의학석사 학위논문

소아 조혈모세포 이식 후 발생하는 폐 합병증에 대한 연구

Pulmonary complications after hematopoietic stem cell transplant in children

2016년 1월

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Abstract

Pulmonary complications after hematopoietic stem cell transplant in children

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Background: Despite advances in transplantation and supportive care, a considerable number of patients still have poor prognosis with pulmonary complications (PCs) after hematopoietic stem cell transplant (HSCT). This retrospective study evaluated the clinical characteristics, outcomes, and prognostic factors of PCs in HSCT recipients followed-up for 2 years.

Method: We retrospectively analyzed the medical records of 109 recipients of HSCT between 2010 and 2012.

Results: In this study, 55 PC episodes developed in 38 recipients. Non-invasive diagnostic work-ups were preferred, including sputum examination, serology test, and chest computed tomography (85.5%, 72.7%, and 76.4%, respectively). Infection was the most commonly discovered etiology of PCs (61.8%). The incidence of PCs was lower

in patients who received autologous transplantation than in those who received other type of transplantation (65.8% vs. 49.3%, p=0.009). Analysis of PCs and morbidities revealed that the mortality rate was 32.7% in 18 episodes that were closely related with multi-organ dysfunction syndrome (MODS) when the PCs were diagnosed (OR, 26.178; p = 0.001). Hematological dysfunction was the main factor for poor outcome in PCs (OR, 11.6; p = 0.03). Of the HSCT recipients with PCs, 41.8% were transferred to the pediatric intensive care unit (PICU) for respiratory failure, and the associated mortality rate was 73%. After PICU admission, continuous renal replacement therapy was significantly more commonly administered in patients who died than in those who survived (70.6% vs 16.7%, respectively; p = 0.041). Five patients with 16 fatal primary PCs after HSCT who survived showed lesser progress to MODS and received corticosteroid therapy for acute respiratory distress syndrome more frequently than did those who died.

Conclusions: Physicians must closely observe for the existence of any other organ dysfunction in HSCT recipients with PCs, especially hematologic conditions. To manage MODS, early intervention with PICU admission should be considered.

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Key words: hematopoietic stem cell transplant, pulmonary complication, mortality, pediatric

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LIST OF TABLES AND FIGURE

LIST OF ABBREVIATIONS

HSCT	Hematopoietic stem cell transplant
GVHD	Graft-versus-host disease
PCs	Pulmonary complications
VOD	Veno-occlusive disease
PICU	Pediatric intensive care unit
DAH	Diffuse alveolar hemorrhage
IPS	Idiopathic pneumonia syndrome
BO	Bronchiolitis obliterans
BOOP	Bronchiolitis obliterans organizing pneumonia
CMV	Cytomegalovirus
PFT	Pulmonary function test
MODS	Multi-organ dysfunction syndrome
MV	Mechanical ventilation
CRRT	Continuous renal replacement therapy
CPR	Cardiopulmonary resuscitation
ECMO	Extracorporeal membrane oxygenation
TRALI	Transfusion related acute lung injury
OS	Overall survival
ARDS	Acute respiratory distress syndrome

Introduction

In pediatric populations, hematopoietic stem cell transplant (HSCT) is an important therapeutic option for many malignant and non-malignant conditions including disorders of the immune system, inherited metabolic disorders, hemoglobinopathies, and bone marrow failure syndromes [1]. Despite the increasing indications of HSCT over the past decade and improvements in survival, concerns have grown about the adverse effects of HSCT. Infections, graft-versus-host disease (GVHD), and organ damage are associated with mortality after HSCT except recurrent malignant condition [2]. Post-transplantation infectious complications are a well-known major cause of death [3]. The risk of infections among HSCT recipients is determined by the selected transplantation modality, immune reconstitution rate, and GVHD severity [4-6]. Because infections with different pathogen and epidemiological backgrounds can occur after HSCT, prophylaxis and empirical treatments have been recommended [7, 8]. For allogeneic transplant recipients, the existence and severity of GVHD also affect the early and late transplant-related mortality [9]. In fact, patients die not only of GVHD but also of side effects related to immunosuppressive drugs used to treat disease. Finally, overall survival (OS) is associated with organ failure, caused by prior therapy, morbidity due to the underlying disease, the conditioning regimen, or multiple infectious and non-infectious complications such as GVHD and veno-occlusive disease (VOD) [10].

Pulmonary complications (PCs) after HSCT are particularly frequent, lead to pediatric intensive care unit (PICU) admission for mechanical ventilation (MV), and are related with poor outcome [11-13]. PCs can be classified as either infectious or non-infectious

and vary depending on the time course post-HSCT [14]. Infectious PCs include bacterial, viral, fungal, and *Pneumocystis carinii* pneumonia. Numerous distinct acute lung injury syndromes have been described as the non-infectious PCs, including periengraftment respiratory distress syndrome, diffuse alveolar hemorrhage (DAH), idiopathic pneumonia syndrome (IPS), bronchiolitis obliterans (BO), and bronchiolitis obliterans organizing pneumonia (BOOP). Although the incidence of infectious PCs has diminished because of effective prophylactic therapy, non-infectious PCs have emerged as a major cause of post-HSCT morbidity and mortality [15]. PCs can be influenced by the HSCT type, degree of HLA matching, conditioning regimen, pre-transplantation pulmonary function abnormalities, and the existence of acute and chronic GVHD [16-18]. Thus, because multifactorial conditions after HSCT lead to PCs, various treatment approaches are required.

Such above mentioned complications often require the patient to be admitted to the PICU for higher level of care. Post-transplantation PICU admissions reportedly occur in 17-35% of transplant recipients [19-22]. Advances in transplantation medicine and critical care management have led to a noticeable and steady decrease in PICU mortality in 16 - 58% of HSCT recipients [19-21, 23-25]. Despite the improved survival, recent studies revealed that especially need for MV or renal replacement therapy in children still associated with poor outcome and higher post-HSCT mortality rates [24-27]. Furthermore, once MV became necessary, mortality remained unchanged at 41-52% in the years studied [20, 21, 27, 28]. For the purpose of providing early intervention to deteriorated patients and predicting outcomes, several authors have studied the prognostic factors among patients who received MV after HSCT [26-28]. However, those risk factors

and outcomes cannot be generalized to patients among different hospitals, because those studies included heterogeneous recipients with different diseases and HSCT types, and the hospitals had different characteristics.

This study aimed to describe the current prevalence and types of PCs, risk factors, and mortality due to fatal PCs in pediatric HSCT recipients at a single center and identify the factors that improve the outcomes of patients with PCs that are generally fatal.

Materials and Methods

Patients

Between January 2011 and December 2012, 143 pediatric patients underwent HSCT at the Seoul National University Children's Hospital. Each recipient was followed-up for 2 years after HSCT or until death, whichever came first. We excluded 12 recipients who were lost to follow-up or transferred to another hospital because of a relapsed underlying disease within 2 years after the transplantation. Furthermore, seven patients were excluded because they required further chemotherapy, radiation therapy, or HSCT for the treatment of relapsed diseases. Fifteen patients underwent a second HSCT because of the loss of graft or as a planned transplantation. In those cases, we considered only the second HSCT conducted within the study period. Ultimately, 109 pediatric patients were eligible for and enrolled in this study.

Data collection

We collected data about the patients' clinical characteristics, overall outcomes, and PCs. The clinical characteristics assesses were age, sex, diagnosis, previous lung disease, the number of HSCTs, HSCT type, stem cell source, and the number of HLA matches of the allograft. The underlying disease was categorized as leukemia/lymphoma, solid tumor, or non-malignant disease. The transplantations were conducted for primary immunodeficiency, aplastic anemia, fanconi anemia, or osteopetrosis. A previous lung disease was identified when the patients had an active lung problem at the time of the HSCT infusion. We counted the number of HSCT procedures performed before the current transplantation. The overall

outcomes assessed were underlying disease progression and mortality from any causes within the 2-year follow-up period.

Table 1. Criteria for the diagnosis of multi-organ system failure

I. Cardiovascular
1. Systolic blood pressure, mmHg
≤65 in infants, ≤75 in children, ≤85 in adolescents
2. Heart rate, beats/min
<50 or >220 in infants
<40 or >200 in children
3. Continuous infusion of inotropic agents
4. Serum pH < 7.20 (with a normal $PaCO_2$)

II. Respiratory
1. Respiratory arte, breaths/min
>90 in infants, >70 in children
2. PaO_2/FiO_2 <200 (in the absence of congenital heart disease)
3. Mechanical ventilation (>24 h in a postoperative patient)
4. $PaCO_2$ >65 torr
5. PaO_2 <40 torr (in the absence of congenital heart disease)

III. Neurologic
1. Glasgow Coma Scale score < 5
2. Fixed and dilated pupils

IV. Hematologic
1. Hemoglobin level < 5g/dL
2. White blood cell count < 3000/mm^3
3. Platelet count < 20,000/mm^3
4. Prothrombin time > 20 s or activated partial thromboplastin time, >60 s

V. Renal
1. Blood urea nitrogen level > 100 mg/dL
2. Creatinine level > 2.0 mg/dL (in the absence of preexisting renal disease)
3. Dialysis

VI. Gastrointestinal
1. Blood transfusion of > 20mL/kg in 24 h because of hemorrhage

VII. Hepatic
1. Total bilirubin level > 5 mg/dL and aspartate aminotransferase or lactate dehydrogenase levels greater than twice the normal level (without evidence of hemolysis)

PCs were diagnosed by using any non-invasive or invasive work-up. The non-invasive work-ups were sputum examination, serology test (cytomegalovirus antigen test, aspergillus antigen test, and mycoplasma antibody), chest computed tomography (CT), and

pulmonary function test (PFT). Sputum was collected by using nasopharyngeal aspiration, a swab, or transtracheal aspiration if the patient was already intubated, and subjected to a polymerase chain reaction, gram stained, and cultured. Invasive work-ups were thoracentesis, bronchoalveolar lavage (BAL), and a sono-guided or video-assisted lung biopsy.

We also investigated the detected comorbidities including acute or chronic GVHD, hepatic VOD, cytomegalovirus (CMV) infection, and organ dysfunction. Acute and chronic GVHDs were assessed as described elsewhere [29, 30]. Hepatic VOD was evaluated by using clinical symptoms, physical examination, liver Doppler sonography, and laboratory tests. When the CMV antigenemia assay results showed less than 10 antigen-expressing cells/200,000 polymorphonuclear leukocytes (PMNs), we started preemptive treatment with half-dose ganciclovir and evaluated the CMV disease. Moreover, the patients whose CMV antigenemia results showed more than 10 antigen-expressing cells/200,000 PMNs received induction therapy. CMV disease was diagnosed by using tissue biopsy, culture, or ophthalmic examination. The need for preemptive or curative induction therapy was considered CMV infection in this study. Organ dysfunction was identified by using the specific Pediatric Critical Care Medicine criteria published in 2003 (Table 1) [31]. Criteria for identifying organ dysfunction within the cardiovascular, respiratory, neurological, hematological, renal, gastointestinal, and hepatic systems were adapted from Wilkinson et al. [32]. Multi-organ dysfunction syndrome (MODS) was defined as the simultaneous occurrence of dysfunction in two or more organs.

PC outcomes were assessed on the basis of with PICU transfer and directly or indirectly related mortality. After PICU admission, the

life-sustaining therapies used were MV, continuous renal replacement therapy (CRRT), vasoactive agents, extracorporeal membrane oxygenation (ECMO), and cardiopulmonary resuscitation (CPR) [33]. In particular, we focused on the patients with PCs who were admitted to the PICU and experienced fatal progression with MV and respiratory failure due to a primary lung problem and not combined comorbidities. Their medical charts were reviewed and details collected, including treatment changes, progress of MODS, and length of PICU stay.

Definition of PCs

PCs, both infectious and non-infectious, were diagnosed by integrating clinical symptoms and an invasive or non-invasive work-up [14, 34-36]. An infectious PC, such as pneumonia, was defined by the presence of new or progressive pulmonary infiltrate on chest CT associated with clinical symptoms and signs like body temperature > 38.5℃, cough, sputum, dyspnea, desaturation, and tachypnea. If the specific pathogens were revealed in a diagnostic work-up, infectious PCs were classified as bacterial, viral, fungal, or *Pneumocystis jirovecii* pneumonia. However, if there was only clinical suspicion without a discovered pathogen, we classified those cases as unknown pneumonia. A non-infectious PC was diagnosed when patients who developed clinical respiratory symptoms and when radiological findings showed lung disease without any evidence of infection. Pulmonary edema or effusion was defined as the presence of characteristic infiltrates or pleural effusion, negative cultures, and beneficial response to diuresis. BO was diagnosed primarily by the presence of obstructive pulmonary dysfunction accompanied by chest CT findings of the areas showing patchy infiltration, bronchial dilatation, and hypo-attenuation or increased density. PCs with both

BO and chronic GVHD in allogeneic HSCT recipients were identified as lung GVHD. Patients were diagnosed with IPS if their chest X-rays and CT findings showed evidence of bilateral diffuse parenchymal interstitial/alveolar infiltrates in the absence of infection. Although a histologic diagnosis is required to identify patients with BOOP, only one case of BOOP was diagnosed by using chest CT in this study. The diagnostic criteria for DAH are multi-lobar pulmonary opacities seen at imaging and a progressively bloodier return at BAL or endotracheal tube aspiration in the absence of infection. Transfusion-related acute lung injury was identified whenever a patient developed a hypoxemic respiratory insufficiency during or shortly after transfusion of any blood product, according to outlined diagnostic criteria. When patient met the standards of both infectious and non-infectious PCs, they were identified as having mixed PCs.

Table 2. Definition of non-infectious pulmonary complications

1. Pulmonary edema or effusion Presence of characteristic infiltrates or pleural effusion, negative cultures, and beneficial response to diuresis
2. Bronchiolitis obliterans Presence of obstructive pulmonary dysfunction accompanied by chest computed tomography (CT) findings of the areas showing patchy infiltration, bronchial dilatation, and hypo-attenuation or increased density.
3. Lung graft-versus-host disease Pulmonary complications with both bronchiolitis obliterans and chronic graft-versus-host disease in allogeneic stem cell transplantation
4. Idiopathic pneumonia syndrome Chest radiography and CT findings showing evidence of bilateral diffuse parenchymal interstitial/alveolar infiltrates in the absence of infection
5. Bronchiolitis obliterans organizing pneumonia Demonstration of typical histopathologic features in a patient with a compatible clinical and radiograph pattern in the absence of a contributing factor or disease process
6. Diffuse alveolar hemorrhage Multi-lobar pulmonary opacities seen on imaging and a progressively bloodier return at bronchoalveolar lavage or endotracheal tube aspiration in the absence of infection.
7. Transfusion-related acute lung injury Acute hypoxemic respiratory insufficiency during or shortly after the transfusion of any blood product with bilateral infiltrates on chest radiolgraphy

Statistical analysis

Statistical analysis was performed using SPSS software (version 21; SPSS Inc., IBM, Armonk, USA). Qualitative variables are described as numbers (%). Continuous variables are reported as means (± standard deviation) or medians (interquartile range). The general characteristics were compared between patients with and without PCs via a χ^2-test or Fisher's exact test for categorical data and *t*-test for continuous data. Survival curves were obtained by using the Kaplan-Meier method and compared by using the log-rank test. We performed logistic regression analyses to identify the variables that were significantly associated with 2-year PC related

mortality as measured by an estimated odds ratio (OR) and 95% confidence interval (CI).

Results

General patient characteristics

We prospectively evaluated 109 consecutive patients who underwent HSCT (Table 3). There were 75 men and 34 women with a mean age of 10.0 years. Fifty-six patients had leukemia and lymphoma (51.4%), 38 had solid tumors (34.9%), and 15 had nonmalignant disease (13.8%). Thirty-three recipients (30.3%) had a lung disease prior to HSCT. Most of the patients had undergone only one HSCT, while 21 had received more than one HSCT. The majority of the HSCT procedures were allogeneic (56; 51.4%) and autologous (49; 45%) with peripheral blood (94; 86.2%). In the allogeneic condition, 35 patients (62.5%) received the transplantation from an unrelated donor.

Of the 109 patients, 38 (34.9%) developed PCs. Those patients who developed PCs had a significantly higher incidence of haploidentical or allogeneic transplantation (65.8% vs. 49.3%, p = 0.009). Furthermore, patients who received peripheral blood stem cells (PBSC) had lower incidence of PCs than did those who received stem cells from other sources (94.4% vs. 71.1%, p = 0.003). HSCT recipients with PCs showed higher HLA compatibility with their donors than did those without PCs; however, the difference was not statistically significant (9.1 ± 1.4 vs. 9.7 ± 0.7, p = 0.054). The remaining characteristics such as age, sex, underlying disease, and multiple transplantation did not differ significantly between patients with PCs and those without PCs.

Table 3. General characteristics and overall outcome of the hematopoietic stem cell transplant recipients.

	All patients n = 109 (%)	With PCs n = 38 (%)	Without PCs n = 71 (%)	p-value
Age, median (range)	10.0 (0.7-22.2)	8.7 (0.7-19.0)	10.2 (1.3-22.2)	0.243
Sex				0.999
Male	75 (68.8)	26 (68.4)	49 (69.0)	
Female	34 (31.2)	12 (31.6)	22 (31.0)	
Underlying disease				0.391
Leukemia/lymphoma	56 (51.4)	22 (57.9)	34 (47.9)	
Solid tumor	38 (34.9)	9 (26.3)	28 (39.4)	
Nonmalignant	15 (13.8)	6 (15.8)	9 (12.7)	
Previous lung disease	33 (30.3)	15 (39.5)	18 (25.4)	0.134
Infection	10 (30.3)	6 (40.0)	4 (22.2)	
Non-infection	8 (24.2)	6 (40.0)	2 (11.1)	
Cancer	15 (45.5)	3 (20.0)	12 (66.7)	
Number of HSCT				0.376
1st	87 (79.8)	29 (78.4)	58 (81.7)	
≥2nd	21 (19.2)	8 (21.6)	13 (18.3)	
HSCT type				0.009
Autologous	49 (45)	13 (34.2)	36 (50.7)	
Haploidentical	4 (3.7)	3 (7.9)	1 (1.4)	
Allogeneic	56 (51.4)	22 (57.9)	34 (47.9)	
Related	21 (37.5)	7 (31.8)	14 (41.2)	
Unrelated	35 (62.5)	15 (68.2)	20 (58.8)	
Stem cell source				0.003
Peripheral blood	94 (86.2)	27 (71.1)	67 (94.4)	
Bone marrow	10 (9.1)	7 (18.4)	3 (4.2)	
Cord blood	5 (4.6)	4 (10.5)	1 (1.4)	
Number of HLA matches (10/10) in allogenic HSCT, mean±SD	9.5±1.1	9.1±1.4	9.7±0.7	0.054
Underlying disease progression	8 (7.3)	3 (7.9)	5 (7.0)	0.574
Overall mortality	26 (23.9)	19 (50.0)	7 (9.9)	<0.001
Cause of death				
Pulmonary complication	9 (34.6)	9 (47.3)	0	
Underlying disease progression	6 (23.1)	1 (5.3)	5 (71.4)	
Shock/multi-organ failure	9 (34.6)	8 (42.1)	1 (14.3)	
Sudden arrest	2 (7.7)	1 (5.3)	1 (14.3)	
Time of death from HSCT days, median (IQR)	89.0 (44.0-194.5)	78.0 (41.8-146.0)	198.0 (84.0-257.0)	0.052

PC, pulmonary complication; HSCT, hematopoietic stem cell transplant; IQR, interquartile range

Of the 109 recipients, underlying disease progression was confirmed in 8 (7.3%), while 26 patients died of some reason within 2 years (23.9%). The mortality rate was higher in recipients with PCs than in those without PCs (50.0% vs. 9.9%, $p < 0.001$). In the 2-year study period, 19 patients with PCs died within a median period of 78 days (41.8 – 146.0), whereas 7 patients without PCs died within a median period of 198 days (84.0 – 257.0); however, the difference was not statistically significant.

Diagnosis of PCs

A total of 55 episodes of PCs were identified in 38 recipients. The diagnostic work-ups performed during the study period are shown in Table 4. The most preferred methods for evaluating PCs were sputum examination, serology test, and chest CT (85.5%, 72.7%, and 76.4%, respectively). Invasive work-ups were performed in 13 episodes (23.6%); among them, the treatments were changed in 6 (10.9%), according to the results.

Table 4. Performed diagnostic work-ups for pulmonary complications

	Total cases, n=55 (%)
Non-invasive work-up	
Sputum examination	47 (85.5)
Serology test	40 (72.7%)
Chest computed tomography	42 (76.4)
Pulmonary function test	14 (25.5)
Invasive work-up	13 (23.6)
Thoracentesis	3 (5.5)
Bronchoalveolar lavage	9 (16.4)
Sono-guided needle biopsy	1 (1.8)
Video-assisted thoracoscopic surgery	4 (7.3)

After various evaluations, infectious and non-infectious PCs were diagnosed in 34 (61.8%) and 16 (29.1%) episodes (Table 5). Among the cases of infectious PCs, the pathogen was identified in 16 episodes (47%), but not in the other 18 (32.7%). Ten of the infectious PCs (18.2%) were diagnosed as the most common viral pneumonia. Among the 16 episodes of the non-infectious PCs, pulmonary edema or effusion was the most common in 6.

Table 5. Diagnosis of pulmonary complications

Diagnosis	N (%)
Infectious PCs	34 (61.8)
Viral	10 (18.2)
RSV	3
rhinovirus	2
parainfluenza virus type 1	2
enterovirus	1
coronavirus	1
CMV	1
Fungal	2 (3.6)
Pneumocystis carinii	1 (1.8)
Mixed organism	3 (5.5)
Probable fungal + RSV	
Pseudomonas aeruginosa + RSV + probable fungal	
Tb + P. aeruginosa + MPV + coronavirus	
No pathogen isolated	18 (32.7)
Non-infectious PCs	16 (29.1)
Pulmonary edema or pleural effusion	6
Lung graft-versus-host disease	4
Pulmonary hemorrhage	2
Tansfusion-related acute lung injury	1
Idioopathic pneumonia syndrome	1
BO	1
BOOP	1
Infectous + non-infectious PCs	5 (9.1)
Pneumonia + lung graft-versus-host disease	2
Pneumonia + interstitial lung disease	2
Parainfluenza pneumonia + bleomycin induced pneumonitis	1

PCs, pulmonary complications; RSV, respiratory syncytial virus; CMV, cytomegalo-virus; Tb, tuberculosis; MPV, metapneumovirus; BO, bronchiolitis obliterans; BOOP, bronchiolitis obliterans organizing pneumonia

Outcome and prognostic factors of PCs

The eighteen (32.7%) patients with PCs died of related causes. Table 6 shows the risk factors associated with PC-associated mortality. Univariate analysis revealed that VOD, CMV treatment and MODS within 48 h after PC diagnosis were significantly higher in non-surviving group with PCs. However, multivariate analysis confirmed that concurrent MODS with PCs and, in particular, hematological dysfunction was a significant risk factor among them (OR 26.178, p = 0.001 and OR 11.6, p = 0.033). General characteristics including sex, age, underlying disease, HSCT type, and stem cell source had no impact on survival. In addition, there was no difference in mortality among different PC types.

Recipients with PCs required PICU admission after HSCT in 23 episodes (41.8%), primarily because of respiratory failure (16; 69.6%). Three episodes required PICU admission for BAL, while the others required it for CRRT, post-operation, or post-CPR management. All but one of the episodes who died were transferred to the PICU (94.4%); in contrast, only six of the episodes who survived were admitted PICU (16.2%). Thus, the mortality rate of patients with PCs after PICU admission was 73.9%. Regarding life-sustaining therapy at the PICU, 16 episodes in the non-surviving group (94.1%) required MV compared with 5 in the surviving group (83.3%). CRRT was needed in significantly more patients in the non-surviving group than in those in the surviving group (70.6% vs. 16.7%, p = 0.041). Vasoactive agent administration, ECMO, and CPR had been performed only in patients in the non-surviving group.

Table 6. Risk factors related with mortality of pulmonary complications after hematopoietic stem cell transplant

	Total (n = 55)	Non-surviving (n = 18)	Surviving (n = 37)	Univariate p - value	Multivariate OR (95% CI)	Multivariate p - value
All patients with PCs						
Type of PCs				0.448		
Infectious	34 (61.8)	25 (67.6)	9 (50.0)			
Noninfectious	16 (29.1)	9 (24.3)	7 (38.9)			
Infectious + noninfectious	5 (9.1)	3 (8.1)	2 (11.1)			
Active GVHD	30 (54.5)	8 (44.4)	17 (45.9)	0.916		
Acute	10 (18.2)	6 (33.3)	4 (10.8)	0.052		
Chronic	15 (36.3)	2 (11.1)	13 (35.1)			
VOD	11 (20.0)	8 (44.4)	3 (8.1)	0.004		0.113
CMV treatment	13 (23.7)	8 (44.4)	5 (13.5)	0.016		0.208
Organ failure within 48 h	15 (27.3)	13 (72.2)	5 (27.8)	0.000	26.18 (4.14-165.44)	0.001
Cardiovascular	9 (16.4)	8 (44.4)	1 (2.7)	0.003		0.462
Respiratory	13 (23.6)	9 (50.0)	4 (10.8)	0.003		0.460
Neurological	4 (7.3)	2 (11.1)	2 (5.4)	0.454		
Hematological	15 (27.3)	11 (61.1)	4 (10.8)	<0.001	11.60 (1.22-110.70)	0.033
Renal	7 (12.7)	6 (33.3)	1 (2.7)	0.011		0.337
Gastrointestinal	2 (3.6)	2 (11.1)	0	0.999		
Hepatic	4 (7.3)	3 (16.7)	1 (2.7)	0.099		
The patients transferred to PICU with PCs						
PICU transfer	23 (41.8)	17 (94.4)	6 (16.2)	0.000		
PICU length of stay, days (IQR)	10.0 (4.0-23.0)	14.0 (5.5-30.5)	8.5 (3.0-24.3)	0.728		
Time of PICU admission from HSCT days, median (range)	50 (33-128)	50.0 (18-122)	55.5 (38.3-891.5)	0.104		
Life-sustaining therapy						
Mechanical ventilation	21 (91.3)	16 (94.1)	5 (83.3)	0.439		
CRRT	13 (56.5)	12 (70.6)	1 (16.7)	0.041		
Vasoactive agent	15 (65.2)	15 (88.2)	0	0.999		
ECMO	2 (8.7)	2 (11.8)	0	0.999		
CPR	9 (39.1)	9 (52.9)	0	0.999		
Number of therapy				0.011		
1	5 (21.7)	1 (5.9)	4 (66.7)			
2	1 (4.3)	0	1 (16.7)			
≥3	15 (65.2)	15 (88.3)	0			

PCs, pulmonary complications; HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; VOD, veno-occlusive disease; CMV, cytomegalovirus; PICU, pediatric intensive care unit; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation; IQR, interquartile range; CMV treatment includes curative and preemptive treatment;

Figure 1 (A) compares the 2-year survival rates according to MODS or not in PCs. The difference in survival rates according to PICU admission is described in Figure 1 (B). Median survival was 432days (95% CI, 327.2 - 536.2) for patients with PCs, 74 days (14.7 - 133.3) for those with both MODS and PCs, and 124 days (41.0 - 206.9) for those who required PICU admission ($p < 0.001$). The 1-year OS rate was significantly lower among PCs patients with MODS and with PICU admission than among those without anything (6.7 ± 6.4 vs. 77.5 ± 6.6 %; 26.1 ± 9.2 vs. 81.3±6.9%, $p < 0.001$).

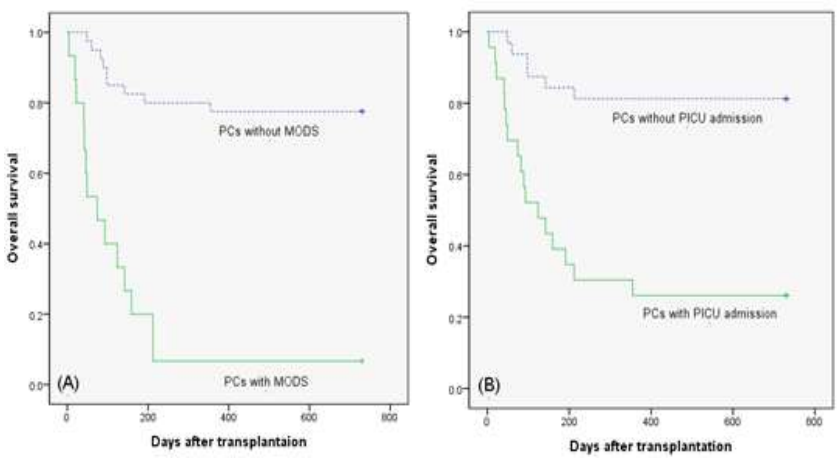

Figure 1. Comparison of 2-year overall survival rate according to (A) multi-organ dysfunction syndrome (MODS) and (B) requiring pediatric intensive care unit (PICU) admission in pulmonary complications (PCs) by using Kaplan-Meier analysis and log-rank test.

Outcome of fatal primary PCs requiring PICU admission

Among the 23 patients admitted to the PICU, 16 needed MV because of primary PCs, and 5 ultimately survived (Table 7). Various underlying diseases, HSCT types, and PCs were observed in both the surviving, and non-surviving groups. However, only one of the surviving patients had one other organ dysfunction during the PICU admission or stay. By contrast, most of the non-surviving patients had MODS with progressive deterioration, especially in the kidneys and hematology, which resulted in septic shock.

All of the patients with fatal PCs received conservative treatments for organ failure such as broad-spectrum antibiotics, CRRT, inotropics, and ECMO. We also used high-dose methylprednisolone or hydrocortisone for acute respiratory distress syndrome (ARDS) in six patients. Four of these patients survived, while the other two died. Among the survivors, three treated with corticosteroids 0, 9 and 4 days after the PICU admission were successfully extubated at an early stage. On the other hand, we used steroid treatments twice at 33 and 54 days after intubation in one patient, who was eventually extubated but stayed in the PICU for 2 months. Of the non-surviving patients, one had received high-dose methylprednisolone four times and the other one was discontinued from steroid pulse therapy within 1 day because of aggravating sepsis. Both died of septic shock. Corticosteroids were not administrated to five patients with neutropenia and two with fungal pneumonia because we were concerned that the infection would worsen.

Table 7. Clinical features of 16 patients with fatal primary pulmonary complications and transferred to pediatric intensive care unit

	Age /Sex	Underlying disease	HSCT type	PCs	GVHD /VOD /CMV	At the time of PICU admission				Outcome	Cause of death	Time from-to	
						Planned admission	Cause of admission	*MODS	Management			HSCT-PCs/ICU /Death	ICU stay
1	4.4 /M	MBL	aPBSCT	Pneumonia	N/N/N	Y	Respiratory failure	N	MV HCS	Alive		68/70	10
2	2.1 /M	ATRT	aPBSCT	ILD Atypical	N/N/N	Y	BAL	N	MV Inotropics mPd pulse	Alive		39/40	64
3	12.5 /M	AML, M4E	uBMT	GVHD	Chronic/ N/Y	Y	Respiratory failure	N	MV mPd pulse	Alive		917/917	4
4	12.2 /M	MBL	aPBSCT	IPS	N/N/N	Y	Post-op, BAL	N	MV HCS	Alive		41/41	11
5	16.8 /F	Cyclic neutropenia	rBMT	Pneumonia	N/N/Y	Y	Respiratory failure	RF	MV,CRRT Vancomycin	Alive		32/33	7
6	15.3 /M	Pre B ALL	uPBSCT	PCP	N/Y/Y	Y	Respiratory failure	RF→ CV,RF	MV,CRRT Inotropics mPd pulse	Death	Septic shock	49/50/93	42
7	10.9 /M	MBL	aPBSCT	ILD	N/Y/N	N	Respiratory failure	RF,HO→ CV,RF, HO	MV Inotropics mPd pulse	Death	Septic shock	11/15/89	74
8	3.9 /M	Osteopetrosis	rPBSCT	Fungal	N/N/Y	Y	Post-op	CV→ CV,RF	MV Inotropics ECMO	Death	ARDS HF	14/116 /159	43
9	9.9 /M	JMML	aPBSCT	Fungal	Chronic /N/Y	Y	Respiratory failure	RF→ CV,RF, HO,LF	MV,CRRT	Death	ARDS	188/210 /212	2
10	5.8 /F	AML, M5	uPBSCT	Viral	Acute /Y/Y	Y	Respiratory failure	CV,RF→ CV,RF,GI ,HO,LF	MV,CRRT Inotropics	Death	Septic shock	82/86/124	38
11	1.26 /M	Pre B ALL	uCBT	Pneumonia	N/Y/N	Y	Respiratory failure	CV,HO	MV Inotropics	Death	ARDS Septic shock	0/18/22	4

12	9.7 /M	AML, M1	rPBSCT	Pneumonia	N/N/N	Y	Respiratory failure	RF,HO→ CV, RF, HO	MV, CRRT Inotropics CPR	Death	Septic shock	169/189 /191
13	7.2 /F	PNET	aPBSCT	Pneumonia	N/Y/N	N	post-seizure arrest	CV, RF, HO, NR	MV, CRRT Inotropics	Death	Septic shock, MOF	4/4/19
14	12.9 /M	Pre T ALL	hBMT	CMV	N/N/Y	N	Respiratory failure	RF→ CV,RF, HO,NR	MV,CRRT Inotropics CPR	Death	ARDS Septic shock	54/68/82
15	12.8 /M	Hodgkin lymphoma	aPBSCT	Pneumonia	N/N/N	Y	Respiratory failure	CV,RF, HO→CV, RF, HB	MCV, CRRT Inotropics	Death	MOF	127/128 /142
16	10.7 /M	CGD	rBMT	GVHD	Chronic /N/Y	Y	Respiratory failure	CV, RF	MV, CRRT Inotropics ECMO	Death	Septic shock	270/332 /355

HSCT, hematopoietic stem cell transplant; PCs, pulmonary complications; GVHD, graft-versus-host disease; VOD, veno-occlusive disease; CMV, cytomegalovirus; PICU, pediatric intensive care unit; MODS, multi-organ dysfunction syndrome; MBL, medulloblastoma; ATRT, atypical teratoid rhabdoid tumor; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; JMML, juvenile myelomonocytic leukemia; PNET, primitive neuroectodermal tumor; CGD, chronic granulomatous disease; aPBSCT, autologous peripheral blood stem cell transplant; uPBSCT, unrelated peripheral blood stem cell transplant; uBMT, unrelated bone marrow transplant; rBMT, related bone marrow transplant; uCBT, umbilical cord blood transplant; hBMT, haploidentical bone marrow transplant; CV, cardiovascualr dysfunction; RF, renal dysfunction; HO, hematological dysfunction; LF, hepatic dysfunction; GI, gastrointestinal dysfunction; NR, neurological dysfunction; MOF, multi-organ failure; ARDS, acute respiratory distress syndrome. *changes of MODS (before PICU admission→after PICU admission)

Discussion

In this study, 34% of all recipients developed PCs within 2 years post transplantation, and the overall PC-related mortality rate was 32.7%. Of our patient cohort, 41.8% required PICU admission, of which 74% ultimately showed PC-related mortality. The development of PCs with MODS was associated with decreased survival, especially with hematological dysfunction. In addition, in patients with fatal PCs requiring MV, the early use of corticosteroids may lead to a positive change.

A significant number of recipients have reportedly experienced mild to fatal PCs after HSCT. In adult recipients, PCs were reported in 40%-60% of patients after HSCT, and 30% of deaths are directly attributable to PCs [40]. Similar to adults, 25% or more of pediatric recipients reportedly developed PCs; in our population, the incidence of PCs was 34% among all recipients [37-39]. Previous studies have reported several risk factors of developing PCs depending on the time of occurrence and the etiology of the PCs, such as conditioning regimen, transplantation type, HLA compatibility, and GVHD development [11, 12, 41-43]. Here, we found that the stem cell source and transplantation type were significantly related with PC development, as evidenced by the lower incidence of PCs in recipients of autologous HSCT or peripheral blood. The low incidence of PCs in autologous HSCT is believed to result from multiple factors such as the faster immunological recovery, absence of GVHD or other alloreactive mechanisms, and lack of immunosuppressive agents for GVHD prophylaxis or treatment [40]. Furthermore, while PBSCs have become a standard stem cell source in our center, Holtick et al. reported that allogeneic PBSC transplantation (PBSCT) was associated with faster engraftment of neutrophils but a higher risk of

GVHD [44]. In addition, bone marrow transplantation (BMT) has been replaced by umbilical cord blood transplantation (uCBT). Although the engraftment rate is lower and the hematopoietic recovery is delayed, the advantages of uCBT include reduced GVHD incidence and severity [43]. These results suggest that early infectious PCs might be more common in uCBT and BMT; on the other hand, PBSCT might result in late infectious or non-infectious PCs with GVHD in allogeneic conditions. However, the difference in the development of late onset non-infectious PCs has not been observed yet in several studies [45-48]. In our study, patients who underwent PBSCT had better long-term outcomes than did those who were administered uCBT or BMT. There were two reasons for this. First, allogeneic PBSCT was not separately analyzed from autologous PBSCT. Second, we did not analyze the correlation between the stem cell source and PCs, by time, after HSCT.

For identifying and diagnosing PCs, non-invasive work-ups including sputum examination, serology, and chest CT were performed in >70% of cases in our center; on the other hand, invasive work-ups were performed in <25% of PC cases. Definite pathogens were not identified in more than one-third of the PC episodes. However, several studies have shown that, in immunocompromised patients, the early identification of the etiology of PC improves survival [49, 50]. Furthermore, the identification of specific infectious etiologies allows therapy to be targeted, thereby minimizing resistance and drug toxicity. Until now, diagnostic approaches have generally relied on history and physical examination, radiological studies, sputum examinations, and serological examinations [35]. Although invasive techniques such as bronchoscopy and surgical biopsy are frequently required, they are difficult to

perform in pediatric patients. Several authors have emphasized the importance of high-resolution CT in the diagnosis of PCs after HSCT [51-55]. However, because it is difficult to rule out PC types on the basis of CT scans alone, a single study reported that no specific CT findings were identified as predictors of antimicrobial or corticosteroid responses [56]. Therefore, to precisely distinguish the etiology of PCs, invasive work-ups with bronchoscopy and lung biopsy should be considered. In previous studies, the diagnostic yield of BAL in HSCT recipients was reportedly 30-73%, with the highest yield for infection within 24 h of presentation or before the initiation of antimicrobial therapy [47, 57, 58]. Lucena et al. recommended early bronchoscopy within 5 days because it had higher diagnostic yield than did late bronchoscopy for PC identification [47]. McCubbin et al. reported a high sensitivity and specificity in 14 pediatric BMT recipients than in open lung biopsy or autopsy recipients [59]. All related pediatric series reported very low rates of serious complications (<4%) when BAL or lung biopsy was conducted in HSCT recipients [35]. However, despite its advantages, as mentioned above, pathogen identification via invasive work-up may not affect mortality [39]. In our study, since the invasive work-up was performed in too few recipients, it is difficult to know the diagnostic yield of BAL and lung biopsy. However, it assisted with treatment decisions in an overall 10% of PCs without procedure-related complications. Thus, to establish an earlier or definitive diagnosis, BAL could be positively considered as an initial diagnostic tool in pediatric HSCT patients with pulmonary dysfunction.

Although the incidence of PCs has diminished as a result of effective prophylactic antibiotics and immunosuppressive therapy for GVHD, pulmonary problems following HSCT are still a major cause

of mortality. Several studies have confirmed that post-HSCT PCs are closely related with considerable morbidity and mortality in both adults and children [37-40]. However, until now, no study has reported the risk factors related with mortality in patients with infectious or non-infectious PCs. An analysis of the patients with comorbidities and PCs revealed that MODS was closely related with mortality. In particular, hematological dysfunction accompanied with PC was the main risk factor of a poor outcome. Acute GVHD, VOD, and need for CMV treatment were more common in non-surviving patients, although the difference was not significance in the multivariate analysis. Unlike the risk factors of developing PCs, there was no significant difference in general characteristics including HSCT type, stem cell source, and previous lung disease. According to reports of post-transplant MODS, organ dysfunction is a frequent complication of HSCT, and the occurrence of single organ system dysfunction in the post-transplantation period reportedly predicts the subsequent development of multi-organ dysfunction and death [60, 61]. Haire et al. showed that pulmonary dysfunction was a significant predictor of any organ dysfunction [60]. The cause of organ dysfunction may be an uncontrolled inflammatory response to some initial event, or mediated by cytokines, complement, and the coagulation system [61]. Further studies on the pathogenesis of MODS in HSCT recipients are needed. In addition, if patients with PCs deteriorate owing to respiratory failure, clinicians should carefully monitor for MODS, the presence of which could predict PC-related outcomes.

Post-transplant PICU admission is required for 17-35% of patients with PCs [20, 21]. In the past few decades, PICU mortality rates for HSCT recipients have decreased impressively from >85% to <44%,

likely because of advances in reduced conditioning, infection prophylaxis, MV, and intensive care [20, 21, 62-64]. In this study, of the HSCT recipients with PCs, 41.8% were transferred to the PICU mainly for respiratory failure, similar to other studies. However, the PICU mortality rate in our study was 73%, which is higher than that of previous studies. This is because our study included HSCT recipients with PCs who required PICU admission, compared with previous studies that included patients admitted to PICU for any cause. According to studies based on the analysis of HSCT pediatric recipients requiring ICU admission, MV care, multi-organ system failure, and CRRT were the common predictors of poor prognosis [24-26, 62-64]. Van Gestel et al. recently reported that severe impairment in oxygenation and CMV viremia were additional independent predictors of mortality in pediatric recipients requiring MV [28]. Rowan et al. also reported a significant association between maximum oxygenation index at any point during MV and ICU mortality; however, they did not evaluate the correlation between outcome and comorbidities with respiratory failure. In our study, multi-organ dysfunction was only strongly related to mortality in HSCT recipients with PCs, as mentioned above. Although renal impairment was not associated with mortality in patients with PCs, the limited analysis aimed at patients requiring PICU admission, and PCs showed that CRRT was associated with poor prognosis, similar to previous studies. Clinical details of fatal primary PCs showed similar results for all PCs. Regarding the fatal PCs, non-surviving patients had MODS at the time of PC diagnosis, and most of them progressed to severe MODS at death, which resulted from septic shock induced by neutropenia. Accordingly, our findings suggest that hematological and renal dysfunctions are predictors of mortality in

patients with fatal primary PCs. However, because the time of admission to PICU due to PCs was not correlated with the outcome in our study, we could not determine whether early intervention of MODS by PICU admission could improve prognosis.

Various infectious and non-infectious conditions lead to pulmonary infiltrates after HSCT. Although non-infectious conditions comprise a growing percentage of pulmonary complications in pediatric HSCT recipients, most of the etiologies associated with acute respiratory failure remain infectious [15]. Therefore, most patients receive empirical anti-microbial therapy during the initial diagnostic work-up if infectious etiology is not excluded. Despite all kinds of antimicrobial therapies, patients who receive HSCT are susceptible to deterioration with respiratory failure such as ARDS with a multifactorial etiology. For immunocompetent patients, corticosteroid administration is controversial but conceptually useful during the early phase owing to its anti-inflammatory effect of inhibiting leukocyte extravasation, macrophage function, or phagocytosis [66]. By contrast, due to these reactions, corticosteroid may lead to an overwhelming infection. In particular, recipients with neutropenia should be closely observed for ARDS. Several studies have reported that a high proportion of patients with neutropenia presented with substantial respiratory deterioration during neutropenia recovery than they did before or after neutropenia recovery [67]. These phenomena have not been explained clearly yet. However, ARDS is more common in neutropenic patients, who show pulmonary infiltrates during neutropenia, delayed or prolonged neutropenia, and fungal pneumonia [67]. Accordingly, routine screening for high-risk patients with neutropenia might be crucial to recognizing the early symptoms of ARDS before biological leukocyte recovery. In our study, 6 of 16

patients with fatal primary PCs received steroids for ARDS. Among them, four showed favorable outcomes, while two died of septic shock after steroid administration. Despite the deterioration in severe respiratory failure with overall antimicrobial treatment, we did not administer the steroids to seven patients with fungal pneumonia and neutropenia. All of these patients showed poor prognosis. Considering that surviving patients with fatal PCs had received steroids, this medication could be a factor of favorable prognosis; however, this was not proven statistically in this study. The worsening of infection following the hematological condition and etiology should be considered before steroid administration on a case-by-case basis.

We retrospectively evaluated the incidence, overall outcome, and risk factors associated with PC-related mortality in pediatric patients after HSCT and focused on the fatal cases. To the best of our knowledge, this is the first report to reveal the factors related with mortality in children with PCs after HSCT. However our study has several limitations. First, we performed follow-up during 2 years; therefore, we did not examine the outcomes of far-late-onset PCs. Second, this study recruited a heterogeneous group of recipients regardless of the time of occurrence of PCs from HSCT or their types. Because the etiologies of PCs differ depending on their time of occurrence after HSCT, this factor could have affected the treatment outcomes. Finally, we did not regard PFT as important for diagnosis. However, recent studies have emphasized the role of PFT in the early diagnosis of late-onset non-infectious PCs.

In conclusion, to improve HSCT outcomes in patients with PCs, early diagnosis and targeted therapy should be considered. Physicians should closely observe the co-existence of other organ dysfunctions with PCs, especially hematological and renal conditions. Because these

factors are related with poor outcome, for managing MODS, early intervention with PICU admission should be considered. If the respiratory insufficiency worsens with full supportive care, corticosteroid therapy can be administrated during early-stage ARDS, depending on the patient condition.

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국문초록

서론: 소아 조혈모 세포 이식에서 이식 기술 및 보존적 치료의 발달에도 불구하고 아직까지 상당수의 환자는 이식 후 폐 합병증으로 불량한 예후를 보이고 있다. 본 후향적 연구는 소아 조혈모 세포 이식 환자에서 폐 합병증의 유병율, 시행된 진단 방법, 사망률 및 치명적 폐합병증에 이르게 하는 위험요인을 파악하고자 한다.

방법: 서울대학교 어린이 병원에서 2010년부터 2012까지 시행된 이식 환자 109명의 의무기록을 후향적으로 분석하였다.

결과: 총 38명에서 55건의 이식 후 폐 합병증이 관찰되었으며 (34.8%), 자가 조혈모 세포 이식을 받은 환자에서 다른 유형의 조혈모 세포 이식보다 폐 합병증이 적게 발생하였다 (65.8% vs. 49.3%, p=0.009). 폐 합병증 진단에 가래 검사 (85.5%), 혈청학적 검사 (72.7%), 흉부 컴퓨터 단층촬영 (76.4%) 등의 비 침습적 검사가 더 선호되었다. 폐 합병증과 연관된 사망률은 18건으로 32.7%이며, 폐 합병증에 동반된 다 장기부전이 나쁜 예후와 통계학적으로 밀접한 관련이 있었다 (OR 26.18, p=0.001). 특히 혈액학적 기능 부전은 폐 합병증 발생 시 사망과 관련된 주요인으로 확인되었다 (OR 11.60, p=0.033). 폐 합병증이 발생한 이식 환자 중 41.8%가 주로 호흡부전으로 소아중환자실에 입실하였으며, 중환자실 전동 후 사망률은 73%였다. 중환자실 입실 후, 생명 연장 치료 중 지속적 신대체 요법은 생존환자보다 사망환자에서 더 많이 수행되었다 (70.6% vs 16.7%, p=0.041). 치명적인 폐 합병증으로 기계 환기 요법을 받은 16명의 환자 중 5명의 생존환자는 사망환자에 비해 대부분 다 장기 부전을 동반하지 않았으며 급성호흡곤란 증후군에 대해 스테로이드 치료를 받았었다.

결론: 본 연구를 통해 소아 조혈 모 세포 이식 후 폐 합병증 발생시 다 장기부전은 사망률과 밀접한 관계가 있어 이에 대한 면밀한 관찰이 필요

하며, 이에 대한 조기중재를 위해 소아 중환자실 입실을 고려할 수 있겠다.

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주요어: hematopoietic stem cell transplant, pulmonary complication, mortality, pediatric

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