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【 ORIGINAL ARTICLE 】

An Analysis of the Clinical Benefit of 37 Bronchoalveolar Lavage Procedures in Patients with Hematologic Disease and Pulmonary Complications

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Abstract:

Objective Since pulmonary complications are a major cause of mortality in patients with hematologic diseases, their rapid detection and treatment are essential. Bronchoalveolar lavage (BAL) is widely performed to diagnose pulmonary infiltrates not evident with non-invasive investigations; however, reports on its clinical benefits for patients with hematologic diseases are limited. The aim of our study was to investigate the utility of diagnostic bronchoscopy with BAL for those patients.

Methods We retrospectively reviewed the clinical records of 37 consecutive BAL procedures in 33 adult patients with hematological diseases and pulmonary infiltrates with at least 6 months of follow-up between August 2013 and September 2017 (total 747 BAL procedures). The BAL results, ensuing treatment modifications, treatment outcomes, survival times, and adverse events were evaluated.

Results Microbiological findings were detected in 11 (29.7%), even though wide-spectrum antibiotics and antifungal drugs had been empirically administered to most patients (>70%) prior to the bronchoscopy procedure. Overall, 25 of the 37 BAL procedures (67.6%) had some impact on the diagnosis of pulmonary diseases. Patients without specific diagnostic findings from BAL had a significantly poorer survival than those with diagnostic findings via BAL (30-day survival: 33.3% vs. 92.0%; 180-day survival: 8.3% vs. 64.0%). Four patients (12.1%) experienced complications associated with bronchoscopy; there were no procedure-related deaths.

Conclusion BAL seems still important for diagnosing pulmonary infiltrates and/or excluding some of the important respiratory tract pathogens in patients with hematological diseases; furthermore, negative specific diagnostic findings from BAL may be associated with poor prognoses.

Key words: bronchoalveolar lavage, pulmonary complication, hematologic disease, hematopoietic stem cell transplantation

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Introduction

Pulmonary complications are a major cause of mortality in patients with hematologic diseases, especially following hematopoietic stem cell transplantation (HSCT) (1-4). Immunocompromised patients with hematologic diseases and/or those undergoing related therapies may experience diverse and severe infectious or noninfectious pulmonary diseases (e.g. bacterial or opportunistic infections, underlying disease-specific infiltration, or drug-induced pulmonary toxicity) (5, 6); therefore, accurate and rapid diagnostic strategies may help improve the outcomes (7). However, diagnosing these conditions might be difficult, as the impaired inflammatory response can reduce clinical or radiological signs, and it is often not feasible to identify etiologies owing

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to the risk of deterioration of the respiratory state and/or hemorrhaging associated with thrombocytopenia. Since the immediate administration of antibiotics is recommended for patients with febrile neutropenia (8), broad-spectrum antibiotics are often administered for most pyrogenic pulmonary complications post-HSCT prior to bronchoscopy. Therefore, identifying specific pathogens can be difficult for such patients.

Diagnostic bronchoscopy with bronchoalveolar lavage (BAL) has conventionally been performed to diagnose pulmonary complications associated with hematologic diseases (5), but the utility of this procedure in real-world clinical settings remains controversial. For instance, several early, retrospective, single-center studies suggest that BAL outcomes did not result in treatment modifications or an improved survival (9, 10). Furthermore, BAL procedures in patients with acute respiratory failure may cause respiratory status deterioration without providing a diagnostic benefit (11). However, a recent prospective cohort revealed that BAL was highly effective in determining the etiology of pulmonary disease, with a diagnosis rate of 63%; the investigators recommended that BAL be performed early after the onset of pneumonia (12). Overall, however, studies of the clinical benefit of BAL in patients with hematological diseases and pulmonary infiltrates remain very limited (13).

In current clinical practice, the recent progress of noninvasive diagnostic modalities, such as chest computed tomography (CT) and microbiological tests that use sputum or blood, has certainly reduced the requirement of BAL for patients with pulmonary infiltrates and concurrent hematologic disease. Therefore, respiratory or hematological physicians might be reluctant to order BAL in such severely ill patients or might have several clinical questions, such as how safely the BAL procedure can be conducted, how useful the results of BAL are for a final diagnosis, and how the prognosis of patients is affected by the BAL results. The aim of the present study was therefore to investigate the utility of diagnostic bronchoscopy with BAL for patients with hematologic diseases in a real-world clinical setting; parameters such as diagnostic yields, subsequent treatment modifications, treatment outcomes, survival times, and adverse events were identified in patients with pulmonary complications who underwent this procedure.

Materials and Methods

Study subjects

We retrospectively analyzed 33 consecutive patients (37 procedures) with hematological diseases and pulmonary infiltration who underwent diagnostic bronchoscopy with BAL between August 2013 and September 2017 at Chiba University Hospital; a total of 747 BAL procedures were performed during this period. In four patients, BAL was performed twice for different lung lesions at different timings with intervals of at least one month; we determined the survival time in all patients. All patients completed at least six months of follow-up.

Inspection method

Blood tests, radiography, and CT were performed in all patients within one month before the BAL procedure. Bronchoscopy was performed in the bronchoscopy room or at the bedside in critical care units. After local anesthesia with 2-4% lidocaine, a bronchoscope was inserted orally with the tip wedged into the segmental, subsegmental, or subsubsegmental bronchus experiencing the pulmonary complication. After washing with 50-150 mL of 0.9% saline, the BAL sample was obtained. A transbronchial lung biopsy (TBLB) and bronchial brushing were conducted after BAL in some cases. All BAL samples were analyzed using a standard protocol (i.e. total cell counts, differential cell counts, bacterial and fungal culturing, and Gram and Ziehl-Neelsen staining). A galactomannan test for *Aspergillus spp.*, cryptococcal antigen, *Pneumocystis jirovecii* (*P. jirovecii*) DNA polymerase chain reaction (PCR), and *Cytomegalovirus* (CMV) PCR (or the CMV C7-HRP test) were also performed. In some patients highly suspected of having pneumocystis pneumonia, Grocott-stained BAL samples were prepared.

Clinical data collection

Each patient's background, medical history, laboratory data, BAL data, treatment and response, adverse events with bronchoscopy, and survival time after bronchoscopy were analyzed. The diagnosis of drug-induced interstitial pneumonia was based on a history of drug exposure, exclusion of other causes of lung injury, improvement accompanied by drug discontinuation, treatment reactivity, and BAL differential cell counts. In this diagnostic process, a drug-induced lymphocyte stimulation test and rechallenge with a suspected drug were not performed.

Regarding the diagnosis of organizing pneumonia (OP), we suspected OP in cases showing consolidation with peripheral bronchial vascular bundles on high-resolution CT and infection denied by BAL, depending on whether or not the BAL sample predominantly contained lymphocytes and after excluding the possibility of sarcoidosis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, lymphoid interstitial pneumonia, and lymphoproliferative diseases. We ultimately confirmed the diagnosis of OP based on clinical findings, imaging findings, and therapeutic reactivity after the BAL procedure. Cases diagnosed based on positive results of a galactomannan test for *Aspergillus spp.*, *P. jirovecii* DNA PCR, cryptococcal antigen, CMV PCR test, CMV C7-HRP test, bacterial findings suspected of being pathogens, atypical cells, or hemorrhaging in BAL were also included among the diagnostic BAL cases.

In the present study, the concepts of idiopathic pneumonia syndrome (IPS) and late-onset noninfectious pulmonary complication (LONIPCs) were not considered for the diagnosis, since IPS and LONIPCs include a wide spectrum of

Table 1. Patient Characteristics.

	number of patients (%)		number of procedures (%)	
male : female	25:8		28:9	
age (range)	36-76			
post HSCT	22	(66.7)	26	(70.3)
BMT	9	(27.3)	10	(27.0)
<100 days : ≥ 100 days	4:5		4:6	
CBT	8	(24.2)	11	(29.7)
<100 days : ≥ 100 days	5:3		8:3	
PBSCT	5	(15.2)	5	(13.5)
<100 days : ≥ 100 days	3:2		3:2	
CT image findings				
GGO	16	(48.5)	19	(51.4)
consolidation	9	(27.3)	9	(24.3)
GGO+consolidation	4	(12.1)	5	(13.5)
GGO+nodule	2	(6.1)	2	(5.4)
GGO+granular shadow	1	(3.0)	1	(2.7)
nodule	1	(3.0)	1	(2.7)
fever (BT>38°C)	24	(72.7)	25	(67.6)
oxygen therapy (1L/min-8L/min)	10	(30.3)	12	(32.4)
mechanical ventilation	9	(27.3)	10	(27.0)
administration before bronchoscopy				
antibacterial drug administration	24	(72.3)	28	(75.7)
antifungul drug administration	26	(78.8)	29	(78.4)
PSL administration (>0.5mg/kg)	17	(51.5)	18	(48.6)
immunosuppressant drug administration	20	(60.6)	23	(62.2)
SMX/TMP administration (prophylaxis dosing)	4	(12.1)	4	(10.8)
SMX/TMP administration (therapeutic dosing)	21	(63.6)	23	(62.2)
WBC>10,000/μL	5	(15.2)	5	(13.5)
neutphils<500/μL	5	(15.2)	5	(13.5)
CRP>10mg/dL	11	(33.3)	12	(32.4)

BMT: bone marrow transplantation, BT: body temperature, CBT: cord blood transplantation, CRP: C-reactive protein, GGO: ground glass opacity, PBSCT: peripheral blood stem cell transplantation, PSL: prednisolone, SMX/TMP: sulfamethoxazole/trimethoprim, WBC: white blood cell

diseases.

Statistical analyses

All statistical analyses were performed using the JMP® Pro 13.2.0 software program (SAS Institute, Cary, USA). Survival curves were generated using the Kaplan-Meier method, while the log-rank test was employed to compare the survival rates between the patient groups. A p value of < 0.05 was considered statistically significant for all analyses.

Definition of adverse events

Adverse events included bronchospasm, cardiac arrhythmia, bleeding (>100 mL), pneumothorax, hypoxemia (requiring mechanical ventilation), and death. We considered the adverse event to be related to bronchoscopy if it occurred during or within 24 h after bronchoscopy.

Results

We analyzed data from 37 BAL procedures performed in 33 patients with hematologic diseases and pulmonary complications; 4 patients underwent bronchoscopy twice at different times. We performed TBLB in 17 procedures and bronchial brushing in 3 procedures. Thirty-two procedures were performed in the bronchoscopy room, while five were performed at the bedside in the intensive-care unit.

Patient characteristics

Twenty-two patients (66.7%) had undergone HSCT, and 11 (33.3%) had other hematologic diseases (see "*The hematologic diagnosis*" below). Twelve cases required ≤8 L/min of oxygen therapy. Wide-spectrum antibiotics (75.7%) and antifungal drugs (78.4%) were empirically administered before the bronchoscopy procedure (Table 1).

The hematologic diagnosis

The underlying diseases included acute myelogenous leukemia (27.3%), myelodysplastic syndrome (18.2%), acute lymphoblastic leukemia (15.2%), non-Hodgkin's lymphoma (12.1%), adult T-cell leukemia (6.1%), chronic myelogenous leukemia (3.0%), intravascular lymphoma (3.0%), multiple myeloma (3.0%), myeloid sarcoma (3.0%), aplastic anemia

(3.0%), myelofibrosis (3.0%), and mantle cell lymphoma (3.0%).

Microbiological findings in BAL

One sample showed a positive microbiological finding classified as *P. jirovecii* by Grocott staining; another sample was positive for *P. jirovecii* as detected using PCR. Three samples were CMV C7-HRP-positive, four were CMV-positive on PCR, one produced a positive Galactomannan test, and one produced cryptococcal antigen. In the remaining 26 samples, specific microbiological findings were not obtained (e.g. contamination and/or colonization).

Diagnostic BAL for pulmonary infiltrates

Possible or definite diagnoses were obtained based on BAL results in 25 of 37 procedures (67.6%) (Table 2). Three of the seven CMV C7-HRP-positive or CMV PCR-positive BAL samples were definitively diagnosed as CMV-related pneumonia, and two were suspected of being or diagnosed as OP. Two samples were positive for *P. jirovecii* on PCR or Grocott staining and were diagnosed as pneumocystis pneumonia. One BAL sample was positive for *Aspergillus* on the Galactomannan test and was diagnosed as invasive pulmonary aspergillosis. Another sample was positive for cryptococcal antigen and was diagnosed as cryptococcal pneumonia with drug-induced interstitial pneumonia. Thirteen BAL samples predominantly contained lymphocytes (>30%); 7 of these were suspected of being or diagnosed as OP, and 2 were lymphoproliferative diseases. Lymphoproliferative diseases were diagnosed based on atypical lymphocytes in BAL cytology. In two cases, the BAL sample was hemorrhagic and was diagnosed as diffuse alveolar hemorrhaging (see Table 2 for details). Treatment changes after BAL procedures are described in Fig. 1 and Table 2.

The final diagnosis of pulmonary disease

A TBLB was performed in 17 patients. Two of them were diagnosed with OP pathologically (see Table 2), and in the remaining 15 patients, specific pathological findings were not obtained. Furthermore, an autopsy was performed in three patients. One of them was diagnosed with acute fibrinous and organizing pneumonia (AFOP), and the specific diagnoses of pulmonary diseases were not confirmed in the remaining two patients. Overall, the diagnoses in 25 patients were confirmed based on clinical findings, imaging findings, BAL results, TBLB results, therapeutic reactivity, and autopsy results (see Table 2). The BAL diagnostic suggestions were inconsistent with the final diagnoses in 7 of 25 patients. Two of these cases were finally diagnosed as mucosa associated lymphoid tissue (MALT) lymphoma and intravascular lymphoma pathologically. Four of these cases had other etiologies in addition to a BAL diagnostic suggestion. The remaining case was initially diagnosed as CMV pneumonia based on blood and BAL C7-HRP-positivity; however, no treatment response with anti-cytomegaloviral drugs was obtained, so the final diagnosis was not confirmed.

The survival

The 30-day survival rates in all cases, diagnostic BAL cases, and nondiagnostic BAL cases (including post-HSCT, post-HSCT diagnostic BAL, and post-HSCT nondiagnostic BAL cases alone) were 73.0%, 92.0%, and 33.3% (73.1%, 89.5%, and 28.6%), respectively, and t corresponding 180-day survival rates were 46.0%, 64.0%, and 8.3% (46.2%, 57.9%, and 14.3%), respectively. A survival analysis indicated that patients associated with diagnostic BAL procedures had significantly better survival rates than those with nondiagnostic BAL procedures ($p<0.001$) (Fig. 2) and that patients associated with post-HSCT diagnostic BAL procedures had significantly better survival rates than those associated with post-HSCT nondiagnostic BAL procedures ($p=0.003$) (Supplementary material).

Adverse events

Two patients required non-invasive positive pressure ventilation within 24 hours after bronchoscopy, while 1 required invasive ventilation; the latter patient was extubated successfully 5 days after bronchoscopy. One patient developed pneumothorax after the TBLB; however, no procedure-related deaths occurred.

Treatment outcomes of pulmonary complications

Regarding pulmonary disease after BAL, the condition of 19 patients improved, 5 experienced no change in their condition, and the condition of 13 worsened within 7 days after BAL (Fig. 1, Table 2). Nineteen patients died during the follow-up period.

Discussion

In this study, several conclusions can be drawn regarding the use of BAL for patients with hematological diseases and pulmonary infiltrates. First, although wide-spectrum antibiotics and antifungal drugs were empirically administered in most patients (>70%) before the bronchoscopy procedure, microbiological findings were still detected in 11 (29.7%). Overall, 25 of the 37 BAL procedures (67.6%) had some impact on the diagnosis. Second, the survival rates in diagnostic BAL cases were obviously better than those in nondiagnostic BAL cases (30-day survival: 92.0% vs. 33.3%; 180-day survival: 64.3% vs. 8.3%), suggesting that negative diagnostic findings from BAL may be associated with a poor prognosis. Third, 4 patients (12.1%) experienced complications associated with bronchoscopy; however, there were no procedure-related deaths. These results support the idea that BAL is still an important diagnostic modality in clinical practice for patients with hematological diseases and pulmonary infiltrates not evident on conventional non-invasive investigations.

Bacteria, fungi, and viruses were detected in 2.7%, 10.8%, and 16.2% of the samples, respectively, in our study.

Table 2. BAL Diagnostic Suggestion, Final Diagnosis, Change of Management, and Outcome in the Study Patients.

No.	age	sex	hematologic diagnosis	disease status	BAL diagnostic suggestion	final diagnosis	change of management	treatment outcome
1	65	male	MDS	post-BMT day 65	OP	OP	change	response
2	61	male	myeloid sarcoma	post-BMT day 111	OP	OP	change	response
3	54	male	AML	post-BMT day 167	OP	OP (pathologically diagnosed)	change	response
4	53	male	ALL, CMV antigenemia	post-PBSCT day 32	OP	OP	change	response
5	42	male	AML	post-PBSCT day 63	OP	OP	no change	response
6	54	male	ATL, CMV antigenemia	post-CBT day 132	OP	OP	change	response
7	49	male	AML	post-CBT day 113	OP (post bacterial infection)	OP (post bacterial infection)	change	response
8	52	female	aplastic anemia	post-BMT, immunosuppressive therapy against BO s/o	OP (post bacterial infection)	OP (post bacterial infection)	no change	response
9	67	male	DLBCL	post-PBSCT day 422	OP (post PCP)	OP (pathologically diagnosed) (post PCP)	no change	response
10	39	male	ALL	post-BMT day 32	OP (post CMV infection)	OP (post CMV infection)	no change	response
11	65	male	AML	post-CBT day 39	OP	OP, bacterial pneumonia	no change	progression
12	65	male	MDS	post-BMT day 92	diffuse alveolar hemorrhage	diffuse alveolar hemorrhage	change	progression
13	50	male	AML	post-BMT day 197	diffuse alveolar hemorrhage	diffuse alveolar hemorrhage	no change	progression
14	62	female	ATL	post-BMT day 97	CMV pneumonia	CMV pneumonia, sepsis, ARDS	change	response
15	38	female	ALL	post-CBT day 31	CMV pneumonia	CMV pneumonia	change	progression
16	41	male	AML	post-CBT day 46	CMV pneumonia	nondiagnostic	change	progression
17	42	female	AML	post-CBT day 202	PCP	PCP	change	response
18	70	female	DLBCL	post-PBSCT day 880	PCP	PCP, nocardiosis	no change	response
2	61	male	myeloid sarcoma	post-BMT day 1155	IPA	IPA, bacterial pneumonia	change	response
19	52	male	CML	dasatinib therapy	OP	OP	no change	no change
20	65	male	MM	VCD therapy	OP	OP	no change	response
21	58	male	follicular lymphoma	CR	drug induced IP	drug induced IP	change	response
22	58	male	MDS	no treatment	lymphoproliferative disorders	MALT lymphoma	no change	no change
23	58	male	IVL	no treatment	lymphoproliferative disorders	IVL	change	response
24	63	female	ALL	induction therapy	cryptococcal pneumonia, drug induced IP	cryptococcal pneumonia, drug induced IP	change	response
25	36	male	AML	post-BMT day 109	nondiagnostic	nondiagnostic	no change	no change
26	53	male	MDS	post-PBSCT day 72	nondiagnostic	nondiagnostic	no change	progression
27	62	female	AML	post-CBT day 20	nondiagnostic	nondiagnostic	no change	no change
15	38	female	ALL	post-CBT day 31	nondiagnostic	nondiagnostic	change	progression
16	41	male	AML	post-CBT day 46	nondiagnostic	nondiagnostic (at autopsy)	change	progression
28	54	male	MDS	post-CBT day 61	nondiagnostic	nondiagnostic (at autopsy)	change	no change
11	65	male	AML	post-CBT day 61	nondiagnostic	nondiagnostic	change	progression
29	60	male	MDS	no treatment	nondiagnostic	nondiagnostic	change	response
30	76	male	MDS	no treatment	nondiagnostic	nondiagnostic	no change	progression
31	62	male	AML	relapse on therapy	nondiagnostic	nondiagnostic	change	progression
32	67	female	2ndMDS, NHL	azacytidine therapy	nondiagnostic	AFOP (at autopsy)	change	progression
33	75	male	mantle cell lymphoma	bendamustine therapy	nondiagnostic	nondiagnostic	no change	progression

AFOP: acute fibrinous and organizing pneumonia, ARDS: acute respiratory distress syndrome, ATL: adult T-cell leukemia-lymphoma, ALL: acute lymphoid leukemia, BMT: bone marrow transplantation, BO: bronchiolitis obliterans, CBT: cord blood transplantation, CMV: *cytomegalovirus*, CR: complete remission, DLBCL: diffuse large B-cell lymphoma, IPA: invasive pulmonary aspergillosis, IP: interstitial pneumonia, IPS: idiopathic pneumonia syndrome, IVL: intravascular lymphoma, MDS: myelodysplastic syndrome, MM: multiple myeloma, NHL: non-Hodgkin's lymphoma, OP: organizing pneumonia, PBSCT: peripheral blood stem cell transplantation, PCP: pneumocystis pneumonia, VCD: bortezomib, cyclophosphamide and dexamethasone

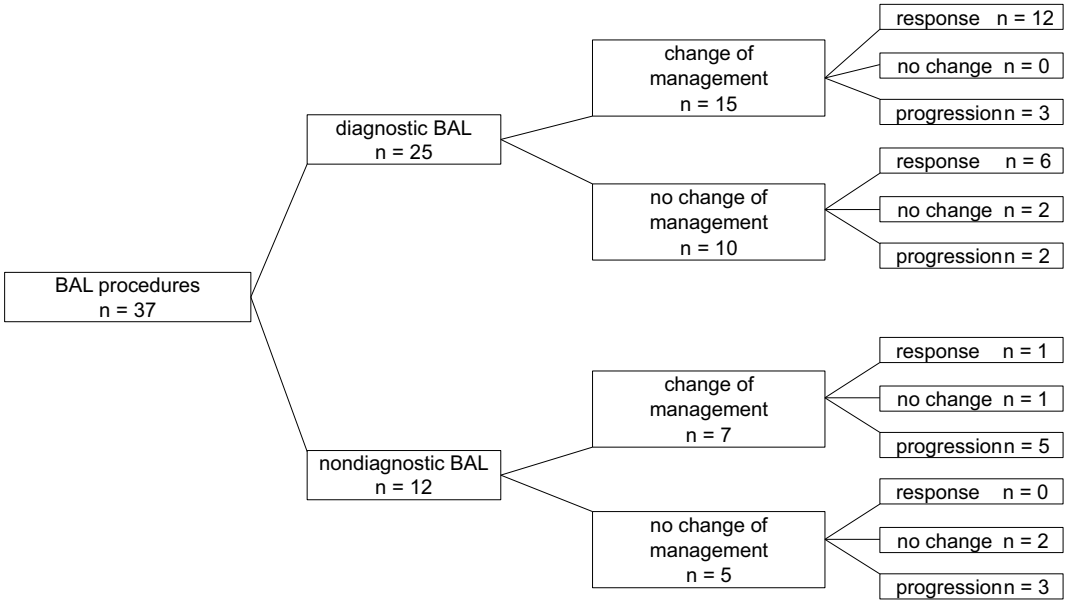

Figure 1. **Flowchart showing the changes in the management and outcomes following a diagnosis with bronchoalveolar lavage (BAL).**

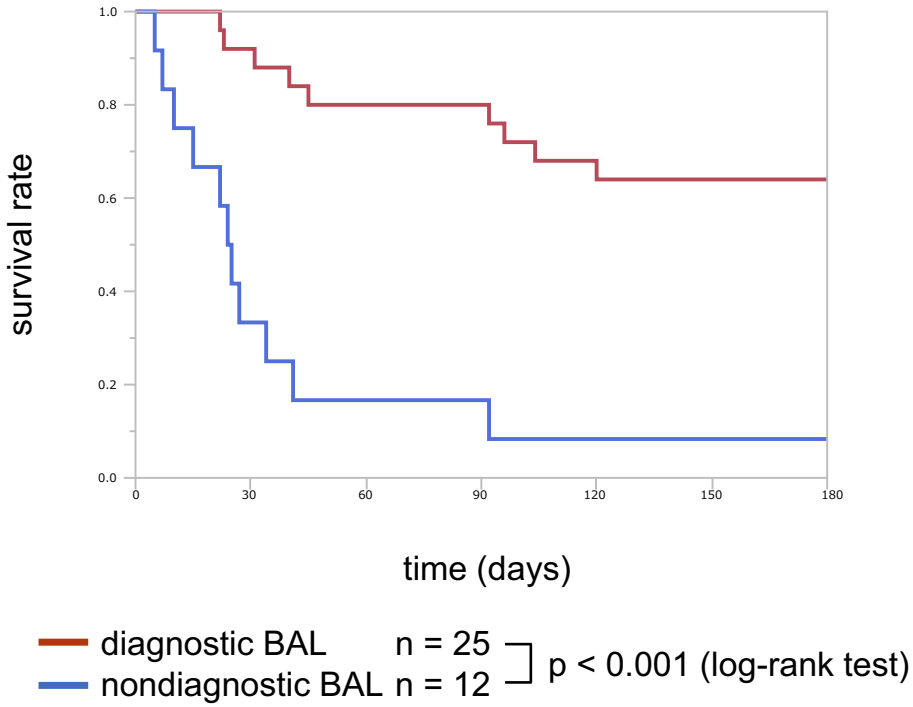

Figure 2. **Kaplan-Meier survival curves for patients in the diagnostic bronchoalveolar lavage (BAL) versus nondiagnostic BAL groups. There was no censoring within 180 days after BAL in all cases.**

Thirteen BAL samples (35.1%) predominantly comprised lymphocytes, among which 7 (18.9%) were diagnosed as OP. In our study, wide-spectrum antibiotics (75.7%), wide-spectrum antifungal drugs (78.4%), prednisolone (>0.5 mg/kg) (48.6%), and other immunosuppressant drugs (62.2%) were administered prior to bronchoscopy, which may have interfered with the identification of the pathogenic agent using BAL. Furthermore, many patients with bacterial pneumonia, fungal pneumonia, or autoimmune disorders who were treated with wide-spectrum antibiotics and/or antifungal drugs might not have been enrolled in the present study because they would have recovered without undergoing BAL. Such possibilities may have affected the diagnostic rate of pathogenic microbes in our present study.

In general, OP is diagnosed pathologically. However, there are cases in which TBLB cannot be performed due to

critical conditions or bleeding tendencies in patients with hematologic disease. Even if it can be performed, appropriate samples cannot always be obtained. Thus, in such cases, the pathological diagnosis of OP can be difficult. A previous report suggests that the diagnosis of OP without a biopsy may be considered in patients who are critically ill or if the clinical diagnosis is considered highly probable by an experienced physician (14). Furthermore, the histologic features of OP are sometimes nonspecific and can be seen in other lung diseases (15). Jara-Palomares et al. reported that the combined use of BAL and high-resolution CT is useful for making an OP diagnosis (16). In the present study, a TBLB was performed in 10 patients with suspected OP, but only 2 were pathologically diagnosed. Therefore, we should clarify that several cases in the present study were diagnosed as OP without specific pathological findings (see "Clinical data collection" and "pathologically diagnosed" in Table 2). Of the 37 cases, 13 were diagnosed with OP, including 11 of the 26 HSCT cases (42.3%) and 2 of the 11 non-HSCT cases (18.2%). The incidence of OP after HSCT in previous studies has been reported to range from 1% to 10% (17, 18). Although the diagnostic rate of OP in our study differed from that reported in the literature, the difference may have been due to differences in the patient populations, differences in the diagnostic criteria, and the small number of patients included in this study (see the limitations paragraph below).

In 15 of 25 diagnostic BAL cases, treatments were modified within 72 hours after BAL, and a survival analysis indicated that diagnostic BAL patients had a better survival rate than their non-specific diagnostic BAL counterparts. Some previous reports have suggested that positive bronchoscopy data in HSCT recipients was not associated with an improved survival (9, 10, 19). However, a prospective observational study by Shannon et al. found a survival advantage for diagnostic BAL in HSCT recipients presenting with pulmonary infiltrates if performed within four days of the onset of symptoms (20). Among the 25 diagnostic BAL cases in the present study, 13 were diagnosed as OP, and all but 2 responded to treatment. Furthermore, only three patients in this group who experienced original disease exacerbation [one patient with adult T-cell leukemia and two with acute myeloid leukemia (AML)] died within the observation period. These results indicate that a diagnosis based on BAL results (especially of OP) may correlate with a favorable prognosis. However, among the 12 nondiagnostic BAL cases, 1 was diagnosed as AFOP at the autopsy, and a final diagnosis of pulmonary disease was not made in the other 11.

In 2011, the American Thoracic Society (ATS) comprehensively reviewed and updated the concept of IPS, which is noninfectious acute lung dysfunction following HSCT (21). Since IPS is a diverse spectrum of disease associated with favorable to poor prognoses (22), we did not adopt the concept of IPS as the final diagnosis in our present study. IPS is generally associated with a poor prognosis, and the overall mortality rates of IPS in allogeneic HSCT recipients range from 60% to 80% (21), suggesting that some patients following HSCT in the present study might have had a poor prognosis due to their having IPS. Furthermore, among the 12 nondiagnostic BAL cases, 10 BAL samples predominantly contained neutrophils (>25%). These patients were refractory to antibacterial drugs, and six cases were consistent with the Berlin definition of acute respiratory distress syndrome (23). This might explain the poor prognosis of the nondiagnostic BAL cases (24).

Adverse events associated with bronchoscopy were encountered in 4 of 37 procedures (10.8%), although there were no treatment-related deaths in this study. Adverse events after bronchoscopy were encountered in 3 of 20 procedures (15%) for which a TBLB and/or bronchial brushing were performed, compared with 1 of 17 procedures (5.9%) for which a TBLB or bronchial brushing was not performed. Previous studies have found that the rate of adverse events defined as those due to bronchoscopy in immunocompromised or post-HSCT patients with pulmonary complications ranged from 2.9% to 8% (25, 26). In addition, Dunagan et al. reported 2 bronchoscopy adverse event-related deaths among a total of 71 procedures performed (26). Taken together, these findings suggest that BAL was performed without any adverse event-related deaths, although the rate of adverse events associated with bronchoscopy was slightly higher than that previously reported.

Several limitations associated with the present study warrant mention. Since this study was a retrospective, single-institution setting and had a small sample size (n=37), the patient population and the results might not be consistent with those of other previous studies. Furthermore, BAL may not have been consistently performed in patients with a severe overall condition, which may have resulted in selection bias. Nevertheless, the study describes real-world clinical data from well-defined consecutive patients undergoing BAL using a standardized procedure that includes extensive microbiological sampling.

Conclusion

BAL appears to still be important for diagnosing pulmonary infiltrates and/or excluding important respiratory tract pathogens in patients with hematological diseases; furthermore, negative specific diagnostic findings from BAL may be associated with poor prognoses.

All study procedures involving human participants were approved by the Ethical Review Board of the Graduate School of Medicine of Chiba University. The study protocol was conducted in accordance with the ethical principles of the 1964 Declaration of Helsinki and subsequent amendments.

The authors state that they have no Conflict of Interest (COI).

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