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■ Original Article ■

Extracorporeal Membrane Oxygenation Support in Adult Patients with Hematologic Malignancies and Severe Acute Respiratory Failure

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Background: Administering extracorporeal membrane oxygenation (ECMO) to critically ill patients with acute respiratory distress syndrome has substantially increased over the last decade, however administering ECMO to patients with hematologic malignancies may carry a particularly high risk. Here, we report the clinical outcomes of patients with hematologic malignancies and severe acute respiratory failure who were treated with ECMO.
Methods: We performed a retrospective review of the medical records of patients with hematologic malignancies and severe acute respiratory failure who were treated with ECMO at the medical intensive care unit of a tertiary referral hospital between March 2010 and April 2015.
Results: A total of 15 patients (9 men; median age 45 years) with hematologic malignancies and severe acute respiratory failure received ECMO therapy during the study period. The median values of the Acute Physiology and Chronic Health Evaluation II score, Murray Lung Injury Score, and Respiratory Extracorporeal Membrane Oxygenation Survival Prediction Score were 29, 3.3, and -2, respectively. Seven patients received venovenous ECMO, whereas 8 patients received venoarterial ECMO. The median ECMO duration was 2 days. Successful weaning of ECMO was achieved in 3 patients. Hemorrhage complications developed in 4 patients (1 pulmonary hemorrhage, 1 intracranial hemorrhage, and 2 cases of gastrointestinal bleeding). The longest period of patient survival was 59 days after ECMO initiation. No significant differences in survival were noted between venovenous and venoarterial ECMO groups (10.0 vs. 10.5 days; p = 0.56).
Conclusions: Patients with hematologic malignancies and severe acute respiratory failure demonstrate poor outcomes after ECMO treatment. Careful and appropriate selection of candidates for ECMO in these patients is necessary.

Key Words: hematologic neoplasms; extracorporeal membrane oxygenation; respiratory insufficiency.

Introduction

Patients with hematologic malignancies are susceptible to infection because they have an immunocompromised status due to the disease process or chemotherapy. In particular, pneumonia and acute respiratory failure (ARF) are the most life-threatening complications, and these complications are the main reason for admitting patients with hematologic malignancies to the intensive care unit (ICU).[1,2] Despite notable advances in oxygen therapy such as high-flow nasal cannulas[3] and non-invasive ventilation,[4]

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most patients with hematologic malignancy and ARF need invasive mechanical ventilation.[5] The mortality rates of these patients are very high and exceed 50% in such circumstances.[6]

Recently, the use of extracorporeal membrane oxygenation (ECMO) as a rescue therapy in ARF patients has received significant attention.[7] Since meaningful results were obtained after administering ECMO to pandemic influenza A (H1N1)-induced acute respiratory distress syndrome (ARDS) patients in 2009,[8,9] and reported in a randomized trial,[10] the use of ECMO for the treatment of severe ARDS has been recommended.[11] However, administering ECMO to patients with hematologic malignancies and ARF is the subject of debate because they might be expected to demonstrate high mortality and a high rate of complications such as bleeding and infection.[6,12,13]

There are limited studies on administering ECMO to patients with hematologic malignancies, and these studies report different outcomes.[14-16] It is thus necessary to determine if applying ECMO to such high-risk groups is suitable considering the limited medical resources and high cost of ECMO. The purpose of our study was to present the clinical outcomes of patients with hematologic malignancies and ARF who were treated with ECMO.

Materials and Methods

This study was based on a retrospective review of the clinical courses of all adults patients (≥16 years of age) with hematologic malignancies and ARF who were treated with ECMO at the medical ICU of a tertiary referral hospital (Asan Medical Center of Seoul, Korea) in Korea between January 2010 and April 2015. All study patients met the criteria of severe ARDS, which were recently defined.[17] ECMO was applied when the patient had severe and life-threatening refractory hypoxemia despite high levels of positive end-expiratory pressure or excessively high inspiratory pressure, which lead to the failure of proper volume- and pressure-limiting strategies during mechanical ventilation.[7] Patients who received ECMO only due to cardiogenic shock were not included in the analysis. ECMO support was implemented using the Capiox Emergency Bypass System (Terumo, Tokyo, Japan) and Permanent Life Support (Maquet Cardiopulmonary AG, Hirrilingen, Germany). The vascular access was established through femoral artery in arterial cannulation, and femoral vein or internal jugular vein in venous cannulation. The size of cannula was determined by the patient's body surface area and ranged from 14 F to 25 F in arterial cannula; 17 F to 34 F in venous cannula. Heparin or nafamostat mesylate was given to maintain the desired whole blood activated clotting time of 160 to 180 seconds. We tried to maintain the ECMO blood flow to meet the goal of arterial oxygen saturation > 85%. Red blood cells and platelets were transfused to maintain the hemoglobin > 7 g/dL, hematocrit > 30%, and platelet > $50 \times 10^3/\mu L$.

The patient demographics and characteristics of the hematologic malignancies, including type, date of diagnosis, previous therapy, days since therapy and remission status of the malignancy were collected before ECMO initiation. We calculated the Acute Physiology and Chronic Health Evaluation (APACHE) II Score, and Murray Lung Injury Score (LIS) to assess disease severity at ICU admission.[18,19] In addition, the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) Score was also calculated to evaluate the adequacy of ECMO initiation and compare with hospital survival.[20] The etiology of ARF and laboratory tests, including complete blood cell count, chemistry, coagulation and arterial blood gas parameters (pH, PaO_2, PCO_2, lactate) were recorded, both before and 24 hours after ECMO were recorded. The parameters associated with ECMO such as mode of ECMO (venoveous [VV], venoarterial [VA] and venovenoarterial), ECMO duration time, use of vasopressor use and anticoagulants, hemofiltration during ECMO, successful weaning of ECMO, and adverse events during ECMO (e.g., bleeding, infection, device-related complications) were also recorded.[7] Major bleeding was defined as a decrease in

the hemoglobin levels by > 2.0 g/dL or requiring > 2 units of packed red blood cells due to an obvious bleeding event, surgical interventions, or intracranial hemorrhage.[15] Finally, ICU and hospital outcomes were assessed by survival or death. The data are presented as the median and interquartile range (25-75%) for continuous variables or number and percentage for non-continuous variables. Survival was analyzed using the Kaplan-Meier method. In this study, $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

This study was approved by the institutional review board of Asan Medical Center (No. 2016-0352). The requirement for informed consent was waived by the institutional review board due to the retrospective nature of the analysis.

Results

During the study period, a total of 15 patients received ECMO treatment. Nine of these patients were men, and the median age was 45 years (31-54 years). The individual characteristics of the study population are provided in Table 1. The etiology of ARF was viral or bacterial pneumonia in all patients. All patients also fulfilled the criteria of severe ARDS.

1) Hematologic malignancies

The types of hematological malignancies in our current study population included the following: 8 patients had leukemia (acute myeloid leukemia [n = 4], chronic myeloid leukemia [n = 2], biphenotypic acute leukemia [n = 1], and the transformation of myelodysplasia syndrome to acute myeloid leukemia [n = 1]), 2 patients had lymphoma (precursor T-cell lymphoma [n = 1] and diffuse large B-cell lymphoma [n = 1]), 1 pa-

Table 1. Individual patient characteristics and clinical outcomes

Patient no.	Sex/Age	Malignancy	Therapy and disease status (days since therapy)	APACHE II Score	LIS	RESP Score (group)	ECMO duration hours (days)	Type of ECMO	ECMO weaning	Bleeding	Cause of death
1	M/54	CML	HSCT (294), CR	29	3.5	0 (III)	245 (11)	VV	No	Major	DAH
2	M/26	Precursor T-cell lymphoma	HSCT (260), Relapsed	17	3.3	-4 (IV)	266 (12)	VA	No	Major	ICH
3	F/16	AA	HSCT (1)	29	3.8	0 (III)	108 (5)	VV	Yes	Minor	Sepsis
4	F/56	MM	HSCT (34)	41	3.5	-4 (IV)	394 (17)	VA	No	Minor	Sepsis
5	M/28	CML	HSCT (221), CR, graft failure	26	3.3	4 (II)	92 (4)	VA	Yes	-	Sepsis
6	F/43	MDS	HSCT (20)	25	3.8	-2 (IV)	18 (1)	VA	No	-	MOF
7	F/33	HLH	HSCT (20)	19	3.5	-13 (V)	4 (1)	VV	No	-	Pneumonia
8	F/51	AML	Consolidation (19), CR	31	3.5	0 (III)	4 (1)	VA	No	-	Sepsis
9	M/41	AML	HSCT (14), CR	29	3.0	-6 (V)	7 (1)	VA	No	-	Pneumonia
10	F/45	BAL	HSCT (1519), CR	40	2.5	-8 (V)	452 (19)	VV	No	-	Sepsis
11	M/51	Diffuse large B-cell lymphoma	Induction on ECMO	29	3.3	-2 (IV)	176 (8)	VV	No	-	MOF
12	M/62	AML	HSCT (0), CR	39	3.0	-2 (IV)	4 (1)	VV	No	-	Pneumonia
13	M/58	Transformation of MDS to AML	-	39	2.3	0 (III)	36 (2)	VV	No	-	Sepsis
14	M/54	AML	Induction (61), CR	14	3.5	-4 (IV)	42 (2)	VA	Yes	-	MOF
15	M/31	MDS	Azacitidine, Danazol	31	2.8	-2 (IV)	36 (2)	VA	No	-	Sepsis

APACHE II score: The Acute Physiology and Chronic Health Evaluation II score; LIS: lung injury score; RESP score: respiratory extracorporeal membrane oxygenation survival prediction score; ECMO: extracorporeal membrane oxygenation; CML: chronic myeloid leukemia; HSCT: hematopoietic stem cell transplantation; CR: complete remission; VV: venovenous; DAH: diffuse alveolar hemorrhage; VA: venoarterial; ICH: intracranial hemorrhage; AA: aplastic anemia; MM: multiple myeloma; MDS: myeloid dysplasia syndrome; MOF: multiple organ failure; HLH: hemophagocytic lymphohistiocytosis; AML: acute myeloid leukemia; BAL: biphenotypic acute leukemia.

tient had hemophagocytic lymphohistiocytosis, 1 patient had aplastic anemia, 1 patient had multiple myeloma, and 2 patients had myelodysplastic syndrome. Ten patients had undergone hematopoietic stem cell transplantation (HSCT). The median number of days since HSCT was 27 (10.8-268.5). Among the 10 HSCT patients, 6 had recently (within 90 days) undergone this treatment. These cases underwent ARF during admission for HSCT, and ARF occurred after a median of 17 days. The diagnosis of hematologic malignancy was made after ECMO initiation in 1 patient (patient no. 7) with hemophagocytic lymphohistiocytosis. There was 1 patient (patient no. 11) who received chemotherapy during ECMO support. No chemotherapy was administered to 1 patient (patient no. 13) who was diagnosed with acute myeloid leukemia being transformed from myelodysplasia syndrome because ARF occurred immediately after diagnosis.

2) Baseline characteristics

Immediately before ECMO support, the median APACHE II score was 29 (25-39), and LIS was 3.3 (3.0-3.5). The median RESP score was -2 (-4-0). Patients were categorized as having an RESP score of group II (1 patient; 6.7%), III (4 patients; 26.7%), IV (7 patients; 46.7%), or V (3 patients; 20%). Leukopenia was present in 10 patients, with a median leukocyte count of 1.1 (0.1-8.2) $\times 10^3/\mu L$, and thrombocytopenia was present in all patients with a median platelet count of 51 (23.0-64.0) $\times 10^3/\mu L$. The median absolute neutrophil count was 0.4 (0.0-7.1) $\times 10^3/\mu L$ with showing below 1 $\times 10^3/\mu L$ in 10 patients. Arterial blood gas analysis revealed the following findings prior to ECMO initiation: pH, 7.22 (7.14-7.29); pCO_2, 52.0 mmHg (44.0-68.4); PaO_2, 45.0 mmHg (36.0-57.0); PaO_2/FiO_2 ratio, 47.0 (36.0-57.0); and lactate, 4.7 mmol/L (1.9-7.0) (Table 2).

3) ECMO treatment

ECMO treatment was initiated at the decision of the treating intensivist. The duration of mechanical ventilation prior to ECMO initiation was < 2 days in 11 patients, 2-7 days in 2 patients, and > 7 days in 1 patient. There was 1 patient who was placed in the prone position, and no patients received nitric oxide prior to ECMO initiation. All patients received anticoagulation with unfractionated heparin or nafamostat mesylate during ECMO treatment. Seven patients received VV ECMO, whereas 8 patients received VA ECMO because of cardiac dysfunction and sepsis-related shock. The median ECMO duration was 2 (1-11) days, but less than 2 days in 8 patients. Weaning of ECMO was successful in 3 patients (1 VV and 2 VA ECMO patients). All patients received vasopressors in order to obtain a proper blood pressure, and 8 patients underwent continuous renal replacement therapy during ECMO treatment (Table 2). At 24 hours after ECMO initiation, arterial blood gas analysis revealed a median pH of 7.35 (7.25-7.40), 41.5 mmHg pCO_2 (29.0-50.5), 87.0 mmHg PaO_2 (51.8-94.8), and 4.1 mmol/L lactate (2.0-12.3) in 10 patients. There were no arterial blood gas data at 24 hours after ECMO initiation in 5 patients because they died within 24 hours.

Table 2. Characteristics at before ECMO initiation (n = 15)

Characteristic	Value
Arterial blood gas analysis	
pH	7.22 (7.14–7.29)
$PaCO_2$ (mmHg)	52.0 (44.0–68.4)
PaO_2 (mmHg)	45.0 (36.0–57.0)
PaO_2/FiO_2 ratio	47.0 (36.0–57.0)
Lactate (mmol/L)	4.7 (1.0–7.0)
Complete blood cell count	
Leukocyte ($\times 10^3/\mu L$)	1.1 (0.1–8.2)
Hemoglobin (g/dL)	10.7 (8.4–11.7)
Platelet ($\times 10^3/\mu L$)	51.0 (23.0–64.0)
Vasopressor, n (%)	15 (100)
Hemofiltration, n (%)	8 (53)

The data are presented as the median and interquartile range (25–75%) for continuous variables or number and percentage for non-continuous variables. ECMO: extracorporeal membrane oxygenation.

4) Adverse events

There were hemorrhage complications in 4 patients. Major bleeding occurred in 2 patients. These complications included diffuse alveolar hemorrhage (patient no. 1)

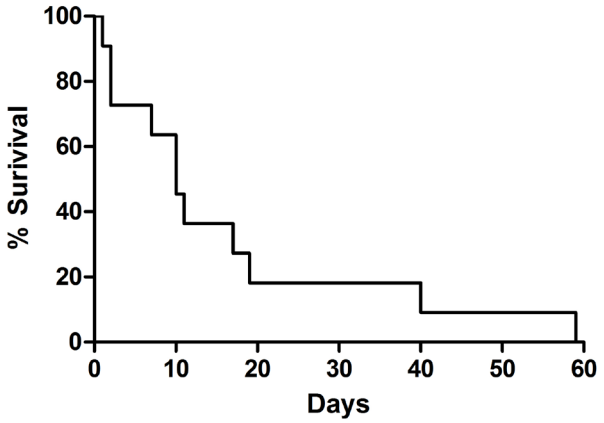

Fig. 1. Kaplan-Meier survival analysis of the study patients with hematological malignancies and severe acute respiratory failure. The median survival period was 10 days after ECMO initiation. ECMO: extracorporeal membrane oxygenation.

and intracranial hemorrhage (patient no. 2). Minor bleeding included gastrointestinal hemorrhage (patient nos. 3 and 4). Anticoagulants were temporarily stopped or nafamostat mesylate was used instead of unfractionated heparin when bleeding was severe. There were 2 mechanical complications: hemolysis (patient no. 10) and lower-limb ischemia (patient no. 14).

5) ICU and hospital outcome

Of the 3 patients with successful ECMO weaning, only 1 patient (patient no. 14) was transferred to the general ward at 10 days after ECMO initiation. The median survival period was 10 days (Fig. 1). The longest survival period was 59 days (patient no. 3). Seven patients died within 2 days after ECMO initiation. There was no significant difference in survival between the VV and VA ECMO group (10.0 vs. 10.5 days; p = 0.56).

Discussion

Despite recent improvements in the outcomes of critically ill patients with hematologic malignancies, their survival rates still remain poor.[6] Thus, ECMO could be proposed as the ultimate therapy. Previous studies on this issue were mainly focused on pediatric patients[21-23] because ECMO is established as the standard therapy for neonates and children with ARF that is refractory to conventional management strategies.[24] In this study, we present the additional results on adult hematologic malignancy after studies of other investigators.[14-16]

Recently, technological advances in membrane oxygenators, pumps and catheters have progressed markedly. Accordingly, many intensivists use ECMO in a safer and simpler manner than in the past in a variety of clinical situations than past. However, the role and proper use of ECMO in patients with ARF have not been definitively established.[7] In addition, the use of ECMO in patients with hematologic malignancies has potential medical risks as well as ethical and economic challenges.

Although Wohlfarth et al.[15] and Gow et al.[16] reported some feasible results in select patients with hematologic malignancies and ARF, Kang et al.[14] reported disparate results like our current study. A simple comparison of our present findings with those of other studies would not be appropriate since our series, and that of Kang et al.[14] mostly included leukemia patients whereas the study of Wohlfarth et al.[15] mostly comprised lymphoma patients and that of Gow et al.[16] patients with solid tumors. Moreover, the different outcomes in these reports might not be due to the lack of experience using ECMO because our hospital is a tertiary referral hospital that treats many ECMO patients (> 100 cases/year). In our current study series, more patients who received HSCT (n = 10) than in other studies, and pneumonia and ARF occurred during cytopenia immediately after high-dose chemotherapy (n = 6). The median absolute neutrophil count of the patients who received HSCT within 90 days (6 patients) was 0.0 (range 0-0.5) $\times 10^3/\mu L$. These severe impairment of immunity would contribute poor control of infection. There was even one case of graft failure (patient no. 5) and a patient whose malignancy relapsed at several months after HSCT (patient no. 2). Furthermore, there was a patient who received over 7 days of ventilation (patient no. 7) and a patient who did not received chemotherapy for malignancy (patient no. 13). Hence, the survival was poor among our

study patients. Besides poor conditions of the patients with hematologic malignancies and ARF, it should be considered that the pharmacokinetics of many of medications administered to patients receiving ECMO were complex.[25] In particular, there are very limited data to guide antibiotics dosage and administration interval in patients receiving ECMO. Follow-up study is needed to deal with minimal inhibitory concentration of antibiotics and suggest guideline for dose and interval of antibiotics during ECMO.

The period of present analysis occurred before the publication of the RESP score.[20] ECMO initiation was performed according to clinical indications and the clinical judgment of the intensivist. Looking back at the RESP scores of our current study population, these were very poor and the majority of the patients were below group IV. The RESP scores did not correlated with the survival time, but most of our patients with a RESP score below group IV died within 7 days. The RESP score consists of 12 variables and includes the acute respiratory diagnosis group, immunocompromised status, and other variables that are determined before ECMO initiation.[20] Basically, it is difficult for patients with hematological malignancy and pneumonia to exceed a RESP score of 1 (i.e., group III) since the presence of immunocompromised status and viral/bacterial pneumonia result in score -2 and 3, respectively. Therefore, the early application of mechanical ventilation (score 3 for < 48 hours, or score 1 for 48 hours to 7 days) and the use of neuromuscular blockade (score 1) before ECMO initiation is needed to increase the RESP score in such patients and, if possible, in young patients (score 0 for 18-49 years) who are expected to receive ECMO treatment.

Bleeding events were observed in 4 patients (27%) in our study. Among these cases, major bleeding was noted in 2 patients. This value is relatively lower than reported by Wohlfarth et al.[15] Bleeding remains a clinically significant issue despite the evolution in ECMO devices such as hollow-fiber oxygenators, centrifugal pumps and bicaval dual-lumen cannulas over several decades.[7,24] Although the incidence of complications in our present series, including bleeding in patients with hematologic malignancies, was not significantly different from that of immunocompetent patients in the study by Kang et al.[14], it is important to maintain a proper platelet count in patients with hematologic malignancy because bleeding complications result in poorer outcomes.

Despite the poor outcomes of our report, applying ECMO to patients with hematologic malignancies could be still the option of rescue therapy when they are relatively young and have short duration of mechanical ventilator before ECMO initiation. Indeed, at least, the weaning of ECMO was successful in three young patients (patient no 3, 5, and 14) who had complete remission status of hematologic malignancy and a short period of mechanical ventilator to ECMO. The incidence of complications related to ECMO in these patients would be similar to those in immunocompetent patients with ARF.[14]

Our study had several limitations of note. First, this was a retrospective study with a small number of patients. However, it would be nearly impossible to perform a randomized prospective study since there are considerable medical and ethical issues. Second, all of the patients in our current study had poor baseline characteristics including poor hematologic disease status, APACHE II score, LIS, and RESP score, which led to rescue therapy. Third, they were only a very small portion of patients among critically ill patients with hematologic malignancies who underwent respiratory failure during the study period. Therefore, the outcomes of our study cannot be generalized since the patients were from a highly select group.

In conclusion, patients with hematologic malignancies and severe ARF demonstrate poor outcomes after ECMO treatment. Careful and appropriate selection of ECMO candidate is needed. The RESP score would help in choosing proper candidate of ECMO so far. Relatively young patients who have short duration of ventilator and received neuromuscular blocker before ECMO initiation wound benefit from ECMO support. However, in addition to the RESP score, comprehensive judgement about

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medical, ethical and economical issues is needed to initiate ECMO in these patients. Further randomized controlled research is also warranted to clarify the adequacy of ECMO in patients with hematologic malignancy and severe ARF.

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