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Surgical lung biopsy in children after hematopoietic cell transplantation

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ABSTRACT

Background/Purpose: Pulmonary complications are some of the leading causes of morbidity and mortality in immunocompromised pediatric patients. We sought to assess the value of surgical lung biopsy (SLB) in hematopoietic cell transplantation (HCT) pediatric patients.
Methods: A retrospective review of patients who underwent SLB within one year of HCT between 1999 and 2015 was performed.
Results: Twenty-nine patients (15 females, 14 males) with a median age of 10 years (range, 0.6–23) were identified. Median interval between HCT and SLB was 114.8 days (range, 16–302). At surgery, 11 (38%) patients were intubated, and 7 (24%) were receiving supplemental oxygen. The most common histological finding was cryptogenic organizing pneumonia in 8 cases (27%), followed by infection in 7 (24%). Perioperative complications (17%) included bronchopleural fistula (n = 2), splenic laceration from a trocar injury (n = 2), and hemothorax (n = 1). Changes in therapy occurred in 25 patients (86%). Twenty-four (83%) patients survived more than 30 days post SLB, and the overall survival rate was 41% with a median follow-up of 8.5 years (range, 1–13).
Conclusion: SLB appears to be safe and informative in pediatric patients after HCT and led to changes in therapy in most patients. However, long-term survival after this procedure was <50%, reinforcing the fact that pulmonary complications are some of the leading causes of mortality in these patients.
Type of Study: Retrospective analysis.
Level of Evidence: Level IV.

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Hematopoietic cell transplantation (HCT) is currently the standard-of-care procedure for many disorders. Despite improved immunosuppressive regimens, successful HCT is frequently compromised by early and long-term side effects which remain the major limitations to the success of HCT. Pulmonary complications have been reported in 40% to 60% of adult HCT recipients, and 30% of deaths after HCT are directly attributable to pulmonary complications [1–3]. In children, the incidence and natural history of pulmonary complications are not completely understood. An infectious etiology is the most common cause of respiratory dysfunction after HCT [4,5]; however, pulmonary complications include various non-infectious conditions, like pulmonary edema, bronchiolitis obliterans, cryptogenic organizing pneumonia, idiopathic pneumonia syndrome, diffuse alveolar damage and graft-versus-host disease, which has been reported with an incidence as high as 65% in allogeneic HCT recipients [6].

Surgical lung biopsy (SLB), though invasive and not free of complications, is considered the gold standard procedure for the diagnosis of pulmonary disease in both adults and children [7–10]. Some studies have reported a low diagnostic accuracy based on SLB specimens in pediatric HCT recipients [10–12]. Additionally, in this population, depending on the patients' underlying disease and the degree of immunosuppression, complication rates can vary from 2% to 52% [9–17]. However, it is difficult to define the diagnostic sensitivity, the rate of complications and clinical benefit of SLB due to the heterogeneity of reports about this procedure in immunocompromised children.

Over the last decades, surgical techniques for lung biopsy have advanced and the spectrum of pulmonary infectious diseases in immunocompromised pediatric patients has changed [5].

This study aimed to evaluate the impact of SLB in pediatric HCT recipients who developed pulmonary complications.

1. Patients and Methods

We retrospectively evaluated the medical records of patients who underwent SLB in an attempt to diagnose a pulmonary complication within one year after an HCT at St Jude Children's Research Hospital between January 1, 1999, and June 30, 2015. The study was approved by the Institutional Review Board. We collected data regarding patient characteristics including age at the procedure, gender, primary diagnosis, type of transplant and date, imaging findings, absolute neutrophil

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Table 1
Patient characteristics.

Pt #	Age	Gender	Primary diagnosis	HCT type	Interval days between HCT and SLB	Chest CT findings	CMV reactivation	Neutropenia	Active GHDV
1	3	F	Neuroblastoma	Autologous	58	BDP	Yes	No	No
2	14	M	SAA	Allogenic MRD	88	BDP	No	Yes	No
3	3	M	AML	Allogenic MUD	154	UNP	Yes	Yes	Yes
4	7	F	AML	Allogenic MUD	51	BNP	No	No	No
5	11	M	B Cell Lymphoma	Allogenic MRD	95	BDP	Yes	No	No
6	2	F	ALL	Allogenic MRD	258	BDP	Yes	No	Yes
7	16	M	ALL	Allogenic MUD	16	BNP	Yes	Yes	No
8	5	M	SAA	Allogenic MRD	148	BNP	No	No	No
9	2	M	ALL	Allogenic MUD	169	BNP	No	No	No
10	6	M	Medulloblastoma	Autologous	191	BDP	No	No	No
11	11	F	HL	Autologous	54	BDP	No	No	No
12	17	F	SAA	Allogenic MUD	58	BDP	Yes	No	Yes
13	10	M	ALL	Allogenic MRD	271	BNP	No	No	No
14	6	F	ALL	Allogenic MUD	184	BDP	Yes	No	Yes
15	14	F	ALL	Allogenic MUD	66	BDP	Yes	No	No
16	0.6	F	Osteopetrosis	Allogenic MRD	28	BDP	Yes	No	Yes
17	19	F	SAA	Allogenic MUD	31	BDP	No	No	No
18	13	M	X-linked LPD	Allogenic MUD	135	BDP	Yes	No	No
19	0.9	F	ALL	Allogenic MRD	37	BNP	Yes	No	No
20	1	M	ALL	Allogenic MRD	17	UNP	No	Yes	No
21	17	M	T cell NHL	Autologous	136	BDP	No	No	No
22	16	F	AML	Allogenic MUD	21	UDP	No	No	No
23	18	F	RMS	Allogenic MRD	293	BDP	No	No	Yes
24	15	F	T cell NHL	Allogenic MRD	302	BDP	No	No	Yes
25	13	M	ALL	Allogenic MRD	102	BDP	Yes	No	No
26	15	M	LCH	Allogenic MUD	63	BDP	Yes	Yes	No
27	8	M	AML	Allogenic MUD	43	UDP	Yes	Yes	No
28	11	F	SCD	Allogenic MRD	211	BDP	No	No	No
29	23	F	ALL	Allogenic MUD	52	BDP	Yes	No	No

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; BDP: bilateral diffuse pattern; BNP: bilateral nodular pattern; CMV: cytomegalovirus; CT: computed tomography; F: female; GVHD: graft versus host disease; HCT: hematopoietic cell transplantation; HL: Hodgkin lymphoma; LCH: Langerhans cell histiocytosis; LPD: lymphoproliferative disorder; M: male; MRD: matched related donor; MUD: matched unrelated donor; NHL: non-Hodgkin lymphoma; Pt: patient; RMS: rhabdomyosarcoma; SLB: surgical lung biopsy; SAA: severe aplastic anemia; SCD: sickle cell disease; UNP: unilateral nodular pattern; UDP: unilateral diffuse pattern.

count (ANC), clinical/respiratory status at the time of biopsy, histologic result of biopsy and procedure-related characteristics including biopsy date, time from transplant and respiratory illness onset to SLB, surgical approach, number and location of the samples, duration of postoperative thoracostomy tube, postoperative complications, therapeutic changes and clinical outcome after these changes, morbidity and mortality rates.

Patients were included if they had a HCT followed by a respiratory complication within a year that led to SLB to clarify the diagnosis. Patients who underwent a complete lobectomy were excluded. Nodular disease pattern on computed tomography (CT) was defined as the presence of nodular lesions, whereas diffuse disease pattern was characterized by disseminated lesions without a nodular pattern. SLB was performed in an operating room (OR), under general anesthesia, by video-assisted thoracoscopic surgery (VATS) if the patient could tolerate single-lung ventilation, or by thoracotomy if the patient could not tolerate single-lung ventilation or an aspergilloma was suspected. Biopsy sites were chosen by the surgeon based on the location of imaging findings. Pathology and microbiology results from the lung biopsies were reviewed by a pathologist (TS) and an infectious disease specialist (GM) respectively. The specimens obtained from the lung biopsies were considered diagnostic when consistent with a definitive etiology. Change in therapy was defined as a modification to medication or management due to a biopsy result. Morbidity was defined as postoperative complication occurring within 30 days post-SLB and included bleeding that required transfusions, return to the OR, prolonged chest tube duration (>7 days) and failure to extubate patients who were not intubated prior to SLB. Postoperative intubation time >48 h was considered a prolonged intubation. Improvement in clinical status was considered when patients had a satisfactory postoperative evolution and were discharged from hospital. Overall mortality included all deaths through the follow-up of the patients until June 30, 2015. SLB was considered to be beneficial to the patient if there were changes in therapy and management based on biopsy results, and if the patient survived the procedure.

2. Results

This study included 38 SLBs performed in 29 patients who underwent HCT between January 1, 1999 and June 30, 2015. Two specimens were obtained at the time of SLB in nine patients. There were 15 females and 14 males with a median age of 10 years (range, 0.6–23). The most common primary diagnosis requiring HCT was leukemia (n = 14, 10 acute lymphoblastic leukemia and 4 acute myeloid leukemia) followed by severe aplastic anemia (n = 4), non-Hodgkin lymphoma (n = 3), Hodgkin lymphoma (n = 1), histiocytosis (n = 1), neuroblastoma (n = 1), medulloblastoma (n = 1), rhabdomyosarcoma (n = 1), osteopetrosis (n = 1), X-linked lymphoproliferative disorder (n = 1) and sickle cell disease (n = 1). Twenty-five (86%) patients underwent allogeneic HCT (13 from matched unrelated donor and 12 from matched related donor) and 4 (14%) autologous HCT. Median time between HCT and SLB was 114.8 days (range, 16–302) (Table 1).

Preoperative chest CT revealed a diffuse pattern in 20 (69%) patients (bilateral in 19, unilateral in 1) and a nodular pattern in 9 (21%) patients (bilateral in 7, unilateral in 2). Clinical symptoms at the time of SLB ranged from respiratory insufficiency to asymptomatic patients with pulmonary lesions detected in routine imaging studies. The most common clinical sign was fever (44.8%). Eleven (38%) patients who presented with respiratory insufficiency were on mechanical ventilatory support at the time of SLB; 7 (24%) additional patients required supplemental oxygen. Eleven (38%) patients were asymptomatic at the time of SLB. Fifteen patients had cytomegalovirus reactivation at the time of SLB, 6 had neutropenia and 7 had active graft-versus-host disease.

Seventeen (59%) patients underwent a less invasive diagnostic test prior to SLB, 12 had a bronchoalveolar lavage (BAL) and 5 a lung needle biopsy (NB) by interventional radiology. Of the 12 BALSs, only 2 (17%) were diagnostic (cryptogenic organizing pneumonia for both cases). In 8 of the 12 cases with unspecific non-infectious BAL results, the SLB specimen provided a definitive diagnosis. One sample was nondiagnostic for both, BAL and SLB. One BAL results was considered a false-positive

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