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Therapeutic Impact and Complications Associated with Surgical Lung Biopsy after Allogeneic Hematopoietic Stem Cell Transplantation in Children

Bryan V. Dieffenbach[1,2,*], Arin L. Madenci[1,2,3], Andrew J. Murphy[4], Christopher B. Weldon[1,5], Brent R. Weil[1,5], Leslie E. Lehmann[1,5]

[1] *Boston Children's Hospital, Boston, Massachusetts*
[2] *Brigham and Women's Hospital, Boston, Massachusetts*
[3] *Harvard T.H. Chan School of Public Health, Boston, Massachusetts*
[4] *St. Jude Children's Research Hospital, Memphis, Tennessee*
[5] *Dana-Farber and Boston Children's Hospital Cancer and Blood Disorders Center, Boston, Massachusetts*

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A B S T R A C T

Hematopoietic stem cell transplantation (HSCT) in the pediatric population is associated with pulmonary complications in 25% of recipients. The role of surgical lung biopsy (SLB) remains unclear because of concerns about both the therapeutic impact and morbidity associated with the procedure. A retrospective review of consecutive allogeneic HSCT recipients at Dana-Farber and Boston Children's Hospital Cancer and Blood Disorders Center between 2006 and 2016 was performed. All recipients who underwent SLB during the study period were identified and charts reviewed for perioperative complications, histopathologic findings, and changes in therapy delivered. Pearson's chi-square test and Student's *t*-test (or appropriate nonparametric test) were used to evaluate the associations between perioperative complication and categorical and continuous variables, respectively. Five hundred fifty-five HSCTs were included, among which 48 SLBs (8.6%) were identified. Median follow-up time was 24 months (range, 0 to 139). Thirty-day postoperative morbidity was 16.7% and 30-day postoperative mortality 10.4% (n = 5). The overall 30-day postoperative complication rate (including mortality) was 20.8% (n = 10). No mortalities were directly attributable to SLB. Definitive diagnoses were identified in 70.8% of SLBs (n = 34), and therapeutic changes occurred in 79.2% (n = 38). Overall, 83.3% of SLBs (n = 40) either provided a diagnosis or led to a change in therapy. SLB has an acceptable risk of perioperative complications in this medically complicated and often severely ill population. In most HSCT patients, SLB aids in defining the etiology of pulmonary infiltrates and can inform therapeutic decisions in patients where noninvasive diagnostic modalities have failed to provide a definitive diagnosis.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is offered as treatment for a variety of pediatric conditions [1]. Pulmonary complications are common in HSCT recipients, affecting 30% to 60% of adult and at least 25% of pediatric recipients [2,3]. Nearly 30% of post-transplant mortalities are related to pulmonary complications [4-6]. Pulmonary disease processes can occur at any time during transplant. Early etiologies can be from infections, pulmonary edema, or idiopathic pneumonia syndrome [7]. Later pulmonary manifestations can also be due to infection or bronchiolitis obliterans (BO), a progressive fibrotic process that can occur with or without other manifestations of chronic graft-versus-host disease (GVHD) [8]. Whenever possible, treatment should be targeted to the underlying etiology because potential interventions include systemic immunosuppression and/or antimicrobial regimens, both of which have associated toxicities. Thus, an accurate diagnosis can allow for both the addition of targeted therapies and the elimination of unnecessary therapies, thereby optimizing outcomes while limiting toxicities.

Initial evaluation of the HSCT recipient with pulmonary infiltrates generally involves extensive laboratory studies including serum assays for pulmonary pathogens and chest imaging. Fiber-optic bronchoscopy is pursued when noninvasive workup fails to identify a definitive diagnosis [9,10]. Unfortunately, the diagnostic yield in both adult and pediatric

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* Correspondence and reprint requests: Bryan V. Dieffenbach, MD, Department of Surgery, 300 Longwood Avenue, Fegan 3, Boston, MA 02115.
E-mail address: bryan.dieffenbach@childrens.harvard.edu (B.V. Dieffenbach).

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HSCT recipients is relatively poor, ranging from 29% to 68%, and is especially problematic in the identification of noninfectious etiologies that require tissue for diagnosis [5,9-14]. Surgical lung biopsy (SLB) is often considered in an attempt to secure a definitive diagnosis and guide therapeutic decision-making. SLB is uniquely valuable in that it provides tissue for histopathologic interrogation even though the reported diagnostic yield is variable, ranging from 37% to 97% [12,15-17]. The impact of SLB on the management of HSCT recipients with pulmonary complications is not clear because subsequent changes in therapy are reported to occur in 40% to 90% of patients [17-21]. Furthermore, complication rates after SLB have been reported in 11% to 15% of adult recipients and may be higher (12% to 47%) in pediatric recipients [16-20].

The objective of this study was to evaluate in detail a large and diverse cohort of pediatric HSCT patients from a single center, thus ensuring relative consistency in both referrals for SLB and surgical approaches. We defined the early postoperative morbidity and mortality associated with SLB and assessed the impact of SLB on therapeutic strategies used by the care team to further delineate the risks and benefits of SLB in this vulnerable and complex group of patients.

METHODS

Population

We performed a retrospective review from medical records of consecutive patients who underwent allogeneic HSCT at Dana-Farber and Boston Children's Hospital Cancer and Blood Disorders Center between October 2006 and June 2016 and followed through July 2018. This study was approved by the Institutional Review Board of the Dana-Farber Cancer Institute before data collection.

Patient characteristics including age, sex, and pulmonary history were collected. Pulmonary history was defined as any pulmonary diagnosis before HSCT including radiation pneumonitis, prior pneumonia or pulmonary nodules, asthma or reactive airways disease, lung disease of prematurity, or other interstitial lung diseases. The indication for HSCT (categorized in Supplemental Table 1), type of HSCT, donor source, conditioning regimen, laboratory results, imaging, and bronchoscopic findings before SLB were also collected. The reported date of HSCT reflects the day of donor stem cell infusion.

Every patient who underwent SLB for diagnosis of pulmonary infiltrates was identified and operative notes reviewed in detail. If a patient underwent more than 1 SLB during the study period, any SLB after the initial procedure was excluded. Data regarding clinical status and respiratory support before biopsy, preoperative laboratory values including absolute neutrophil count, and platelet count were recorded. The operative approach was determined at the discretion of the operating surgeon and categorized into thoracoscopy or thoracotomy based on review of operative notes. Thoracoscopic procedures required the use of 3 ports, most commonly two 5-mm ports and one 12-mm port. Preoperative cross-sectional imaging was used to assist in locating the optimal biopsy site, and all surgical biopsies were performed as wedge resections using a surgical stapling device. Data regarding intraoperative complications, 30-day postoperative morbidity and mortality, and histopathologic result of the biopsy were collected. Postoperative chest tubes were removed at the discretion of the operating surgeon and/or when there was no evidence of pulmonary air leak and the character and quantity of the chest tube output was acceptable.

Outcome Measures

The primary outcome assessed was safety of SLB as measured by 30-day postoperative morbidity and mortality. The secondary outcome was diagnostic yield and therapeutic impact of SLB, defined as a modification to the therapeutic plan including initiation, continuation, or discontinuation of either anti-infective or anti-inflammatory therapies after pathology review of the SLB specimen. All biopsies underwent a standard set of diagnostic studies and included bacterial and fungal cultures, Gram stain, cytomegalovirus, Epstein-Barr virus, and adenovirus stains. Other diagnostic tests were requested at the discretion of the managing physicians as clinically indicated. Specimens were considered diagnostic if the findings were consistent with a definitive diagnosis as determined by the bone marrow transplant team. Change in therapy after SLB did not require a definitive diagnosis (eg, initiation of anti-inflammatory therapy based on nonspecific inflammatory changes without identification of any infectious pathogens on biopsy pathology). All medical records were independently reviewed by an HSCT specialist (L.E.L.) to determine if a change in therapy occurred.

Statistical Analysis

Descriptive statistics were tabulated for HSCT recipients who did and did not undergo SLB. Univariable analysis was used to identify factors associated with SLB among all HSCTs and to identify factors associated with 30-day mortality among those who underwent SLB. Pearson's chi-square test and Student's *t*-test were used to evaluate the association between perioperative complications and categorical and continuous variables, respectively. Nonparametric tests were used when appropriate. Data were analyzed using SAS (SAS Institute, Inc., Cary, NC).

RESULTS

Over the study period, 555 HSCTs were performed in 531 patients. The median follow-up time was 24 months (interquartile range, 10 to 50), 55.3% were male subjects (n = 307), and median age at HSCT was 8.8 years (range, .1 to 25.2). The indications for HSCT were hematologic malignancies (59.2%, n = 328), primary immunodeficiencies (19.6%, n = 109), bone marrow failure disorder (12.4%, n = 69), benign hematologic disease (4.7%, n = 26), storage diseases (3.4%, n = 19), and other conditions (.7%, n = 4). Stem cell donor source was bone marrow in 84.0% of patients (n = 466). A diagnosis of lung disease before HSCT was present in 20.7% of patients (n = 115). The overall mortality of the entire HSCT cohort from time of HSCT to the end of the study period (July 2018) was 25.4% (n = 141).

Forty-eight SLBs (8.6%) were performed during the study period. The median interval between HSCT and SLB was 106 days (range, 20 to 2814). Recipients who underwent SLB were older at HSCT than those who did not (13.2 years [range, 8.9 to 16.9] versus 8.4 years [range, 3.0 to 13.8], $P < .001$). Characteristics of those who did and did not undergo SLB are shown in Table 1.

The 30-day morbidity and mortality after SLB are shown in Table 2. The 30-day postoperative mortality after SLB was 10.4% (n = 5). Four patients died from progressive respiratory

Table 1
Characteristics of Individuals Who Underwent Allogeneic HSCT from 2006 to 2016

Characteristic	SLB (n = 48)	No SLB (n = 507)	*P*
Male sex	31 (64.6)	276 (54.5)	.23
Age at HSCT, median [IQR]	13.2 [8.9-16.9]	8.4 [3.0-13.8]	<.001
Indication for HSCT			.44
Bone marrow failure	6 (12.5)	63 (12.4)	
Benign hematologic	2 (4.2)	24 (4.7)	
Hematologic malignancy	34 (70.8)	294 (58.0)	
Storage disease	0 (0)	19 (3.7)	
Immunodeficiency	6 (12.5)	103 (20.3)	
Other	0 (0)	4 (.8)	
Donor source			.45
Bone marrow	39 (81.2)	427 (84.2)	
Cord blood	9 (18.8)	65 (12.8)	
Peripheral blood	0 (0)	10 (2.0)	
Bone marrow plus cord blood	0 (0)	5 (1.0)	
Conditioning TBI	27 (56.2)	240 (47.3)	.30
History of pulmonary disease	14 (29.2)	101 (19.9)	.19
Second HSCT	3 (6.2)	25 (4.9)	.96
Available follow-up since HSCT, mo, median [IQR]	23.9 [9.7-32.7]	24.1 [10.1-51.5]	.22
Alive at follow-up	28 (58.3)	386 (76.1)	.01

Values are n (%) unless otherwise defined. IQR indicates interquartile range; TBI, total body irradiation.

Table 2
Thirty-Day Postoperative Morbidity and Mortality Among Patients Who Underwent SLB

Postoperative Complications	No. of Cases (%)
30-day mortality	5 (10.4)
30-day mortality attributable to surgery	0 (0)
30-day morbidity	8 (16.7)
Prolonged chest tube duration (>7 days)	2 (25.0)
Ipsilateral pneumothorax requiring new chest tube	2 (25.0)
Ipsilateral pleural effusion requiring new chest tube	1 (12.5)
Hemothorax requiring blood transfusion	1 (12.5)
Reintubation postoperatively	1 (12.5)
Splenic injury	1 (12.5)
30-day morbidity or mortality	10 (20.8)

failure and 1 patient from refractory hemorrhagic cystitis. No deaths were directly attributable to SLB. However, 3 of these 5 patients had experienced 30-day surgical morbidity. Two patients died of progressive respiratory failure without any postoperative surgical complications. The overall 30-day cumulative postoperative morbidity or mortality was 20.8% (n = 10). Among those who had 30-day surgical morbidity, 2 patients required prolonged postoperative chest tube duration > 7 days (median cohort duration, 3 days [interquartile range, 2 to 4]), 3 developed an ipsilateral pneumothorax or pleural effusion requiring new chest tube placement, 1 had postoperative hemothorax requiring blood transfusion, 1 required reintubation on the day of operation, and 1 patient had an intraoperative splenic capsular injury during retraction of the diaphragm requiring exploratory laparotomy and splenorrhaphy. No patients suffered more than one 30-day morbidity. There were no postoperative surgical site infections or bronchopleural fistulas.

Factors associated with 30-day postoperative mortality after SLB are shown in Table 3. Of the patients who underwent SLB, 50% (n = 24) required some form of preoperative noninvasive respiratory support and 16.7% (n = 8) were intubated preoperatively. At the time of biopsy, 87.5% of patients (n = 42) were inpatients and 39.6% (n = 19) were in the intensive care unit. Before transfusional support, 22.9% of patients (n = 11) were neutropenic (absolute neutrophil count ≤ 1500) and 50% (n = 24) were thrombocytopenic (platelets < 100). No preoperative variables analyzed were clearly associated with 30-day mortality after SLB.

Diagnostic yield and therapeutic impact of SLB are shown in Table 4. Thirty-four SLB specimens (70.8%) were determined to be diagnostic: 9 (18.8%) showed BO/GVHD, 8 (16.6%) revealed noninfectious etiologies other than BO/GVHD, 11 (22.9%) had infectious etiologies determined, and 6 (12.5%) had other diagnoses. Among the infectious results, 3 (27.3%) were fungal alone, 3 (27.3%) were bacterial alone, 2 (18.2%) were cytomegalovirus alone, 1 (9.1%) was human herpesvirus-6 alone, 1 (9.1%) was Epstein-Barr virus alone, and 1 (9.1%) had both cytomegalovirus and fungal components. Thirty-eight SLBs (79.2%) resulted in a change in therapy. Of these, 76.3% (n = 29) were changes in anti-inflammatory therapy (28 initiation of new or escalation of existing anti-inflammatory therapy and 1 wean off anti-inflammatory therapy), 28.9% (n = 11) were changes in anti-infectious therapy (initiation or narrowing), and 2.6% (n = 1) was initiation of treatment for severe pulmonary arteriopathy believed to represent pulmonary hypertension. Of those patients with a diagnostic lung biopsy (n = 34), therapy was changed in 94.1% of cases (n = 32). Of the patients with a nondiagnostic lung biopsy (n = 14), therapy was changed in 42.9% of cases (n = 6). Taken together, SLB provided a definitive diagnosis or sufficient information to warrant a therapeutic change in 83.3% of cases (n = 40). Figure 1 shows the therapeutic impact of SLB based on diagnostic pathology.

DISCUSSION

This study examines a large, diverse cohort of pediatric allogeneic HSCT recipients to define the early postoperative morbidity and mortality associated with SLB and to assess the diagnostic utility and impact of SLB on the therapeutic strategies used by the care team. SLB was performed in nearly 10% of HSCT recipients with a 30-day complication rate of 21% and 30-day postoperative mortality of 10%. No mortalities were directly attributable to SLB. The diagnostic yield was 71%, and

Table 3
Comparison of Characteristics Among Individuals Who Did and Did Not Experience Mortality within 30 Days of SLB

Characteristic	No 30-Day Mortality (n = 43)	30-Day Mortality (n = 5)	*P*
Interval between HSCT and SLB, days, median [IQR]	119 [53-220]	42 [38-77]	.08
Respiratory support before SLB			.23
No supplemental oxygen	16 (37.2)	0 (0)	
Noninvasive support	20 (46.5)	4 (80)	
Intubated	7 (16.3)	1 (20)	
Clinical status before SLB			.51
Outpatient	6 (14.0)	0 (0)	
Inpatient hospital ward	21 (48.8)	2 (40)	
Intensive care unit	16 (37.2)	3 (60)	
Neutropenia at SLB			>.99
ANC ≤ 1500	10 (23.3)	1 (20)	
ANC > 1500	33 (76.7)	4 (80)	
Thrombocytopenia at SLB			.06
Platelets ≤ 100,000	19 (44.2)	5 (100)	
Platelets > 100,000	24 (55.8)	0 (0)	
Biopsy approach			.59
Thoracoscopy	35 (81.4)	3 (60)	
Thoracotomy	8 (18.6)	2 (40)	

Values are n (%) unless otherwise defined. ANC indicates absolute neutrophil count.

Table 4
Diagnostic Utility and Therapeutic Impact of SLB

	No. of Cases (%)
Histopathologic diagnosis	
Any diagnosis	34 (70.8)
BO/GVHD	9 (18.8)
Noninfectious other than BO/GVHD*	8 (16.6)
Infectious	11 (22.9)
Other†	6 (12.5)
Nondiagnostic	14 (29.2)
Change in therapy‡	
Any change	38 (79.2)
No change	10 (20.8)
Change in anti-inflammatory therapy	29 (76.3)
Initiation or escalation	28
Discontinuation or de-escalation	1
Change in anti-infectious therapy	11 (28.9)
Initiation, escalation, or continuation	11
Discontinuation or de-escalation	0
Other change in therapy	1 (2.6)
Change in therapy by diagnosis	
Any diagnosis (n = 34)	32 (94.1)
BO/GVHD (n = 9)	9 (100)
Noninfectious other than BO/GVHD* (n = 8)	7 (87.5)
Infectious (n = 11)	10 (90.9)
Other† (n = 6)	6 (100)
Nondiagnostic (n = 14)	6 (42.9)
Overall impact	
Any diagnosis or change in therapy	40 (83.3)

* Noninfectious other than BO/GVHD included idiopathic pneumonia syndrome (n = 4), diffuse alveolar hemorrhage (n = 1), and cryptogenic organizing pneumonia (n = 3).

† Other histopathologic diagnoses included severe pulmonary arteriopathy (n = 1) and diffuse alveolar damage consistent with acute respiratory distress syndrome (n = 5).

‡ Three patients had changes in both anti-infectious and anti-inflammatory therapy.

change in therapy occurred in 79% of cases. SLB yielded a definitive diagnosis or a change in therapy in 83% of patients.

SLB is invasive, and both surgeons and transplant physicians are often concerned about the safety of this procedure in HSCT patients. There is scant literature addressing these concerns, but past series have reported perioperative mortality rates as high as 60% [22,23]. Factors that may contribute to increased perioperative mortality include early post-HSCT thrombocytopenia often requiring perioperative blood product transfusion and neutropenia with accompanying concerns about infection and would healing. Additionally, all allogeneic recipients have sustained immune compromise after HSCT because of the transplant itself and the immunosuppressive medications given for GVHD prophylaxis. In our cohort, 10% of recipients died within 30 days of SLB, although no mortality could be directly attributed to the SLB and no surgically associated infections were found. This is comparable with the work by Rothenberg et al. [24], who report an 8% perioperative mortality rate after SLB in immunocompetent children with all deaths attributable to primary disease progression. Furthermore, a systematic review and meta-analysis of SLB in both adult and pediatric HSCT recipients showed that biopsy-related perioperative mortality was less than 1%. This suggests that perioperative mortality attributable to SLB is quite low and should not impact the decision to pursue SLB if the procedure is clinically indicated [19]. With respect to complications, rates in our pediatric cohort are consistent with those of immunocompetent patients who required SLB for workup of chronic pulmonary disease, suggesting that the immunosuppressed status associated with HSCT may not contribute heavily to the postoperative complication rate [25,26]. We also did not identify any clear risk factors for 30-day all-cause mortality after SLB in our cohort, including time from HSCT or level of respiratory support before SLB.

Given the acceptable risk profile, the decision to pursue SLB ultimately depends on the likelihood that the procedure will narrow the differential diagnosis and, more importantly, influence the therapeutic plan. Diagnostic bronchoscopy with bronchoalveolar lavage is often pursued before SLB with limited efficacy, particularly in patients with noninfectious pathology [27,28]. In contrast, the overall diagnostic yield of SLB in our cohort was 71%, slightly lower than rates as high as 95% reported in other studies [12,17]. This may reflect differences in the definition of diagnostic yield and variations in institutional indications for and timing of SLB. Despite this discrepancy, the distribution of histopathologic diagnoses in this cohort was consistent with other reports, with noninfectious etiologies the most common findings: BO/GVHD followed by other noninfectious diagnoses. Notably, a diagnostic biopsy was not essential for therapeutic impact in this population, and the absence of diagnostic findings on histopathologic evaluation can also provide valuable information to providers. For example, biopsies that show nonspecific inflammatory changes without evidence of infectious organisms may provide reassurance to a provider who is considering high-dose corticosteroid treatment or other intensive immunosuppressive regimens.

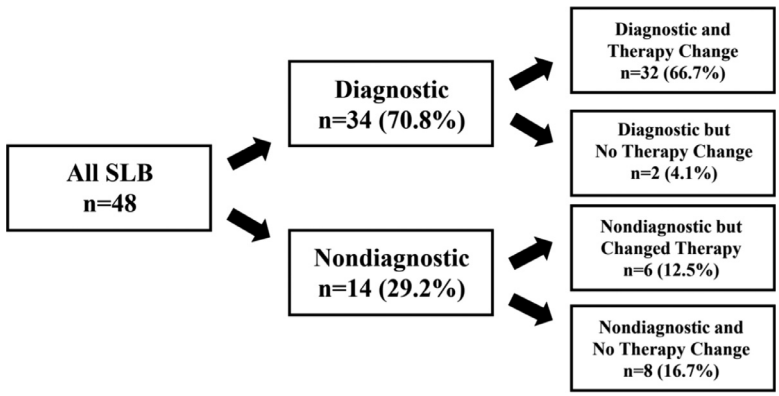

Figure 1. Diagnostic biopsies and impact on therapeutic plan.

Thus, we also evaluated the impact that the SLB results had on the therapeutic plan. In our cohort, 79% of patients had a change in therapy after SLB. Among these patients, nearly all changes involved the addition of further immunosuppressive or antimicrobial medications. Of the biopsies that were neither diagnostic nor influenced any therapeutic change (n = 8), 1 patient was on maximal therapy and the SLB results could not influence addition of further empiric therapy, 1 specimen had insufficient tissue for diagnosis, and the remaining 6 specimens were unable to provide convincing evidence to effect change in the current therapeutic regimen.

There are important limitations to consider in this study. First, the retrospective nature limits the ability to understand the medical decision-making that led to the decision to undergo SLB. Similarly, because the indications for SLB are ill-defined and these patients are often quite sick, SLB may have not been considered by the care team in certain patients, resulting in reporting bias. Second, we cannot know whether broad empiric therapy with both antimicrobial and immunosuppressive regimens would have led to similar patient outcomes without the need for SLB. Finally, some histopathologic diagnoses including BO are often difficult to treat, and knowledge of the diagnosis may not affect outcome, but this knowledge remains valuable for prognostication and family discussions.

In summary, progressive pulmonary infiltrates are common in the pediatric HSCT population, and because of the immunocompromised status of these patients, the differential diagnosis is often quite broad. Both infectious and immune-mediated etiologies are common and have considerably different treatment approaches. Many patients remain undiagnosed after noninvasive workup and bronchoscopy with bronchoalveolar lavage, leaving SLB as the final diagnostic option. SLB aids in defining the etiology of pulmonary infiltrates in most HSCT recipients with an acceptable risk for complications despite the baseline severity of clinical illness in these recipients and may inform therapeutic decision-making in those where SLB fails to provide a definitive diagnosis. We argue that SLB should be considered early in those pediatric HSCT recipients where noninvasive diagnostic modalities have failed to provide a definitive diagnosis.

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SUPPLEMENTARY MATERIALS

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