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ORIGINAL ARTICLE

Outcome and predictors of mortality in patients requiring invasive mechanical ventilation due to acute respiratory failure while undergoing ambulatory chemotherapy for solid cancers

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Abstract
Purpose Acute respiratory failure that requires invasive mechanical ventilation is a leading cause of death in critically ill cancer patients. The aim of this study was to evaluate the outcome and prognostic factors of patients requiring invasive mechanical ventilator for acute respiratory failure, within 1 month of ambulatory chemotherapy for solid cancer.
Methods A retrospective observational study of patients who underwent ambulatory chemotherapy at Samsung Medical Center, between January of 2007 and April of 2009, was employed for this study.
Results A total of 51 patients met the inclusion criteria and were included in the study. The median age was 65 years (25–87) and the majority of the patients were male (n=38, 74.5 %). There were 42 patients (82.3 %) with lung cancer. The most common cause of acute respiratory failure was pneumonia (n=24, 47.1 %), followed by acute respiratory failure due to extra-pulmonary infection, drug-induced pneumonitis, alveolar hemorrhage, and cancer progression. The intensive care unit (ICU) mortality was 68.6 % and the most common cause of death in the ICU was uncorrected cause of acute respiratory failure. Before adjustment for others factors, prechemotherapy Eastern Cooperative Oncology Group (ECOG) Performance Scale (PS) (P=0.03), Sequential Organ Failure Assessment score (P=0.01), and anemia (P=0.04) were significantly associated with ICU mortality. However, when adjusted for age, sex, and Acute Physiologic and Chronic Health Evaluation II score, only poor ECOG PS (≥2) was significantly associated with ICU mortality [OR 6.36 (95 % CI (1.02–39.5))].
Conclusions The outcome of patients with acute respiratory failure needing invasive mechanical ventilation during ambulatory chemotherapy for solid cancer is poor. Prechemotherapy performance status is an independent predictor of mortality.

Keywords Cancer · Chemotherapy · Intensive care unit · Mortality · Respiratory failure

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Introduction

The survival rate of critically ill cancer patients has improved over the past two decades [1–3]. The reasons for this improvement likely include advances in the management of organ failure in the intensive care unit (ICU) [4–6], the use of non-invasive mechanical ventilation [5, 7] and the introduction of new treatments for solid tumors or hematologic malignancy [8, 9]. However, acute respiratory failure

with the need for invasive mechanical ventilation still remains the leading cause of death in critically ill cancer patients [10–12]. Consequently, when a cancer patient faces acute respiratory failure, mechanical ventilation is often considered futile [13–15].

Cytotoxic chemotherapy is being administered in an increasing number of solid cancer patients [16] on an intermittent drug dose schedule, allowing ambulatory treatment. While undergoing ambulatory chemotherapy, patients may develop respiratory failure, requiring mechanical ventilation. Approximately 5 % of patients with solid cancers experience acute respiratory failure during the course of their disease [17, 18]. However, to date, the outcome and prognostic factors specific for this patient population have not been reported in the literature. Here, we evaluated the outcome and prognostic factors of acute respiratory failure requiring invasive mechanical ventilation in solid cancer patients within one month of ambulatory chemotherapy.

Methods

Patients

This retrospective study included patients admitted to the medical ICU of Samsung Medical Center (a university-affiliated, tertiary referral hospital in Seoul, Korea) between January of 2007 and April of 2009. Solid cancer patients with acute respiratory failure requiring invasive mechanical ventilation and who had received ambulatory chemotherapy within 1 month of ICU admission were included. Patients were excluded from this study when they were less than 18 years old or stayed in the ICU for less than 24 h. Permission was obtained from the Institutional Review Board of the Samsung Medical Center to review and publish information from patients' records. Informed consent was waived because of the retrospective nature of the study.

Data collection

Epidemiological and clinical data available at the time of ICU admission were collected from patients' medical records. Data included age, sex, smoking history, comorbid conditions, type of solid cancer, time from last dose of chemotherapy to ICU admission, performance status (PS) within the preceding week before chemotherapy, severity-of-illness scores, reason for acute respiratory failure, laboratory values, therapeutic interventions during the stay in the ICU such as vasopressor use, renal replacement therapy or tracheostomy, ICU mortality, hospital mortality, and cause of death.

PS was measured with the Eastern Cooperative Oncology Group (ECOG) Scale (PS 0: fully active; PS 1: restricted in physically strenuous activity; PS 2: ambulatory and capable of all self-care, but unable to carry out any work activities; PS 3: confined to bed or chair more than 50 % of waking hours; PS 4: bedridden) [19].

For assessment of severity-of-illness, Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were calculated. APACHE II which was originally developed to predict hospital mortality of patients admitted to the ICU but is also used to assess severity-of-illness [20, 21]. Age, type of the ICU admission, chronic health status, and worst value of 12 physiologic variables in the first 24 h of the ICU admission are used to calculate a composite score [20, 21]. The SOFA score is a scoring system to determine the extent of a patient's organ dysfunction [22]. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems [22].

Definitions

Acute respiratory failure was defined as symptoms of respiratory distress with the need for invasive ventilator support [17]. Clinically diagnosed pneumonia was defined as the presence of a new infiltrate on chest radiography plus at least one of the following: fever (body temperature >38.2 °C) or hypothermia (temperature <35.0 °C), new cough with or without sputum production, pleuritic chest pain, dyspnea, or altered sound of breathing on auscultation, as previously described [23]. Microbiologically documented pneumonia was defined as the presence of $>10^4$ colony forming units/ml in the bronchoalveolar lavage (BAL) fluid or the presence of $>10^5$ colony forming units/ml in the endotracheal aspirate culture [24]. The presence of *Pneumocystis jiroveci* or *Aspergillus* spp. in the BAL was considered diagnostic. Viral pneumonia was diagnosed when a virus was recovered from either the BAL or the nasopharyngeal specimens in a patient with clinical features consistent with viral pneumonia [17]. Ventilator-associated pneumonia was referred to as pneumonia that arises more than 48 h after endotracheal intubation [25]. Cardiogenic pulmonary edema was diagnosed when that the echocardiography showed left ventricular dysfunction and serum B-type natriuretic peptide was elevated. Bilateral pleural effusions and rapid improvement in pulmonary status after diuresis were typically observed in patients with cardiogenic pulmonary edema [26]. Alveolar hemorrhage and pulmonary infiltration by malignancy were diagnosed using previously reported criteria [27, 28]. In patients with alveolar hemorrhage, the retrieved BAL was hemorrhagic and contained hemosiderin-laden macrophages. The diagnosis of antineoplastic agent-induced pulmonary toxicity depended upon an appropriate history of drug exposure and the exclusion of other causes of respiratory failure, including infection, cardiogenic pulmonary edema, diffuse alveolar hemorrhage and lymphangitic spread of

the cancer [29, 30]. Bronchoscopy with BAL was used to exclude infectious process and diffuse alveolar hemorrhage. Leukopenia was defined as a leukocyte count of less than 1,000 cells/mm^3 [31] and anemia was defined as a hemoglobin level less than 12 g/dl [32].

Statistical analyses

Data are presented as the median (interquartile range (IQR)) for continuous variables and as the number (%) for the categorical variables. Data were compared using the Mann–Whitney *U* test for continuous variables and the Chi square test or Fisher's exact test for categorical variables. A logistic regression model was used to adjust for potential confounding factors in the association between prognostic factors and ICU mortality. Each variable was adjusted for age, sex and APACHE II score. Data are presented as the odds ratio (OR) with a 95 % confidence interval (CI). All tests were two-sided, and a *P* value of less than 0.05 was considered statistically significant. Data were analyzed using the PASW Statistics software version 15 (SPSS Inc, Chicago, IL).

Table 1 Demographic and clinical characteristics of patients

Variables	Subjects (*n*=51)
Age, year	65 (25–87)
Sex(male)	38 (74.5 %)
Smoking[a]	
Smoker	28 (54.9 %)
Non-smoker	20 (39.2 %)
Comorbid conditions	
DM	4 (7.8 %)
HTN	7 (13.7 %)
Pulmonary TB	1 (2.0 %)
COPD	2 (3.9 %)
Primary site of solid cancer	
Lung	42 (82.3 %)
Colon	2 (3.9 %)
Stomach	5 (9.8 %)
Pancreas	1 (2 %)
Breast	1 (2 %)
Time from chemotherapy to admission in ICU (days)	7 (3–22)
ECOG PS	
0	2 (3.9 %)
1	8 (15.7 %)
2	38 (74.5 %)
3	3 (5.9 %)
SOFA	8 (5–14)
APACHE II	17 (7–32)
Treatment in ICU	
Vasopressor therapy	25 (49.0 %)
Renal replacement therapy	12 (23.5 %)
Tracheostomy	8 (15.7 %)
Duration of mechanical ventilation	4.5 (1–80)
Median ICU stay	7 (1–80)

Data are presented as median (IQR) or *n* (%)

DM diabetes mellitus, *HTN* hypertension, *TB* tuberculosis, *COPD*, chronic obstructive pulmonary disease, *ICU* Intensive Care Unit, *ECOG PS* Eastern Cooperative Oncology Group Performance Scale, *SOFA* Sequential Organ Failure Assessment, *APACHE* Acute Physiology And Chronic Health Evaluation

[a] Missing data: *n*=3

Results

Patient characteristics

During the study period, 51 patients who met the inclusion criteria were included in the analysis. Their main demographical and clinical characteristics are summarized in Table 1. The median age was 65 (25–87) years. A majority of the patients were male (*n*=38, 74.5 %). The most common primary site of solid cancer was the lung (*n*=42, 82.3 %). Forty-seven patients (92.2 %) had distant metastasis. The median duration from last chemotherapy to ICU admission was 7 (3–22) days. Ten patients (19.6 %) had ECOG PS 0 or 1 and 41 patients (80.4 %) had ECOG PS 2 or 3. The median SOFA score was 8 (5–14) and the median APACHE II score was 17 (7–32). Twenty-five patients

Table 2 The cause of acute respiratory failure

The cause	Subject (*n*=51)
Pneumonia	24 (47.1 %)
Microbiologically documented	17 (33.4 %)
Clinically suspected	7 (13.7 %)
Drug-induced pneumonitis	7 (13.7 %)
Pulmonary hemorrhage	2 (3.9 %)
Hemoptysis	2 (3.9 %)
Cancer progression	2 (3.9 %)
Pulmonary embolism	1 (2 %)
COPD acute exacerbation	1 (2 %)
IPF acute exacerbation	1 (2 %)
Extra-pulmonary infection	11 (21.5 %)
Intra abdominal infection	5 (9.8 %)
Urinary tract infection	2 (3.9 %)
Catheter related infection	2 (3.9 %)
Unknown origin infection	2 (3.9 %)

Data are presented as *n* (%)

COPD chronic obstructive pulmonary disease, *IPF* interstitial pulmonary fibrosis

Table 3 The cause of death in ICU

The cause	Subject (n=35)
Uncorrected respiratory failure	
Pneumonia	13 (37.1 %)
Drug-induced pneumonitis	2 (5.7 %)
Cancer progression	3 (8.6 %)
Extra-pulmonary sepsis	6 (17.1 %)
Hemoptysis	2 (5.7 %)
IPF exacerbation	1 (2.9 %)
Pulmonary embolism	1 (2.9 %)
Ventilator-associated pneumonia	5 (14.3 %)
Arrhythmia	2 (5.7 %)

Data are presented as *n* (%)

IPF interstitial pulmonary fibrosis

(49.0 %) received vasopressor treatment and 12 patients (23.5 %) received renal replacement therapy. The median duration of mechanical ventilation was 4.5 (1–80) days. The median duration of ICU stay was 7 (1–80) days.

Causes of acute respiratory failure

The most common cause of acute respiratory failure needing mechanical ventilation was pneumonia (n=24, 47.1 %). Seventeen patients (33.4 %) had microbiologically documented pneumonia. *Acinetobacter baumannii* (n=4, 23.5 %) and *Staphylococcus aureus* (n=4, 23.5 %) were the most common pathogens. The other organisms documented were *Streptococcus pneumoniae* (n=3, 17.6 %), *Pseudomonas aeruginosa* (n=2, 11.8 %), *Klebsiella pneumoniae* (n=2, 11.8 %), *Stenotrophomonas maltophilia* (n=1, 5.9 %) and *Cytomegalovirus* (n=1, 5.9 %). Eleven patients (21.5 %) had acute respiratory failure due to extra-pulmonary infection. Seven patients (13.7 %) had drug-induced pneumonitis and two patients (3.9 %) had alveolar hemorrhage, and hemoptysis and cancer progression, respectively. Other causes of respiratory failure were pulmonary embolism (n=1, 2 %), acute exacerbation of chronic obstructive pulmonary disease (n=1, 2 %) and acute exacerbation of idiopathic pulmonary fibrosis (n=1, 2 %) (Table 2).

Factors associated with adverse outcome

The ICU mortality was 68.6 % (35 out of 51) and the hospital mortality was 80.4 % (41 out of 51). Most patients died due to progression of the cause of acute respiratory failure (n=28, 80 %), while five patients (14.3 %) died due to newly acquired ventilator-associated pneumonia and two patients (5.7 %) died from arrhythmia (Table 3). ICU survivors and non-survivors were compared in Tables 4 and 5. In the unadjusted logistic regression model, ECOG PS (P=0.03), SOFA score (P=0.01) and anemia (P=0.04) were significantly associated with ICU mortality (Tables 4 and 5). However, after adjusting for age, sex, and APACHE II

Table 4 Unadjusted and adjusted odds ratio and 95 % confidence interval

variables	Survivors	Non survivors	Unadjusted OR (CI) *P* value	Adjusted OR (CI)* *P* value
Age	62.4 (37–75)	59.5 (25–87)	1.051 (0.99–1.115) P=0.101	NA
Sex (male)	13 (34.2 %)	25 (65.8 %)	1.733 (0.405–7.418) P=0.458	NA
N	15 (7–31)	17.5 (12–32)	1.106 (0.996–1.228) P=0.06	NA
Smoking	9 (32 %)	19 (68 %)	1.000 (0.998–1.003) P= 0.942	0.897 (0.997–1.003) P=0.897
Primary site			0.897 (0.194–4.151) P=0.889	0.616 (0.116–3.268) P=0.570
Lung	13 (31 %)	29 (69 %)		
Others	3 (33 %)	6 (67 %)		
Time from chemotherapy (days)	7 (3–22)	10 (5–28)	1.028 (0.989–1.069) P=0.165	1.038 (0.995–1.082) P=0.084
Use of inotropics	10 (62.5 %)	15 (43 %)	2.22 (0.66–7.278) P=0.197	2.45 (0.072–8.943) P=0.174
Poor ECOG PS*	9 (22 %)	32 (78 %)	8.296 (1.776–38.75) P=0.007	6.554 (1.283–33.48) P=0.024
SOFA	7 (3–14)	10 (5–15)	1.179 (0.975–1.426) P=0.089	1.149 (0.939–1.407) P=0.177

Data are presented as median (IQR) or *n* (%)

ECOG PS Eastern Cooperative Oncology Group Performance Scale, *SOFA* Sequential Organ Failure Assessment, *APACHE* Acute Physiology and Chronic Health Evaluation

*After adjusting for age, sex and APACHE II score, only poor ECOG PS was significantly associated with ICU mortality

score, only prechemotherapy ECOG PS≥2 [OR 6.36 (95 % CI (1.02–39.5))] remained a significant predictor of ICU mortality (Tables 4 and 5).

Discussion

To our knowledge, this is the first study conducted specifically for this population of acute respiratory failure patients requiring mechanical ventilation while undergoing ambulatory chemotherapy for solid cancer. The ICU mortality in this population was 68.6 %, while the in-hospital mortality was 80.4 %. A poor prechemotherapy ECOG PS was the most important prognostic factor of ICU mortality in this patient group.

The ICU mortality observed in this study is consistent with previous studies of large cohorts of cancer patients receiving ICU care which report mortality ranging from 50

Table 5 Unadjusted and adjusted odds ratio and 95 % confidence interval

variables	Survivors	Non survivors	Unadjusted OR (CI) *P* value	Adjusted OR (CI)[a] *P* value
Leukopenia[a]				
Yes (10)	4 (40 %)	6 (60 %)	0.621 (0.148–2.601)	0.714 (0.159–3.215)
No (41)	12 (29.3 %)	29 (70.7 %)	*P*=0.514	*P*=0.661
Anemia[b]				
Yes (27)	5 (18.5 %)	22 (81.5 %)	0.269 (0.076–0.947)	1.016 (0.947–1.091)
No (24)	11 (45.8 %)	13 (54.2 %)	*P*=0.041	*P*=0.656
Platelet (µl)	148,350	138,733	0.842 (0.258–2.752)	0.862 (0.245–3.036)
	(5,000–529,000)	(6,000–476,000)	*P*=0.842	*P*=0.817
Albumin (g/dl)	2.6 (1.9–3.5)	2.3 (1.5–3.9)	3.041 (0.916–10.095)	2.359 (0.649–8.580)
			P=0.069	*P*=0.193
Na (mmol/l)	134 (123–145)	135 (124–151)	0.951 (0.851–1.064)	0.942 (0.834–1.064)
			P=0.383	*P*=0.337
K (mmol/l)	4 (2.8–5.9)	4 (2.8–5.6)	1.247 (0.491–3.169)	1.077 (0.395–2.396)
			P=0.643	*P*=0.885
CRP (mg/dl)	21 (5.6–40)	20 (3.6–46)	1.000 (0.998–1.002)	1.000 (0.998–1.002)
			P=0.870	*P*=0.942
BUN (mg/dl)	20 (5.6–40)	24 (3.3–115)	0.994 (0.968–1.021)	0.994 (0.968–1.022)
			P=0.670	*P*=0.692
Cr (mg/dl)	1.02 (0.4–2.3)	1.07 (0.4–4.2)	0.994 (0.933–1.059)	0.994 (0.937–1.060)
			P=0.849	*P*=0.848
NT proBNP	5,972 (136–35,000)	5,833 (14–35,000)	1.000 (1.000–1.000)	1.031 (0.962–1.104)
			P=0.737	*P*=0.387
pH	7.4 (7.1–7.6)	7.3 (7.06–7.56)	0.391 (0.093–1.633)	0.261 (0.025–1.304)
			P=0.198	*P*=0.102
PCO2 (mmHg)	39 (20–93)	41 (21–128)	0.990 (0.958–1.024)	0.986 (0.952–1.022)
			P=0.577	*P*=0.445
PaO2/FiO2 (mmHg)	132 (68–193)	110 (11–270)	1.316 (0.396–4.380)	1.391 (0.391–4.953)
			P=0.654	*s*=0.611

Data are presented as median (IQR) or *n* (%)

[a]Leukopenia define as WBC< 1,000 cells/mm^3

[b]Anemia is defined as hemoglobin <12 (g/dl)

to 83 % [1, 5, 13, 14, 33, 34]. The mortality of cancer patients needing ICU care may vary according to patient populations, level of ICU support, severity of acute illness, and ICU policies. The relatively high ICU mortality in this study may be explained by several reasons. First, only acute respiratory failure patients needing invasive mechanical ventilator support were included. ICU cancer patients treated by invasive mechanical ventilation consistently show an extremely low survival rate [34–38]. Second, it is likely that the reasons for initiating mechanical ventilation may also have influenced the outcome. Patients with sepsis or shock-related and acute hypoxia-related respiratory failure have a worse prognosis compared to those with postoperative acute respiratory failure or cardiogenic pulmonary edema [1, 13, 17]. In this study, the two main reasons for mechanical ventilation were respiratory failure due to pneumonia and sepsis, and there were no patients with postoperative acute respiratory failure or cardiogenic pulmonary edema.

The most important finding in this study was that the ECOG PS within the preceding week before chemotherapy presented a simple, but useful, predictor of outcome in solid cancer patients with acute respiratory failure. ECOG PS (≥2) before last chemotherapy was the only statistically significant predictor of mortality after adjusting for age, sex, and APACHE II. This is consistent with other studies that reported prognostic factors in cancer patients admitted to the ICU. Christodoulou et al. [39] reported that an ECOG PS score of 3 or 4 prior to hospitalization was found to be a simple negative predictor of the short term outcome of cancer patients with solid tumors admitted to the ICU. Soares et al. [33] also demonstrated the impact of ECOG PS score on hospital mortality in general cancer patients admitted to the ICU.

Based on the results of this study, 19.6 % had ECOG PS 0 or 1 and 80.4 % had ECOG PS 2 or 3. Even though the mortality of the patients with ECOG PS ≥2 was higher than that of the patients with ECOG PS ≤1 (78 % vs 30 %), we still cannot conclude that ECOG PS ≤1 is prerequisite for the ICU admission of critically ill solid cancer patients undergoing ambulatory chemotherapy for acute respiratory failure. However, the prechemotherapy ECOG PS score may be useful for clinicians, as an aid in discussing treatment options with patients and their families.

In our patients, the cause of respiratory failure was pneumonia in about half of the patients. The bacteriology in this study was very similar to that of a healthcare-associated pneumonia, and included organisms such as *A. baumannii*, *S. aureus*, *P. aeruginosa*, and *K. pneumoniae*. In fact, 76 % of identified organisms were either methicillin-resistant *S. aureus* or enteric gram-negative bacilli. In these patients, empiric antibiotic therapy should include coverage for multi-resistant gram-negative bacilli and possibly methicillin-resistant *S. aureus* if respiratory secretions are positive for gram-positive cocci.

This study has substantial limitations. First, given its retrospective observational design, we did not have any data regarding patients who were not referred to the ICU, possibly introducing significant selection bias. Second, this study was conducted at a single center with a relatively small number of patients which limits generalization of our findings.

In conclusion, we found that the outcome of patients with acute respiratory failure needing mechanical ventilation during ambulatory chemotherapy for solid cancer was poor and that prechemotherapy ECOG PS was an independent predictor of mortality. Prechemotherapy ECOG PS should be incorporated into the discussion of treatment options with patients and their families in this patient group.

Conflict of interest None to declare.

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