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Pulmonary, Hepatic, and Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Telomere Biology Disorders

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Abstract

Purpose of the Review This study aimed to summarize evidence and provide consensus-based guidelines for management of transplantation in patients with telomere biology disorders (TBD). Specifically, this review focuses on clinical management of lung, liver, and bone marrow transplantation in TBD patients.

Recent Findings TBD patients have specific unique biological vulnerabilities such as T cell immunodeficiency, susceptibility to infections, hypersensitivity to chemotherapy and radiation, and cytopenias. Furthermore, multiple organ involvement at diagnosis makes clinical management especially challenging due to higher degree of organ damage, and stress-induced telomeric crisis. Sequential and combined organ transplants, development of novel radiation and alkylator-free conditioning regimen, and use of novel drugs for graft-versus-host disease prophylaxis are some of the recent updates in the field.

Summary Multidisciplinary management is essential to optimize transplant outcomes in patients with TBD. In this review, we provide consensus-based transplant management guidelines for clinical management of transplant in TBD.

Keywords Telomere biology disorders · TBD · Transplantation · Bone marrow transplant · Lung transplant · Liver transplant

Introduction

Telomere biology disorders (TBDs) are multisystemic disorders which clinically present at degrees of organ involvement such as bone marrow failure (BMF), interstitial lung disease (ILD), non-regenerative hyperplasia (NRH) and/or cirrhosis, and T cell immunodeficiency among others [1–6]. Several factors affect clinical outcomes in patients with TBD such as age of onset, genetic etiology (worse outcomes with autosomal/X-linked recessive variants and *TINF2* variants), and number/pattern of organ involvement among others [1, 7]. Organ-specific transplantation remains the only therapeutic strategy capable of changing the natural history of the disease and offer long-term clinical success. However, there are several inherent challenges, primarily due to the multisystemic nature of TBDs but also due to unique impact of TBD-associated genetic abnormalities that increase their susceptibility to chemo-radiation at the cellular level [8]. Furthermore, organ-specific transplantation is able to overcome the pathology of the transplanted organ but does not correct and may potentially worsen disease in other organs due to the inherent stress associated undergoing transplantation. Due to these unique challenges, transplantation is challenging and necessitates a careful discussion of benefits and risks with the patient and involvement of multi-disciplinary experts. In this review, we present transplant-specific viewpoints in TBD from a multidisciplinary (pulmonary medicine, hepatology, and hematology/stem cell transplantation) team at our institution.

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Lung Transplant in TBDs

ILD is one of the life-threatening consequences of TBDs. The phenotypic presentation of ILD is highly variable with approximately 25% of patients with sporadic idiopathic pulmonary fibrosis (IPF) meeting the criteria for short telomeres, that is, a telomere length below the tenth percentile [9]. Genetic mutations associated with shortened telomeres have also been identified in rheumatoid arthritis associated ILD, pleuroparenchymal fibroelastosis, hypersensitivity pneumonitis, and combined pulmonary fibrosis and emphysema [10, 11]. Patients with ILD and TBD with or without known pathogenic germline variants have more rapid disease progression and decreased transplant-free survival compared to those with normal telomere lengths and regardless of ILD phenotype [10, 12–14].

For patients with TBDs who develop fibrotic ILD, lung transplantation offers a potential lifeline and a chance for improved quality of life [15, 16]. Because of the unique challenges that TBD can pose, such as higher risk of graft failure [10, 17, 18] and complications related to underlying genetic abnormalities, careful consideration and individualized approaches are necessary when selecting, evaluating, and managing these patients. Herein, we explore the role of lung transplantation in ILD with TBD, the specific considerations and challenges involved, and the potential outcomes and future directions in this specialized field of transplantation medicine.

Candidate Selection and Evaluation.

In general pulmonary practice, patients with ILD are usually not screened for TBD. However, we recommend that patients with ILD who are being considered for lung transplant undergo telomere length screening through flow cytometry-based fluorescent in-situ hybridization (Flow-FISH) if they exhibit any of the following: macrocytosis, unexplained cytopenias, premature graying of hair (before 30 years of age), unexplained transaminitis or signs of liver disease, or a significant family history of ILD. The purpose of telomere length screening is not to exclude patients from lung transplantation, but rather to assess the risk of extra pulmonary disease and to create an appropriate post-transplant management plan.

Along with the standard lung transplant evaluation, patients with TBD should have additional evaluation for concomitant bone marrow and liver disease; additional age- and sex-specific cancer screening is also necessary. Bone marrow biopsy should be considered for patients with macrocytosis or overt cytopenias. For those with TBD and ILD undergoing lung transplant evaluation, around 50% have bone marrow morphological abnormalities, with hypocellular marrow and macrocytosis being the most common [19]. The threshold for performing bone marrow biopsy as part lung transplant evaluation is based on center specific protocols due to lack of prospective data. If a bone marrow disorder is identified (such as severely hypocellular marrow), consideration should be given to tandem or sequential hematopoietic stem cell and lung transplantation (NCT01852370) [20].

In addition to liver enzyme and synthetic liver function testing, liver imaging with either ultrasound or non-invasive fibrosis assessment (with liver and spleen stiffness measurement with magnetic resonance elastogram) should be considered in lung transplant candidates with TBD. Routine liver biopsies are unnecessary. If evidence of hepatic fibrosis, portal hypertension, or cirrhosis is identified, consideration should be given to combined liver-lung transplantation [21].

Individuals with TBD have an increased risk of cancers and solid tumors [22]. The most common solid tumors in this population are head and neck squamous cell carcinoma, specifically carcinoma involving the tongue, and cutaneous squamous cell carcinomas [22]. Dental, otorhinolaryngology, and dermatologic evaluation should be considered to screen for these malignancies as part of the lung transplant evaluation.

Lung Transplant Outcomes

Studies suggest that lung transplant recipients with TBD may have a reduced chronic lung allograft dysfunction (CLAD)-free survival [10, 12, 13], with other studies showing conflicting results [15, 23]. Increased risk of CLAD in this population may be due to a variety of factors, such as lower levels of immunosuppression, increased susceptibility to respiratory infections, or a lack of adequate stem cell reserve. Additionally, heightened fibroblast proliferation following graft injury may play a role [24]; however, no significant differences in primary graft dysfunction, acute rejection, or survival have been consistently reported.

Lung transplant recipients with TBD are at increased risk of hematologic complications, most often anemia and leukopenia, but bone marrow failure and myelodysplasia also occur [12, 19]. Specifically, patients with *TERC* mutations may be at particular risk for bone marrow failure post-transplant likely due to exaggerated stress-induced telomeric crisis [10].

After receiving a lung transplant, individuals with TBD may be more vulnerable to the reactivation of cytomegalovirus (CMV), especially if there is a mismatch in CMV status between the donor (positive) and the recipient (negative) [25, 26]. This is likely due to a decrease in overall cellular

immunity [27], and possibly compounded by a shortened anti-CMV prophylaxis due to concern for cytopenias.

Liver Transplantation in TBDs

Background

Development of liver disease, either as a direct consequence of telomere biology disorders (TBD) or as a contributing factor, is common. In fact, after bone marrow and lung, the liver is the third most affected organ system in patients with TBD. In the largest cohort of such patients that is followed prospectively at the National Institutes of Health, 40 out of 100 patients were found to have hepatic involvement, either with liver enzyme elevations, histological changes, or abnormal imaging findings [28]. Of these 40 patients, two were confirmed to have cirrhosis and one was diagnosed with nodular regenerative hyperplasia (NRH). Among the patients with liver enzyme elevations, the pattern was found to be variable (cholestatic, hepatocellular, or mixed). The wide range of the extent of liver involvement demonstrated in this cohort is reflective of the variable phenotypes seen in patients with TBD.

In general, the most severe forms of hepatic involvement of TBD include cirrhosis and nodular regenerative hyperplasia. The former requires investigation for alternative etiologies, and should be suspected in patients diagnosed with cirrhosis and a history of interstitial lung disease or bone marrow failure. While the exact mechanisms of TBD-related cirrhosis are not fully elucidated, limited studies suggest that cellular senescence in hepatocytes associated with telomere shortening leads to impaired liver regeneration, which in turn instigates development of fibrosis [29]. Nodular regenerative hyperplasia is a benign transformation of the liver parenchyma into small regenerative nodules without surrounding fibrosis. As the prevalence of nodular regenerative hyperplasia increases with aging, shortening of telomeres is thought to contribute to development of this condition in patients with TBD. Although it is a benign process and it does not lead to cirrhosis, nodular regenerative hyperplasia is complicated by development of portal hypertension in 50–70% of the patients leading to ascites and variceal bleeding [30].

Management Considerations

When patients with TBD develop complications of cirrhosis and portal hypertension, they should be referred to a transplant center for evaluation for liver transplantation. Because these disorders affect multiple organs and systems, it is very important that the transplant evaluation involves multidisciplinary input. In fact, most patients with TBD-related liver disease present with respiratory conditions, including pulmonary fibrosis, emphysema, and hepatopulmonary syndrome. The latter represents a complication of portal hypertension, characterized by progressive hypoxemia, which can be successfully treated with liver transplant [31]. In addition, patients with TBD need to be screened for other possible extrahepatic manifestations, for a thorough transplant evaluation. Typically, the liver synthetic function is preserved in patients with TBD-related liver disease. Thus, if deemed appropriate candidates, these patients may have a long wait time until a transplant, as liver graft allocation is dictated by MELD-Na scores in most countries. During that time, extrahepatic manifestations, particularly the pulmonary disease, may worsen and lead to the demise of patients [32]. As such, it is essential to follow these patients closely while they are on the wait list.

Outcomes of liver transplant in patients with TBD are increasingly being reported, and are generally favorable. In the largest cohort to date, Mayo Clinic reported the outcomes of four patients who underwent liver transplantation for TBD-related liver disease (three with decompensated cirrhosis and one with non-cirrhotic portal hypertension). At the time of the report with at least 4-year follow-up (range 4–9 years), all patients were alive with excellent graft function [32]. Reports from other institutions with fewer patients support these results [33, 34]. In patients with accompanying hepatopulmonary syndrome, liver transplantation often leads to resolution of the symptoms of hypoxemia. In those with TBD-related liver disease and severe pulmonary fibrosis, serial or simultaneous liver and lung transplantation is feasible and has favorable outcomes [21].

Special Considerations in Post-solid Organ Transplant Management

When dealing with patients who have TBD, it is important to carefully consider their immunosuppression regimens and anti-infective prophylaxis. It is recommended to avoid lymphocyte-depleting agents like anti-thymocyte globulin (ATG) and alemtuzumab for induction, as they have been linked to accelerated telomere shortening, higher risk of infections, and increased cytopenias in TBD patients [35, 36]. If induction is required, then interleukin-2 inhibitors should be preferred. Cell-cycle inhibitors may need to be reduced or initiated at a reduced dose to prevent significant leukopenia. Azathioprine use in patients who have TBD must be avoided as it can accelerate telomere attrition, increase the risk of myeloid neoplasms, and worsen overall outcomes [10, 37, 38]. Calcineurin inhibitors (particularly cyclosporine rather than tacrolimus) have been shown to shorten telomere length more than mammalian target of rapamycin (mTOR) inhibitors [39, 40]. Although data

is relatively limited, consideration can be given to adding mTOR inhibitors to allow for reduction of calcineurin inhibitors in patients with persistent cytopenias. Maintenance on calcineurin-inhibitors does not appear to have a negative impact on extrahepatic manifestations of TBD after liver transplantation. Although mTOR inhibitors have been found to confer protection against age-related conditions in healthy individuals [41], experimental studies have also found that mTOR inhibition in mice with short telomeres leads to decreased survival [42]. It is therefore unclear whether calcineurin or mTOR inhibitors are preferred in TBD patients and would benefit from a randomized comparison study. Theoretically, anti-metabolites (e.g., mycophenolate mofetil) can worsen the pre-existing cytopenia(s) and should be carefully used with lower-than-standard doses. Nonetheless, these drugs are often weaned and stopped within the first year of liver transplantation in most patients regardless of the transplant indication.

Due to the risk of leukopenia, anti-CMV prophylaxis using valganciclovir can be challenging. Pre-emptive prophylaxis with letermovir is strongly encouraged especially given the recent FDA approval in allogeneic hematopoietic stem cell transplantation (alloHCT).

No studies have shown a benefit of danazol following lung transplant. Given the possible increased risk of venous thromboembolic disease and hepatic toxicity with danazol, we do not recommend routine use in either lung or liver transplant recipients with TBD. Given the increased risk of skin and head and neck squamous cell carcinoma, routine (at least, annual) skin checks and dental exams should be performed and medications (such as voriconazole) that have been associated with an increased risk of non-melanoma skin cancers should be avoided.

Allogeneic Hematopoietic Stem Cell Transplantation in TBDs

Background

Telomere shortening has been associated as a risk factor for adverse outcomes post alloHCT. Pre-transplant leukocyte telomere shortening was found to be a predictor of poor outcomes after alloHCT in patients with MDS ($n = 1267, \geq 40$ years old) due to higher nonrelapse mortality (NRM) after adjusting for relevant clinical and genetic variables and regardless of conditioning regimen intensity [43]. The increased NRM was seen in patients who developed acute graft-versus-host disease (GVHD), likely reflective of decreased regenerative potential of mucosal tissues among patients with shorter telomeres [43]. In patients with bonafied TBD such as dyskeratosis congenita, outcomes after alloHCT were poor with a 10-year overall survival of around 30% with 24% frequency of grade II-IV acute GVHD and 37% risk of chronic GVHD [44]. Agarwal et al. have designed a novel radiation and alkylator-free conditioning protocol comprising of fludarabine and alemtuzumab followed by bone marrow graft from at least 7/8 or 8/8 HLA-compatible related or unrelated donors and tacrolimus (or cyclosporine) plus mycophenolate mofetil graft versus host disease prophylaxis. However, the inclusion criteria included pediatric and adult TBD patients without any myeloid clonal evolution and excluded patients with only mismatched or haploidentical donor options (NCT01659606). Therefore, there is a significant area of need to develop novel conditioning regimens and transplant strategies for TBD patients in order to optimize their clinical outcomes and minimize toxicities.

Management Considerations

At our institution, we undertake TBD patients at diagnosis to understand both hematopoietic and extra-hematopoietic organ involvement. At minimum, this includes a bone marrow aspirate/biopsy with cytogenetics and myeloid next generation sequencing assessment, pulmonary function test (PFT) and high-resolution CT scan, magentic resonance elastogram of liver and spleen, bone density scan, quantitative immune cell subsets, and immunoglobulins in addition to standard alloHCT evaluation. There is no prospective data to guide specific indications/timing of alloHCT in TBD and should be individualized but is broadly based on two primary considerations: (a) worsening of cytopenias/bone marrow failure and (b) myeloid clonal evolution detected either through peripheral blood next generation sequencing or bone marrow assessment. Although there is formally lack of clinical evidence of utility, we also send an in vitro raadiosensitivity assay which involves peripheral blood mononuclear cells (PBMCs) patients and healthy controls to low-dose (2 Gy) radiation and checking for lymphocyte subsets and key phosphoprotein associated with DNA double-strand break (DSB) repair pathways (Diagnostic Immunology Laboratory, Nationwide Children's Hospital). This allows identification of TBD patients who are especially sensitive to radiation effects. The conditioning regimen for patients differ among TBD patients with versus without myeloid clonal evolution. In TBD patients without myeloid clonal evolution and availability of matched sibling (MSD) or match unrelated donors (MUD), we try to avoid full-dose radiation and/or alkylator (melphalan (Mel)/busulfan (Bu)/thiotepa/cyclophosphamide (Cy)) containing regimens. The conditioning regimen incorporating Fludaribine (Flu, 30 mg/m2 for 6 days, total dose 180 mg/m^2) and Alemtuzumab (0.2 mg/kg/day for 5 days) followed by bone marrow (BM) infusion is currently under prospective clinical trial investigation (NCT01659606). Alternatives include Flu/low-dose

TBI (2 Gy) non-myeloablative regimen followed by sirolimus/cyclosporine (or tacrolimus)/mycophenolate mofetil as GVHD prophylaxis [45].

In TBD patients with myeloid clonal evolution, we use Flu/Mel or Flu/Bu reduced intensity conditioning (RIC) with tacrolimus plus minidose methotrexate (MTX, 5 mg/m^2, days + 1, + 3, + 6) as GVHD prophylaxis. Especially in TBD patients with myeloid clonal evolution and post-solid organ (lung or liver) transplant, the intensity of conditioning regimen should be carefully guided by weighing relapse risk and NRM due to the necessity of life-long immunosuppression and consequently lack of a graft-versus-leukemia (GVL) effect. Haploidentical donors represent a special challenge due to the necessity of post-transplant Cy (PTCy) in vivo T cell depletion. Even with dose reduction, PTCy use may increase toxicity in TBD patients due to their inherent biological vulnerability to alkylator therapy. Abatacept, a selective T cell co-stimulation modulator, is an alternative for such patients [46]. It is typically used at a dose of 10 mg/kg on days -1, + 5, + 14, and + 28 [46]. Data regarding its use in the haploidentical donor setting is limited, with a study reporting its use in combination with PTCy and a short-course of tacrolimus [47]. However, abatacept seems the best option in TBD patients not only due to its non-cytotoxic nature but also effectiveness in GVHD prevention. Optimization of GVHD prophylaxis in TBD patients post solid-organ transplant is especially critical due to the fact that the hematopoietic stem cell donor product is often mismatched to the transplanted (lung or liver) organ and raises the possibility of rejection. At our institution, we have performed alloHCT on a 58-year-old patient with TBD who was status post bilateral lung transplant for ILD. The reason for alloHCT (around 2 years after lung transplant) was high risk myeloid clonal evolution (PPM1D mutation with monosomy 7). Reduced intensity conditioning regimen (Flu/Mel) was used with abatacept/tacrolimus/mini-dose methotrexate as GVHD prophylaxis. Although the first 180 days were largely uneventful, the patient developed a relapse of his myeloid disease with further myeloid clonal evolution. This case is illustrative of clinical complexity stemming from multiple competing issues such as risk of relapse, limited organ reserve, enhanced TBD-specific chemotherapy and radiation sensitivity, increased risk of secondary cancers, and necessity for lifelong immunosuppression in solid organ transplant recipients thereby limiting post-transplant GVL. Development of specific conditioning and GVHD protocols for TBD patients with clonal evolution is a significant area of need and will only be possible through multi-institution collaborative clinical trials.

In TBD patients with ILD and bone marrow failure (but without myeloid clonal evolution), combined lung and alloHCT can be considered after partial HLA and ABO matching between the hematopoietic stem cell product and cadaveric lung organ as demonstrated by the University of Pittsburgh group (NCT#03500731). In alloHCT, although there is lack of prospective evidence, we do consider danazol use in case cytopenias are exaggerated due to peri-transplant telomeric stress. Infections are a common cause of NRM, and need close monitoring along with appropriate antimicrobial prophylaxis. Quantitative and functional assays of immune cell subsets and immunoglobulins are especially relevant in TBD patients and can guide on the timing of vaccinations and tapering of antimicrobial medications.

Summary

Organ-specific transplantation in patients with telomere biology disorders is a challenging undertaking, but currently, it is the only therapy capable of altering the natural course of the disease. Multi-disciplinary cooperation is essential to optimize clinical outcomes. Prospective multi-center clinical trials with a standard approach on several aspects of management, such as combined or sequential organ transplant, and optimal immunosuppressive therapy are necessary to answer clinically meaningful questions.

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Declarations

Ethics Approval Not applicable.

Competing Interests Authors disclose no relevant conflicts of interest in relation to the manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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