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Infectious Disease

Incidence, Risk Factors, and Outcomes of Idiopathic Pneumonia Syndrome after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Our current knowledge of idiopathic pneumonia syndrome (IPS) predates improved specificity in the diagnosis of IPS and advances in hematopoietic cell transplantation (HCT) and critical care practices. In this study, we describe and update the incidence, risk factors, and outcomes of IPS. We performed a retrospective cohort study of all adults who underwent allogeneic HCT at the Fred Hutchinson Cancer Research Center between 2006 and 2013 (n = 1829). IPS was defined using the National Heart, Lung, and Blood Institute consensus definition: multilobar airspace opacities on chest imaging, absence of lower respiratory tract infection, and hypoxemia. We described IPS incidence and mortality within 120 and 365 days after HCT. We examined conditioning intensity (nonmyeloablative versus myeloablative with high-dose total body irradiation [TBI] versus myeloablative with low-dose TBI) as an IPS risk factor in a time-to-event analysis using Cox models, controlled for age at transplant, HLA matching, stem cell source, and pretransplant Lung function Score (a combined measure of impairment in Forced Expiratory Volume in the first second (FEV_1) and Diffusion capacity for carbon monoxide (DLCO)). Among 1829 HCT recipients, 67 fulfilled IPS criteria within 120 days (3.7%). Individuals who developed IPS were more likely to be black/non-Hispanic versus other racial groups and have severe pulmonary impairment but were otherwise similar to participants without IPS. In adjusted models, myeloablative conditioning with high-dose TBI was associated with increased risk of IPS (hazard ratio, 2.5; 95% confidence interval, 1.2 to 5.2). Thirty-one patients (46.3%) with IPS died within the first 120 days of HCT and 47 patients (70.1%) died within 365 days of HCT. In contrast, among the 1762 patients who did not acquire IPS in the first 120 days, 204 (11.6%) died within 120 days of HCT and 510 (29.9%) died within 365 days of HCT. Our findings suggest that although the incidence of IPS may be declining, it remains associated with post-transplant mortality. Future study should focus on early detection and identifying pathologic mediators of IPS to facilitate timely, targeted therapies for those most susceptible to lung injury post-HCT.

INTRODUCTION

The term *idiopathic pneumonia syndrome* (IPS) is used to define a spectrum of noninfectious, diffuse lung injuries that occur following hematopoietic cell transplantation (HCT). Previous reports estimate that IPS develops in 4% to 12% of HCT recipients with a case fatality of 60% to 86% in the first 100 to 120 days post-transplant [1-4]. However, these estimates predate improvement in the diagnostic specificity of IPS, refinements in transplant practices, and advances in supportive critical care that have led to overall improvement in transplant outcomes [5].

IPS criteria include evidence of widespread alveolar injury with symptoms and signs of pneumonia in the absence of active lower respiratory tract infection [6]. Using updated molecular techniques for the detection of infectious pathogens in the lung, Seo et al. [7] have shown that over half of patients diagnosed with IPS have a virus detected in bronchoalveolar lavage (BAL) samples. The significance of these viruses in the pathogenicity of pneumonia remains unclear, but emerging evidence suggests that at least in the case of Human Herpesvirus 6 (HHV-6), these viruses may lead to lung injury and raise plausible concern that IPS may have been misdiagnosed in earlier studies [4,7,8].

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IPS encompasses a spectrum of clinical presentations and is thought to result from a diversity of lung insults. Previously defined risk factors for the development of IPS after allogeneic HCT have included conditioning intensity, total body irradiation dose (TBI), high-grade acute graft-versus-host disease (GVHD), advanced age, and transplant indication [2,4,9]. However, increased utilization of reduced-intensity conditioning regimens, improvements in prevention and treatment of acute GVHD, the introduction of umbilical cord blood stem cells, and improvements in the prevention and control of infectious complications have changed HCT-recipient exposures and may alter the spectrum of lung injury in patients who have undergone allogeneic HCT [5].

We performed a retrospective cohort study in a contemporary cohort of patients who underwent allogeneic HCT. We rigorously adjudicated IPS status and herein report the updated incidence, risk factors, and outcomes of IPS. We hypothesized that conditioning regimen intensity and TBI dose would remain significant risk factors for the development of IPS and explored the risk of IPS relating to other recipient and transplant factors. Finally, given advances in supportive critical care practices, we hypothesized that mortality in patients who develop IPS would be lower compared with earlier studies.

PATIENTS, MATERIALS, AND METHODS

Study Patients

We performed a retrospective cohort study of all adults who underwent allogeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, Washington, between 2006 and 2013. We included only the first allogeneic HCT performed for each patient during this study period. Patients younger than 18 years and adults who received autologous grafts were excluded. The FHCRC Institutional Review Board approved this analysis.

Transplantation Techniques

All patients received a conditioning regimen followed by infusion of hematopoietic stem cells according to local protocols. Although the conditioning regimens varied, the myeloablative conditioning regimens generally contained (1) busulfan with either cyclophosphamide or fludarabine, (2) treosulfan and fludarabine plus low-dose TBI (<12.0 Gray [Gy]), or (3) cyclophosphamide with or without fludarabine plus high-dose TBI (12.0 to 13.2 Gy) [10]. TBI dose fractionation schedules were tailored to the patient's conditioning protocol. In general, our institution's standard treatment protocol delivers 12-Gy total doses as twice-daily fractions of 2 Gy each over 3 consecutive days and 13.2-Gy total doses as twice-daily fractions of 1.65 Gy each over 4 consecutive days (dose rate, 6 to 25 cGy/min). Reduced-intensity nonmyeloablative regimens contained 2 to 4 Gy TBI with or without fludarabine. Most patients received immunosuppressive drugs, usually a calcineurin inhibitor and mycophenolate mofetil, for GVHD prophylaxis. Antimicrobial prophylaxis consisted of levofloxacin during neutropenia (absolute neutrophil count (ANC) $\leq$500 cells/mm^3), acyclovir, trimethoprim-sulfamethoxazole, and fluconazole or a mold-active triazole. Preemptive therapy was used for cytomegalovirus (CMV) on the basis of weekly antigen or DNA testing [11]. For those with pulmonary symptoms, respiratory specimens were sent for microbiologic evaluation as described below.

Acute GVHD was diagnosed clinically by the treating physician and graded according to previously described criteria [12].

Definition of IPS

IPS was defined using the National Heart, Lung, and Blood Institute consensus definition and required new multilobar airspace opacities on chest imaging, absence of lower respiratory tract infection, and abnormal pulmonary physiology [6].

By standard local practice, a broad panel of microbiologic studies was sent on all BAL samples. Any respiratory tract specimens obtained via BAL or lung biopsy, if performed, were submitted for cytologic and pathologic analyses with conventional staining and culture for bacteria, fungi, mycobacteria, nocardia, and viruses; shell viral centrifugation viral cultures for CMV and respiratory syncytial virus (RSV); and direct fluorescent antibody testing for *Legionella*, *Pneumocystis jiroveci*, CMV, RSV, parainfluenza virus types 1 to 3, and adenovirus. Serum and BAL were routinely tested for *Aspergillus* with the galactomannan index using the Bio-Rad Platelia Assay (Hercules, CA) [13]. In addition, a multiplex quantitative reverse-transcriptase PCR panel was used to detect 12 respiratory viruses, including influenza A, influenza B, RSV, parainfluenza virus types 1 to 4, adenovirus, human metapneumovirus, coronavirus, rhinovirus, and bocavirus [14]. Invasive fungal infections were defined according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria [15]. Bacterial pneumonia was diagnosed if the BAL culture grew 10^4 or more colony-forming units per milliliter of pathogenic gram-positive cocci or if any number of gram-negative rods or other pathogens were isolated in the setting of compatible radiographic changes. Viral pneumonia was diagnosed if $\geq$40 PCR copies/μL of pneumonia-causing respiratory viruses were isolated. Because HHV-6 is a known human pathogen and may play a role in the pathogenesis of IPS [7], we retrospectively tested remnants of clinical BAL samples available in local biorepositories for HHV-6 (n = 74). Participants with HHV-6 identified at $\geq$40 PCR/copies per microliter were censored on date of bronchoscopy (n = 9).

For all potential IPS cases meeting radiographic criteria with indeterminant BAL results, we performed a comprehensive manual chart review and considered factors such as response to medical therapies, relapses, serial BAL results, and autopsy results. IPS cases required sustained or progressive hypoxemia unresponsive to antibiotics or diuretics, defined as peripheral capillary oxygen saturation (SpO_2) <92%, an increase over baseline oxygen requirement to >2 liters per minute (LPM), or a new or increased-from-baseline A-a difference on arterial blood gases. IPS onset was defined as the day on which chest imaging first revealed multilobar infiltrates. Of note, each chest image and all potential IPS case were reviewed by 2 experts and, in the event of disagreement, by a third to achieve consensus in the adjudication of this cohort (Supplementary Table S1).

Statistical Analyses

Patients with IPS were compared with patients without IPS using the Wilcoxon rank-sum test for continuous variables and Pearson's chi-square test for categorial factors. Probability of IPS was estimated by cumulative incidence and incidence rate. We compared the cumulative incidence between predefined groups using Nelson-Aalen curves and log-rank tests.

We examined several potential IPS risk factors using bivariate Cox regression. Host factors of interest included patient age, sex, race/ethnicity, indication for transplant, recipient CMV serostatus, and lung function score (LFS; a combined measure of impairment in FEV_1 and DLCO) [16]. We modeled conditioning intensity as nonmyeloablative, myeloablative with low-dose TBI (<12 Gy), and myeloablative with high-dose TBI ($\geq$12 Gy), consistent with previous analysis of IPS [2]. Additional transplant characteristics included hematopoietic stem cell source (cord blood versus peripheral blood or bone marrow), transplant type (HLA-matched related or unrelated or HLA-mismatched unrelated), and donor CMV serostatus.

We used multivariable Cox regression models to examine the association between the primary exposure of interest, conditioning intensity, and development of IPS while controlling for potential confounders. Variables for the models were chosen a priori based on previous data on host factors and transplant characteristics associated with increased risk for IPS development [2,4,9]. IPS was a rare outcome in our cohort, and to avoid introducing bias by overfitting, we were parsimonious with variable inclusion [17]. We controlled for patient age at transplant, transplant type (HLA matched versus unmatched), stem cell source (cord blood versus alternative source), and pretransplant LFS. Transplant type and stem cell source were dichotomized into hypothesized, clinically relevant categories, and LFS was modeled as a continuous variable.

Severe (grade III to IV) acute GVHD was not included in our final model because severe GVHD is more likely in myeloablative conditioning and may mediate the relationship between conditioning intensity and IPS [18-20]. In sensitivity analysis, we adjusted for severe acute GVHD occurring before IPS onset as a time-dependent covariable. Finally, race was added as a covariate in a separate sensitivity analysis. In our predominately white cohort, black/non-Hispanic race/ethnicity was colinear with HLA match and receipt of umbilical cord stem cells and therefore was not included in our primary model.

We examined associations between IPS and overall survival after HCT using Cox regression, modeling IPS as a time-dependent exposure. Bivariable Cox regression models were used to assess factors associated with post-IPS mortality at 120 days and 365 days after HCT. These factors were chosen based on associations with post-transplant respiratory failure or all-cause mortality [5,16].

We examined Schoenfeld residuals to assess proportional hazards assumptions of each time-to-event model and no violation was found. No adjustments were made for multiple comparisons; we considered 2-sided *P* values less than .05 to be statistically significant.

Analyses were performed using Stata version 15.0 (StataCorp LP, College Station, TX).

RESULTS

Cohort Characteristics and IPS Incidence

Our cohort consisted of 1829 adults who underwent allogeneic HCT at FHCRC between 2006 and 2013. BAL was performed in 332 patients who developed pulmonary infiltrates. Among these patients, pulmonary infections were identified in the specimens collected from 141 patients, which excluded these patients as possible IPS cases. After comprehensive chart review, 127 additional patients were excluded from the IPS group because of

Table 1
Patient and Transplantation Characteristics

Factors	Patients without IPS (n = 1762)	Patients with IPS (n = 67)	*P* Value
Patient age, median (range), yr	49.7 (30.6-59.6)	51.9 (37.9-58.3)	.47
Female	721 (40.9)	29 (43.3)	.77
Race			**.003**
White	1506 (85.5)	53 (79.1)	
Black	27 (1.5)	5 (7.5)	
Asian	101 (5.7)	3 (4.5)	
Alaska Native/Native American	128 (7.3)	6 (8.9)	
Ethnicity Latino	98 (5.6)	5 (7.5)	
Allogeneic HCT prior to 2006			.70
Yes	360 (20.4)	15 (22.4)	
No	1402 (79.6)	52 (77.6)	
Transplant indication			.85
Acute leukemia	848 (48.1)	35 (53.0)	
CML/MDS	401 (22.7)	13 (19.7)	
Other malignancy	445 (25.3)	15 (22.7)	
Lymphoma/CLL	334 (75.1)	12 (80.0)	
Multiple myeloma	110 (24.7)	3 (20.0)	
Other tumors*	1 (0.2)	0.0	
Nonmalignant	68 (3.9)	3 (4.6)	
Conditioning			
Nonmyeloablative	765 (43.4)	25 (37.3)	**.01**
Myeloablative			
TBI, <12 Gy	688 (39.1)	20 (29.9)	
TBI, ≥12 Gy	309 (17.5)	22 (32.8)	
HLA and donor status			.25
Matched related	579 (32.9)	24 (35.8)	
Matched unrelated	718 (40.7)	21 (31.4)	
Mismatched unrelated	308 (17.5)	12 (17.9)	
Stem cell source			.09
Peripheral blood	1364 (77.4)	42 (62.7)	
Bone marrow	241 (13.7)	15 (22.4)	
Cord blood	157 (8.9)	10 (14.9)	
Disease risk*			.31
High	1634 (92.7)	60 (89.6)	
Low	128 (7.3)	7 (10.4)	
Recipient CMV serostatus			.11
Positive	1024 (58.9)	46 (68.6)	
Negative	714 (41.1)	21 (31.4)	
Donor CMV serostatus			.43
Positive	620 (38.6)	19 (33.3)	
Negative	988 (61.4)	38 (66.7)	
Lung function score†			<**.001**
Normal (LFS = 2)	637 (36.8)	19 (29.2)	
Mildly decreased (LFS 3-5)	979 (56.6)	38 (58.5)	
Moderately decreased (LFS 6-9)	110 (6.4)	6 (9.2)	
Severely decreased (LFS 10-12)	3 (0.2)	2 (3.1)	

Values are presented as number (%) unless otherwise indicated.
CLL indicates chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HD, Hodgkin's Disease; MDS, myelodysplastic syndrome; MM, multiple myeloma.
Bolded *P* values represent statistically signficant differences between those with and without IPS in the factors represented in column 1 corresponding to those *P* values. We defined $P < 0.05$ as statistically significant.

* High risk was defined as active, de novo, or relapsed acute myelogenous leukemia, MDS (refractory anemia with excess blasts or excess blasts in transformation), myeloproliferative disorder, acute lymphoblastic leukemia, CLL, non-Hodgkin lymphoma, HD, MM regardless of status, accelerated phase or blastic crisis of CML, or other tumors such as renal cell carcinoma. Low risk was defined as nonmalignant disease, including aplastic anemia, immunodeficiency syndrome, any of the diseases mentioned with unknown disease status or in remission except for MM, CML chronic phase, and MDS (refractory anemia with or without ringed sideroblasts).

† Lung function score [16]. The pretransplant LFS represents the sum of the FEV_1 and DLCO impairment scores, where >80% = 1, 70% to 79% = 2, 60% to 69% = 3, 50% to 59% = 4, 40% to 49% = 5, and <40% = 6.

presumed cardiogenic pulmonary edema responsive to diuretics, rapid response to empiric antibiotics, or presence of extrapulmonary infectious source. Ultimately, 67 patients fulfilled IPS criteria. Median follow-up time was 485 days (range, 1 to 2836 days). The number of IPS cases was similar across calendar years throughout the study period (Supplementary Figure S1).

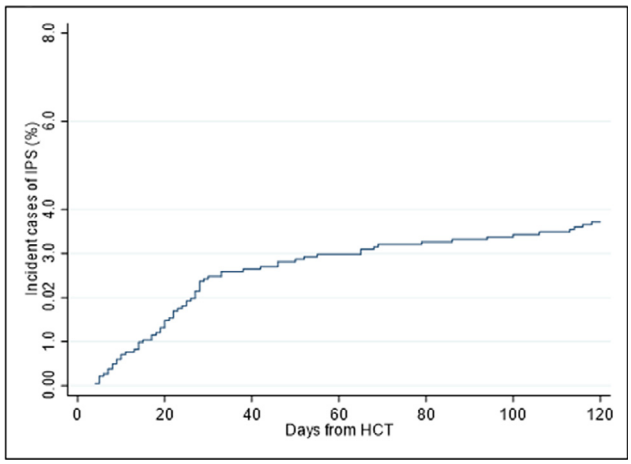

Figure 1. Incidence of IPS within 120 days following HCT. Median time to IPS onset was 25 days after allogeneic HCT (range, 4 to 118 days).

Individuals who developed IPS were more likely to have received myeloablative conditioning that included high-dose TBI, have pretransplant lung function impairment, or be racially/ethnically black/non-Hispanic (Table 1). The cohort was predominantly white/non-Hispanic, and patients of black race were more likely to have received HLA-mismatched or umbilical cord stem cells and therefore more likely to have conditioning regimens that included high-dose TBI (25% versus 18%).

The cumulative incidence of IPS at 120 days after allogeneic HCT was 3.7% (incidence rate 3.1 cases per 10,000 person-days) (Figure 1). Among the 67 patients with IPS, 11 (16.4%) had acute GVHD before the onset of IPS, and 14 (20.9%) additional patients were diagnosed with GVHD following IPS diagnosis.

Unadjusted cumulative incidence curves stratified by conditioning regimen showed no significant difference in cumulative incidence of IPS between patients who received myeloablative versus nonmyeloablative conditioning (Figure 2). However, having received a myeloablative regimen with high-dose TBI (≥12 Gy) compared with receiving either myeloablative conditioning with low-dose TBI or nonmyeloablative conditioning was associated with an increased cumulative incidence of IPS.

Risk Factors for IPS

In our primary analysis, myeloablative conditioning with high-dose TBI (≥12 Gy) was associated with increased risk of IPS in bivariate and fully adjusted models (adjusted hazard ratio [HR], 2.5; 95% confidence interval [CI], 1.2 to 5.2) (Table 2). No increased risk of IPS was observed in patients who received myeloablative conditioning with low-dose TBI compared with nonmyeloablative regimens. In fully adjusted Cox models, baseline lung impairment was associated with IPS development, whereas age and transplant indication, which have previously been identified as IPS risk factors, were not. Myeloablative conditioning with high-dose TBI remained associated with increased risk of IPS after further adjustment for severe acute GVHD (HR, 2.3; 95% CI, 1.1 to 4.8). In addition, adjustment for race/ethnicity did not change the magnitude of the association between conditioning intensity and IPS in fully adjusted models (HR, 2.6; 95% CI, 1.2 to 5.4).

Clinical Course and Outcome of IPS

Among the 67 patients who developed IPS, median time to IPS onset was 25 days after allogeneic HCT (range, 4 to 118 days). The median time between IPS onset and death was 43 days (range, 5 to 1894 days). Thirty-one patients (46.3%) with IPS died within the first 120 days of HCT and 47 patients (70.1%) died within 365 days of HCT. In contrast, among the 1762 patients who did not develop IPS in the first 120 days,

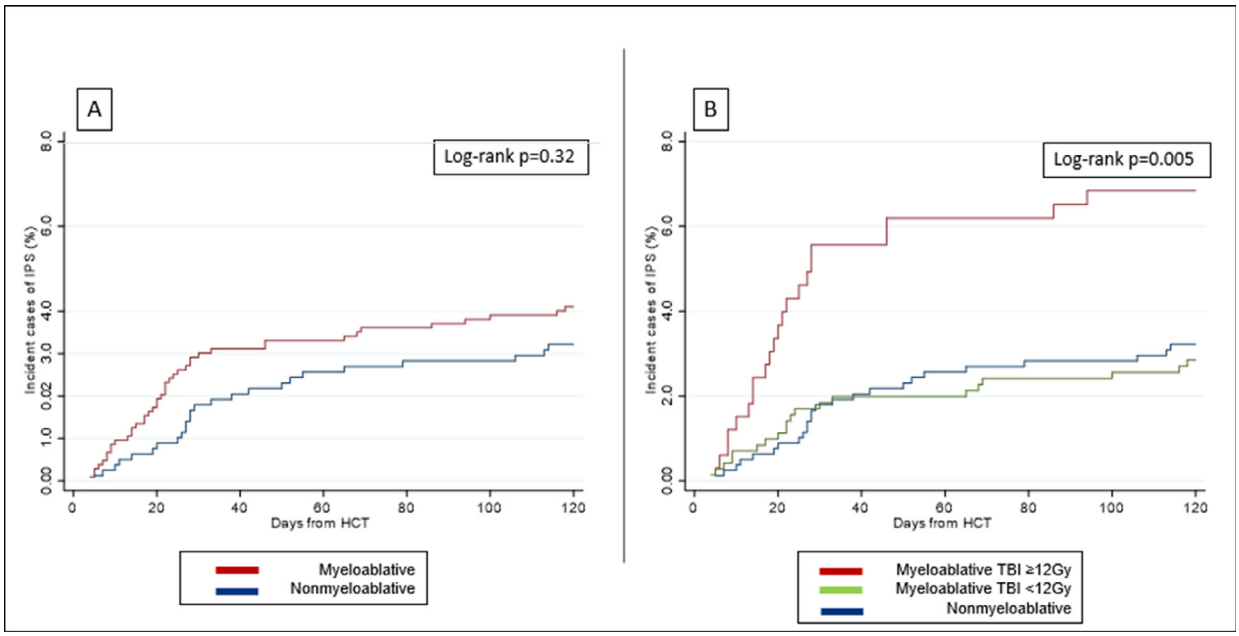

Figure 2. (A) Differences attributable to conditioning. Cumulative incidence of IPS among allogeneic HCT patients after myeloablative (n = 1039) versus nonmyeloablative (n = 790) conditioning. Cumulative incidence rates of IPS at 120 days after myeloablative conditioning (red line) or nonmyeloablative (blue line) conditioning were 4.1% and 3.2%, respectively (P = .32). (B) Differences attributable to total body irradiation and conditioning intensity. Comparing cumulative incidence of IPS among allogeneic HCT patients after nonmyeloablative (blue line, n = 790) versus myeloablative with high-dose TBI (red line, n = 331) versus myeloablative conditioning with low-dose TBI (green line, n = 708) were 3.2% versus 6.6% versus 2.8%, respectively (P = .005).

Table 2
Multiple Cox Regression Analysis of Idiopathic Pneumonia Syndrome Risk Factors

Variable	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)*
Conditioning regimen		
Nonmyeloablative	Reference	Reference
Myeloablative with TBI <12 Gy	0.9 (0.5-1.6)	1.1 (0.6-2.0)
Myeloablative with TBI ≥12 Gy	2.1 (1.2-3.8)	2.5 (1.2-5.2)
Patient age		
Per 10-year increase	0.9 (0.8-1.1)	1.0 (0.8-1.3)
HLA and donor status		
Matched related or unrelated	Reference	Reference
Mismatched	1.4 (1.0-2.0)	1.2 (0.7-2.1)
Stem cell source		
PBSC or BM	Reference	Reference
Cord blood	1.7 (0.9-3.4)	0.9 (0.3-2.8)
Lung function score†		
Per 1-point increase in impairment	1.2 (1.1-1.4)	1.2 (1.1-1.4)
Acute GVHD‡		
Grades 0-II	Reference	
Grades III-IV	3.6 (1.8-7.1)	
Race/ethnicity‡		
White	Reference	
Black	4.7 (1.9-11.8)	
Asian	0.9 (0.3-2.7)	
Alaska Native/Native American	1.3 (0.6-3.1)	
Transplant indication		
Nonmalignant	Reference	
Acute leukemia	1.0 (0.3-3.1)	
CML/MDS	0.7 (0.2-2.6)	
Other malignancy	0.8 (0.2-2.7)	
Recipient CMV serostatus		
Negative	Reference	
Positive	1.5 (0.9-2.5)	
Donor CMV serostatus		
Negative	Reference	
Positive	0.8 (0.5-1.4)	

PBSC indicates peripheral blood stem cell; BM, bone marrow.

* Adjusted model controlled for conditioning regimen (primary exposure), age, type of transplant, stem cell source, and lung function score.

† Lung function score [16]. The pretransplant LFS represents the sum of the FEV_1 and DLCO impairment scores, where >80% = 1, 70% to 79% = 2, 60% to 69% = 3, 50% to 59% = 4, 40% to 49% = 5, and <40% = 6.

‡ Adjusted for in sensitivity analysis.

204 (11.6%) died within 120 days of HCT and 510 (29.9%) died within 365 days of HCT. Among all transplant recipients who died within 365 days of HCT, 11.9% (47/557) died following a diagnosis of IPS. Finally, in the 265 patients who underwent bronchoscopy for pulmonary infiltrates and an alternative diagnosis to IPS was determined, 139 (52.4%) died with 365 days of HCT (Figure 3).

The development of IPS was associated with increased risk of death in the first 120 days post-HCT (HR, 7.5; 95% CI, 5.0 to 11.2) and at 365 days (HR, 4.7; 95% CI, 3.3 to 6.8).

Baseline poor lung function, acute respiratory failure requiring mechanical ventilation, renal insufficiency, and hepatic injury were associated with increased risk of mortality following IPS (Table 3). Mechanical ventilation was initiated in 39 (58%) patients a median of 2.6 days after IPS onset, with a 59% mortality in this group at 120 days post-HCT. Twenty-one IPS cases were liberated from the ventilator, but 5 patients required resumed mechanical ventilation and died by day 120. Ever-ventilated patients with IPS alive at day 120 had an increased risk of death 365 days after HCT (HR, 2.3; 95% CI, 1.3 to 4.3) compared with never-ventilated IPS cases. Notably, myeloablative conditioning with high-dose TBI was not associated with increased risk of death following IPS diagnosis.

DISCUSSION

This study provided important updates in the incidence, risk factors, and outcomes of IPS. We demonstrated a lower incidence of IPS compared with historical reports [1-4,21], which may reflect advances in transplant practices or improved specificity in the diagnosis of IPS. We identified that myeloablative conditioning with high-dose TBI (≥12 Gy) remains an IPS risk factor and are the first to associate pretransplant lung function impairment with risk for IPS development. We observed a lower mortality of patients with IPS 120 days after HCT compared with previous cohorts [1,2], but found that 1-year mortality remained high. This observation confirms that IPS continues to be associated with significant morbidity but that refinements in supportive care, advances in the prevention and care of immune-related toxicity, and/or improved classification of disease may be driving improvements in short-term survival.

TBI was previously identified as an IPS risk factor [22-24], but our study suggests that TBI dose may be the primary mediator of regimen-related pulmonary toxicity. Although myeloablative conditioning regimens that used high TBI doses were associated with IPS risk, myeloablative conditioning regimens with lower TBI doses were not. Experimental and observational studies support the role of TBI in IPS development. Murine models demonstrate that high-dose irradiation has multiple harmful effects in the lung. Radiation causes damage to lung endothelial DNA, resulting in cell death and acute lung injury, and simultaneously reduces tolerance to lung injury by promoting death of alveolar macrophage colony-forming cells, important mediators of pulmonary damage repair [25,26]. In addition to total dose, several other radiation parameters have been identified as risk factors in the pathogenesis of pulmonary toxicity. There is general agreement that fractionated TBI is safer than single-dose TBI with respect to IPS [27]; therefore, our center and others now use fractionated schedules. The role of the rate of delivering each TBI dose is debated [28]; lower dose rates are generally preferred, and current American Society for Radiation Oncology guidelines recommend a dose rate of <0.2 Gy per minute [29,30]. Finally, our center practices lung shielding, a technique to systematically reduce radiation exposure in the lung. The potential benefit from this practice is uncertain [31,32], and optimal protocols remain an area of active study.

Although this study was not specifically designed to examine pretransplant lung function, the novel finding of an association between baseline lung dysfunction and IPS is noteworthy. Pretransplant pulmonary function tests aid in the prognostication and identification of individuals at greater risk for post-transplant complications and mortality [16]. Previous studies have linked impairments in DLCO and FEV_1 to increased risk of post-transplant respiratory failure and all-cause mortality. Together with these prior studies, our finding warrants additional attention in future investigations and justifies continued caution in transplanting patients with severely reduced lung function.

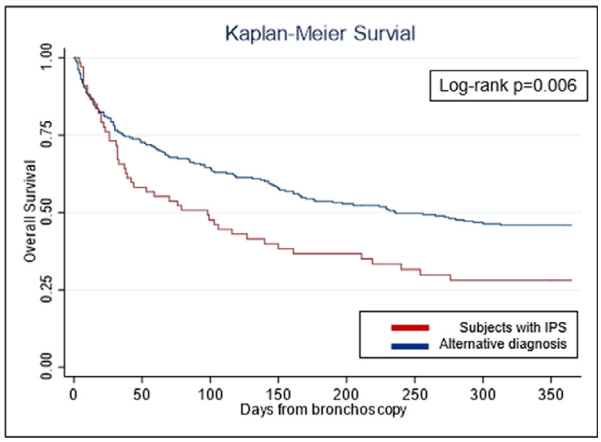

Figure 3. Kaplan-Meier survival curve comparing patients who underwent bronchoscopy in the first 120 days after HCT and were diagnosed with idiopathic pneumonia (red line, n = 67) versus an alternative cause of lung disease (blue line, n = 265). Day 0 = date of bronchoscopy with follow-up time until 365 days. Cumulative 365-day mortality in patients with IPS and without IPS was 70.1% and 52.0%, respectively ($P = .006$). Of note, 39 of 67 (58.2%) patients diagnosed with IPS received mechanical ventilation, whereas only 69 of 265 (26.0%) patients who received bronchoscopy without a diagnosis of IPS received mechanical ventilation.

Previous reports have considered acute GVHD to be a potential IPS risk factor [2,4,7,9,33], arguing that observed associations between acute GVHD and IPS suggest a causal link. We observed that grade III to IV acute GVHD remained highly associated with IPS after adjusting for other risk factors but notably accounted for just a small amount of the observed relationship between conditioning intensity and IPS. One interpretation of this result is that conditioning intensity mediates the development of both acute GVHD and IPS, explaining the high correlation between these 2 syndromes. Interrelated immune mechanisms in GVHD and IPS lend support to this argument. In experimental IPS models, TNF-α and IFN-γ mediate signal transduction cascades that orchestrate noninfectious lung inflammation and injury [9,18,34-36]. In models of acute GVHD, similar cytokine dysregulation promotes expansion of alloreactive donor $CD4^+$ cells [19]. Moreover, it is hypothesized that lipopolysaccharide translocation from intestinal damage resulting from conditioning toxicity or acute GVHD may result in the neutrophilic alveolitis observed in the later stages of experimental IPS [9,37]. Although we agree that immune-mediated lung injury contributes to the development of IPS, our study suggests that GVHD does not account for the totality of risk, and additional factors must be involved in the pathogenesis of early noninfectious lung injury.

Historically, clinical outcomes among patients with IPS after conventional HCT have been uniformly poor. Zhu et al. [4] most recently described an 87% (20/23 patients) 1-year mortality in patients who developed IPS within 120 days of HCT (study cohort 1997 to 2007) using similar diagnostic criteria. In the analysis by Zhu et al. [4], median time to death following diagnosis was just 9 days (range, 3 to 92 days) compared with 43 days in our cohort. Although this may be influenced by longer follow-up in our study, we believe this provides evidence that recent improvements in supportive care along with advances in transplant practices may be responsible for improved short-term mortality. Treatment decisions were at the discretion of the provider, and assessing efficacy of novel treatment strategies was not the aim of this study. However, it should be noted that patients diagnosed with IPS typically received high-dose systemic steroids (2 to 4 mg/kg) and, in select cases of refractory disease, received the addition of etanercept, a soluble TNF-α-binding protein (0.4 mg/kg given twice weekly for a maximum of 8 doses) [38-40]. Despite improvements in short-term outcomes, 1-year mortality remains high. Firm conclusions cannot be drawn about this observation, but we speculate that profound morbidity resulting from IPS drives poor long-term recovery, and our data confirm that short-term survivors of IPS remain a high-risk group of allogeneic HCT recipients. Finally, the associations we found between the need for mechanical ventilation or other organ injury with poor IPS outcomes are consistent with results reported in larger series of HCT recipients [41,42]. Organ injury likely reflects overall illness severity and not necessarily a distinct pathologic entity, but these observations are important and may aid physicians as they counsel patients and families regarding prognosis.

This study had several limitations. Our single-center, predominantly white sample may limit generalizability, but the single-center design allowed for uniformity in practice pattern that may have improved our ability to assess for novel risk factors. The small number of cases restricted our ability to adjust completely for differences between patients with and without IPS, and it is possible that residual confounding exists; however, our very large cohort of well-characterized allogeneic HCT recipients allowed us to make several clinically relevant observations. Despite rigorous adjudication of cases, misclassification of IPS remains possible. We applied modern molecular techniques to identify previously occult viral pathogens, including HHV-6, but the possibility remains that we overestimated the incidence of IPS. Conversely, some patients with IPS might have been missed because of mild illness or because the patient was too ill to undergo an invasive diagnostic procedure. For these reasons, the incidence of IPS might have been underestimated.

The current study suggests that although the incidence and case fatality of IPS may be declining, it remains significantly linked with post-transplant morbidity. Future study should focus on improved classification and early detection. Elucidating the pathogenicity of previously occult viral organisms to determine better the balance between infectious and noninfectious HCT pulmonary complications is critical. Study of serum biomarkers to diagnose IPS noninvasively at an earlier stage in disease development has shown promise and would have significant treatment implications but awaits prospective validation [43]. Finally, understanding the pathologic mediators of IPS (and its unique phenotypes) is essential to the discovery of novel treatment modalities and necessary to further improve long-term outcomes.

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Table 3
Mortality following IPS Onset

Variable	Total Number of Patients	No. (%) Patients Who Died within 120 Days of HCT	HR (95% CI) for Death after IPS and within 120 Days of HCT from Bivariable Cox Regression	No. (%) Patients Who Died within 365 Days of HCT	HR (95% CI) for Death after IPS and within 365 Days of HCT from Bivariable Cox Regression
Mechanical ventilation*					
Not initiated	28	8 (35)	Reference	16 (57)	Reference
Initiated	39	23 (59)	3.0 (1.3-6.6)	31 (79)	2.3 (1.3-4.3)
Renal injury†					
Creatinine <2 mg/dL	51	19 (37)	Reference	32 (63)	Reference
Creatinine ≥2 mg/dL	16	12 (75)	2.7 (1.3-5.6)	15 (94)	3.1 (1.7-6.0)
Hepatic injury‡					
Total bilirubin <4 mg/dL	52	18 (35)	Reference	32 (62)	Reference
Total bilirubin ≥4 mg/dL	15	12 (80)	3.8 (1.8-7.9)	14 (93)	2.4 (1.3-4.5)
Severe acute GVHD (before IPS)					
No or mild acute GVHD	56	25 (45)	Reference	40 (71)	Reference
Severe acute GVHD (grade III or IV)	11	6 (55)	1.3 (0.5-3.2)	7 (64)	1.6 (0.8-3.2)
Conditioning intensity					
Nonmyeloablative	25	12 (48)	Reference	20 (80)	Reference
Myeloablative TBI <12 Gy	20	10 (50)	1.0 (0.4-2.3)	16 (80)	1.0 (0.5-1.9)
Myeloablative TBI ≥12 Gy	22	9 (41)	0.7 (0.3-1.7)	11 (50)	0.5 (0.3-1.0)
Lung function score					
Normal (LFS = 2)	19	9 (47)	Reference	14 (74)	Reference
Mildly decreased (LFS 3-5)	38	16 (42)	0.9 (0.4-2.0)	24 (63)	0.8 (0.4-1.6)
Moderately decreased (LFS 6-9)	6	2 (33)	0.6 (0.1-3.0)	5 (83)	1.2 (0.4-3.3)
Severely decreased (LFS 10-12)	2	2 (100)	8.9 (1.7-46.9)	2 (100)	9.2 (1.8-46.6)

* Ventilator support within 7 days of IPS diagnosis.
† Serum creatinine concentration >2 mg/dL within 3 days of IPS onset.
‡ Total bilirubin concentration >4 mg/dL within 3 days of IPS onset.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.09.034.

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