbidities and general eligibility criteria for LuTx should be considered, with additional attention paid to the risk of hematological relapse, preferably deferring LuTx until at least two years after alloHSCT. The disproportion between the number of patients affected by PcGvHD and the number of them referred as candidates for LuTx might benefit from a consensus statement addressing thresholds for both referral and listing for LuTx for this specific patient population. In order to prevent PcGvHD patients from being too ill or too frail for LuTx, early referral to a LuTx center should be encouraged, providing the potential candidate the opportunity to consider LuTx and allowing the transplant team to fully evaluate transplant candidacy and to address modifiable barriers and

Table 2 Specific Factors to be Addressed in Referral and Selection Criteria for PcGvHD Patients for LuTx alloHSCT - Allogeneic Hematopoietic Stem Cell Transplantation, cGvHD - Chronic Graft-versus-host Disease, LuTx - Lung Transplantation, PcGvHD - Pulmonary Chronic Graft-versus-host Disease

Specific Factors to be Addressed in Referral and Selection Criteria for PcGvHD Patients for LuTx
Impact of underlying hematological disease (malignant vs non-malignant, type of malignancy)
Impact of timing after alloHSCT
Impact of phenotype of PcGvHD (obstructive vs restrictive)
Impact of extrapulmonary cGvHD
Impact of chest wall deformities due to skin sclerosis
Impact of colonization and prior infections
Impact of prior and active immunosuppressive therapy
Impact of immunodeficiency (e.g., hypogammaglobulinemia)
Impact of frailty due to previous alloHSCT and cGvHD
Impact of other alloHSCT-related comorbidities, such as toxicity from prior treatments
Timing of LuTx referral
Timing of LuTx listing
Alongside general factors assessed in LuTx candidates: nutritional status, functional status, presence and severity of comorbidities, psychosocial circumstances

mitigate any potential risks. Finally, formation of an international registry for this rarer LuTx indication with subsequent data analysis might help to better identify risk factors, understand survivorship challenges including quality of life and thereby improve post-LuTx outcomes.

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AZ: conceptualization, manuscript writing. HS, MG, HG, PJ, OS, RA, AMH, RV: critically revised the manuscript. SB: conceptualization, manuscript writing.

Appendix A. Supporting information

Supplemental data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2025.100209.

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