Outcomes of cancer therapy administered to treatment-naïve lung cancer patients in the intensive care unit

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Abstract

**Objectives:** Therapy outcomes for newly diagnosed, critically ill lung cancer patients have seldom been evaluated. This study evaluated therapy outcomes for treatment-naïve lung cancer patients in the intensive care unit (ICU).

**Materials and Methods:** Patients were excluded if they had previously received lung cancer treatment, such as systemic chemotherapy, targeted therapy, radiotherapy, or surgical lung resection before ICU admission. The therapeutic strategies for the treatment-naïve patients were determined while they were in the ICU. The patients’ demographic data, clinical outcomes, and treatment-related toxicities were analyzed.

**Results:** Newly diagnosed lung cancer patients (n = 72) who did not receive any anticancer treatment before ICU admission were included. Most patients had locally advanced disease, and 61 (84.7%) required intensive care due to cancer-related events. In the ICU, 24 (33.3%) patients received chemotherapy, 24 (33.3%) received epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy and 24 (33.3%) received best supportive care (BSC). Patients receiving chemotherapy or EGFR-TKIs in the ICU demonstrated better ICU (p = 0.011) and in-hospital (p = 0.034) survival than those receiving BSC only. Among patients requiring mechanical ventilation, those receiving chemotherapy had higher weaning rates than those receiving EGFR-TKIs or BSC (p = 0.002). In multivariate analysis, receipt of chemotherapy (hazard ratio [HR], 0.443; p = 0.083) and mechanical ventilation (HR, 0.270; p = 0.022) were significantly associated with longer ICU survival after adjusting for clinical factors.

**Conclusions:** Anticancer therapy in the ICU might provide better short-term ICU survival for treatment-naïve, critically ill lung cancer patients.

Key words: Treatment-naïve lung cancer; Intensive care unit; Non-small cell lung cancer; Epidermal growth factor receptor; Tyrosine kinase inhibitor; Small cell lung cancer; Best supportive care

Introduction

Lung cancer remains a leading cause of cancer-related mortality among men and women, worldwide [1]. Patients may present in a critically ill state due to malignancy-related complications or due to underlying co-morbidities. Such patients, admitted to the intensive care unit (ICU), have mortality rates of 42–73% [2–6]. Although critical care advances have improved the survival of these critically ill patients,
not all lung cancer patients have derived benefit from intensive care [7]. Several retrospective studies identified factors associated with the poor ICU outcomes for these patients, including requiring mechanical ventilation [3,4,6,8–10], poor pre-event performance status (PS) [2,6,11], high admission Acute Physiologic and Chronic Health Evaluation (APACHE) III scores with vasopressor use [8], and refractory disease [4,6,8,12]. Nevertheless, treatment outcomes and mortality predictors remain unclear for treatment-naïve lung cancer patients requiring intensive care.

Treatment of locally advanced and metastatic lung cancers, including targeted therapy, chemotherapy, and best supportive care (BSC), are usually administered according to age, patient PS, cancer cell type, and molecular status [13,14]. Patients with extremely poor PS, including critically ill patients, are usually excluded from anticancer therapy prospective clinical trials and their first-line treatment options are usually limited to BSC [13]. Thus, the role of cancer therapies for treatment-naïve, critically ill lung cancer patients remain unclear.

Only a few reports have focused on the management of treatment-naïve lung cancer patients admitted to the ICU due to cancer-related complications or other critical conditions [15, 16]. Therefore, treatment strategies for newly diagnosed, treatment-naïve lung cancer patients in the ICU have never been compared. The present study retrospectively assessed the clinical factors and management (including anticancer therapies and BSC) outcomes for treatment-naïve, lung cancer patients under intensive care. We also investigated the impact of different treatment strategies, and their related side effects, on clinical outcomes.

**Material and Methods**

**Study design and patients**

We retrospectively reviewed the electronic medical records of newly diagnosed lung cancer inpatients in the ICUs of National Taiwan University Hospital (NTUH), Taipei, and the NTUH Yunlin-branch, between January 1, 2001 and September 1, 2013. Patients were excluded if they had received any lung cancer treatment, including systemic chemotherapy, targeted therapy, radiotherapy, or surgical lung resection, before ICU admission. Patients admitted to medical or surgical ICUs due to complications arising from previous anticancer therapies (such as chemotherapy and targeted therapy) or postoperative care were also excluded. For patients meeting the inclusion criteria, but with multiple ICU admissions, only the first admission was included in the analysis. The management and treatment strategies (including BSC, chemotherapy, and target therapy) for treatment-naïve lung cancer patients in the ICU were made by intensivists, often after discussion with oncologists. Patients who had never smoked or who had smoked < 100 cigarettes in their lifetime were categorized as non-smokers [17]. The study protocol was approved by the hospitals’ Research Ethics Committees and the need for informed consent was waived.

**Data collection and outcomes**

After enrollment, demographics and baseline characteristics such as age, sex, co-morbidity, pre-ICU PS (bedridden or non-bedridden), ICU admission diagnosis, and illness severity upon ICU admission (APACHE II score [18]) were recorded for all patients. Other clinical data, including cancer stage [19], lung cancer histologic type (non-small cell lung cancer [NSCLC] or small cell lung cancer [SCLC]) [20], molecular status, and metastases sites were recorded. Extensive cancer disease was defined as stage IIIIB or IV for NSCLC and as extensive-stage for SCLC [19]. We also classified the primary reasons for ICU admission into non-lung cancer-related (e.g., severe sepsis/septic shock, pneumonia, chronic obstructive pulmonary disease with acute exacerbation, cardiac arrhythmia and acute myocardial infarction) and lung cancer-induced (e.g., tumor-related critical airway and obstructive pneumonitis, superior vena cava syndrome, and pulmonary embolism) events.

The lung cancer therapy regimens in the ICU and treatment-related toxicities were recorded [21]. Patients were classified according to their management into the chemotherapy, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs), or BSC (no specific cancer therapy) group. Data regarding ICU management of the patients, such as the use of mechanical ventilation, hemodialysis, vasopressors use, and do-not resuscitation (DNR) orders, were also collected. Additionally, the main study outcomes and the lengths of ICU and hospital stays were also assessed. Survival times were calculated as the interval between the date of ICU/hospital admission and the death date, last follow-up date, or the final follow-up prior to September 2013, whichever came first. We also analyzed the impact of clinical factors associated with study outcomes.

**Statistical analysis**

All categorical variables were analyzed using Pearson’s χ² tests, except where a small sample size (< 5) required the use of Fisher’s exact test. One-way
analysis of variance was used to analyze differences in patient characteristics among the three treatment strategy groups. The ICU and hospital survival times were performed using the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses for ICU and hospital survival were performed using Cox proportional hazards model. The hazard ratios (HRs), 95% confidence intervals (CIs), and p-values are reported. Statistical significance was set at a two-sided p < 0.05. All analyses were performed using SPSS version 18.0 (SPSS, Chicago, IL).

Results

Patient characteristics

Table 1 displays the baseline characteristics of the 1181 treatment-naive lung cancer patients treated in the intensive care unit. The mean patient age was 68.8 years, and 56 (77.8%) were male. NSCLC was diagnosed in 58 (80.6%) patients (stage IIA [n = 1], stage IIB [n = 6], or stage IV [n = 51]) and SCLC was diagnosed in 14 (19.4%) patients (all extensive stage). Among the advanced lung cancer patients, 49 (68.1%) had at least two metastatic sites. A positive EGFR mutation was identified in only two adenocarcinoma patients (an exon 19 deletion and an L858R mutation); the remainder were either wild type (n = 15) or had an unknown (n = 55) mutation status. The mean APACHE II scores were 20.6 in the chemotherapy group and 21.2 in the EGFR-TKI group, not significantly higher than for the BSC group (17.9; p = 0.295). A total of 47 (65.3%) patients were smokers, with a significantly higher proportion of patients in the chemotherapy group being smokers (p = 0.016).

| Table 1. Baseline characteristics of treatment-naive lung cancer patients treated in the intensive care unit |
|---------------------------------------------------------------|
| **Number** | **All patients** | **Best supportive care** | **Chemotherapy** | **EGFR-TKI** | **p-value** |
|-----------|----------------|-------------------------|----------------|------------|----------|
| **Age, years (mean ± SD)** | 68.8 ± 12.8 | 70.7 ± 13.4 | 70.5 ± 10.0 | 65.1 ± 14.4 | 0.238 |
| **Sex, male (n [%])** | 48 (66.7) | 17 (70.8) | 18 (75.0) | 13 (54.2) | 0.269 |
| **APACHE II score (mean ± SD)** | 19.9 ± 7.8 | 17.9 ± 8.8 | 20.6 ± 5.9 | 21.2 ± 8.4 | 0.295 |
| **Smoking (n [%])** | 47 (65.3) | 12 (50.0) | 21 (87.5) | 14 (58.3) | 0.016 |
| **Pre ICU performance (n [%])** |  |  |  |  |
| Non-bedridden | 61 | 18 (75) | 22 (91.7) | 21 (87.5) | 0.248 |
| Bedridden | 11 | 6 (25) | 2 (8.3) | 3 (12.5) | 0.248 |
| **Histologic type** |  |  |  |  |
| SCLC (n [%]) | 14 (19.4) | 3 (12.5) | 11 (45.8) | 0 (0) | < 0.001 |
| NSCLC (n [%]) | 58 (80.6) | 21 (87.5) | 13 (54.2) | 24 (100) | 0.100 |
| Adenocarcinoma | 45 | 17 | 6 | 22 | 0.001 |
| Squamous cell carcinoma | 8 | 3 | 4 | 1 | 0.001 |
| NSCLC-NOS | 2 | 0 | 2 | 0 | 0.001 |
| Sarcomatoid carcinoma | 2 | 0 | 1 | 1 | 0.001 |
| Pleomorphic carcinoma | 1 | 1 | 0 | 0 | 0.001 |
| **Clinical stage** |  |  |  |  |
| I-IIIA or limited stage (n [%]) | 1 (1.4) | 1 (4.2) | 0 (0) | 0 (0) | 0.363 |
| IIIB-IV/extensive stage (n [%]) | 71 (98.6) | 23 (95.8) | 24 (100) | 24 (100) | 0.363 |
| **EGFR mutation (n [%])** |  |  |  |  |
| Wild type or not-available | 70 (97.2) | 23 (95.8) | 24 (100) | 23 (95.8) | 0.598 |
| Mutation | 2 (2.8) | 1 (4.2) | 0 (0) | 1 (4.2) | 0.598 |
| **Metastasis sites** |  |  |  |  |
| 0–1 (n [%]) | 23 (31.9) | 6 (25) | 13 (54.2) | 4 (16.7) | 0.014 |
| > 2 (n [%]) | 49 (68.1) | 18 (75) | 11 (45.8) | 20 (83.3) | 0.014 |
| **Co-morbidities** |  |  |  |  |
| Diabetes mellitus (n [%]) | 20 (27.8) | 7 (29.2) | 8 (33.3) | 5 (20.8) | 0.616 |
| Hypertension (n [%]) | 30 (41.7) | 10 (41.7) | 10 (41.7) | 10 (41.7) | 1.000 |
| COPD (n [%]) | 20 (27.8) | 8 (33.3) | 7 (29.2) | 5 (20.8) | 0.616 |
| Chronic kidney disease (n [%]) | 19 (26.4) | 5 (20.8) | 7 (29.2) | 7 (29.2) | 0.751 |
| Cardiovascular disease (n [%]) | 12 (16.7) | 5 (20.8) | 4 (16.7) | 3 (12.5) | 0.741 |

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; COPD, chronic obstructive pulmonary disease; EGFR, epidermal growth factor receptor; ICU, intensive care unit; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; TKI, tyrosine-kinase inhibitor; SCLC, small cell lung cancer; SD, standard deviation

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### Table 2. Characteristics and outcomes of treatment-naive lung cancer patient treated in an intensive care unit

|                                | All patients | Best supportive care | Chemotherapy | EGFR-TKI | p-value |
|--------------------------------|--------------|----------------------|--------------|----------|---------|
| **Number**                     | 72           | 24                   | 24           | 24       | 0.041   |
| **Primary reasons for ICU admission** |              |                      |              |          |         |
| Non-lung cancer related events (n [%]) |              |                      |              |          |         |
| Pneumonia with respiratory failure (n) | 3 (15.3) | 0 (0)                | 0 (0)        | 2 (27.8) | 0.180   |
| Septic shock (n)               | 2 (9.2)      | 0 (0)                | 0 (0)        | 2 (27.8) | 0.084   |
| COPD with acute exacerbation (n) | 1 (4.5)      | 1 (4.2)              | 0 (0)        | 1 (12.5) | 0.479   |
| Acute coronary syndrome (n)    | 1 (4.5)      | 1 (4.2)              | 0 (0)        | 1 (12.5) | 0.385   |
| Congestive heart failure (n)   | 1 (4.5)      | 1 (4.2)              | 0 (0)        | 1 (12.5) | 0.491   |
| Cardiac arrest (n)             | 1 (4.5)      | 1 (4.2)              | 0 (0)        | 1 (12.5) | 0.041   |
| Lung cancer-related events (n [%]) | 61 (84.7) | 19 (29.2)            | 23 (39.5)    | 19 (79.2) | 0.002   |
| Obstructive pneumonitis (n)    | 27           | 9 (34.8)             | 13 (52.6)    | 5 (20.8) | 0.491   |
| Cardiac tamponade (n)          | 9 (34.8)     | 6 (23.8)             | 2 (8)        | 2 (8)    | 0.030   |
| Massive malignant pleural effusion (n) | 6 (23.8) | 2 (8)                | 2 (8)        | 2 (8)    | 0.030   |
| Critical airway (n)            | 7 (29.2)     | 1 (4.2)              | 4 (16)       | 2 (8)    | 0.030   |
| Lymphangitic carcinomatosis (n) | 7 (29.2)     | 0 (0)                | 2 (8)        | 5 (20.8) | 0.030   |
| Superior vena cava syndrome (n) | 2 (8)        | 1 (4.2)              | 1 (4.2)      | 5 (20.8) | 0.030   |
| Pulmonary embolism (n)         | 3 (11.8)     | 0 (0)                | 1 (4.2)      | 2 (8)    | 0.030   |
| Mechanical ventilator use (n [%]) | 47 (65.3) | 11 (45.8)            | 19 (79.2)    | 17 (70.8) | 0.385   |
| Weaning off MV (n [%])         | 12 (26.7)    | 1/11 (9.1)           | 10/19 (52.6) | 1/17 (5.9) | 0.002   |
| Acute kidney injury (n [%])    | 27 (37.5)    | 7 (29.2)             | 11 (48.8)    | 9 (37.5) | 0.491   |
| Sepsis in ICU (n [%])          | 54 (75.0)    | 13 (54.2)            | 20 (83.3)    | 20 (83.3) | 0.030   |
| Anticancer treatment related   | 20 (27.8)    | -                    | 11 (45.8)    | 9 (37.5) | 0.385   |
| Vasopressor use (n [%])        | 31 (43.1)    | 11 (45.8)            | 8 (33.3)     | 12 (50.0) | 0.479   |
| DNR order in ICU (n [%])       | 43 (60.7)    | 17 (70.8)            | 10 (41.7)    | 16 (66.7) | 0.084   |
| ICU mortality (n [%])          | 31 (43.1)    | 12 (50)              | 6 (25)       | 13 (54.2) | 0.088   |
| In-hospital mortality (n [%])  | 46 (63.9)    | 15 (62.5)            | 14 (58.3)    | 17 (70.8) | 0.656   |

Abbreviations: COPD, chronic obstructive pulmonary disease; DNR, do not resuscitate; EGFR, epidermal growth factor receptor; ICU, intensive care unit; MV: mechanical ventilation; TKI, tyrosine-kinase inhibitor; SD, standard deviation

**Main reasons for ICU admission**

The reasons for ICU admission are listed in Table 2. Cancer-induced events were the main reasons for ICU admission (61/72, 84.7%), including obstructive pneumonitis (n = 27), cardiac tamponade (n = 9), massive pleural effusion (n = 7), lymphangitic carcinomatosis (n = 7), superior vena cava syndrome (n = 2), and pulmonary embolism (n = 3). The other 11 patients were admitted to the ICU due to non-cancer related events. Diagnoses of pneumonia with respiratory failure and septic shock were the most common reasons for ICU admission.

**ICU patient management**

After ICU admission, 48 patients (66.7%) received systemic anticancer therapy, with 24 patients receiving EGFR-TKI therapy (gefitinib or erlotinib) and 24 patients receiving other first-line chemotherapies (Table 3). One squamous cell carcinoma patient and two SCLC patients in the chemotherapy group received concurrent chemotherapy and radiotherapy.

Forty-seven (65.3%) patients demonstrated acute respiratory failure and received mechanical ventilation upon admission, including 11 (45.8%) in the BSC group, 19 (79.2%) in the chemotherapy group, and 17 (70.8%) in the EGFR-TKI group (p = 0.041). Ten (8 SCLC patients and 2 NSCLC patients) of the 19 (52.6%) patients in the chemotherapy group were successfully weaned off mechanical ventilation in the ICU. The chemotherapy group had a higher weaning rate than did the EGFR-TKI (5.9%) or BSC (9.1%) group (p = 0.002).

More sepsis events were noted in the treatment groups (20[83.3%]) than in the BSC group (13[54.2%]) with a p value 0.030. Nevertheless, the anticancer treatment related sepsis events were similar in chemotherapy group (11[45.8%] and EGFR-TKI group (9[37.5%]) (p=0.385) (Table 2). Thirty-one (43.1%) of the ICU patients received vasopressors in the ICU, while with similar proportions of cases in the treatment and BSC groups (p = 0.479). DNR orders were provided by two-thirds of the patients during their ICU course, and were more commonly observed in the BSC and EGFR-TKI groups (p = 0.084).

**Clinical outcomes**

During their ICU course, 6 (25%) patients in the chemotherapy group, 13 (54.2%) in the EGFR-TKI group, and 12 (50%) in the BSC group (p = 0.088) died. The median ICU survival times were 48, 28, and 11 days for patients in the chemotherapy, EGFR-TKI, and BSC groups, respectively (p = 0.011) (Figure 1). The in-hospital mortality rate was 58.3% (14/24) for the chemotherapy group, 70.8% (17/24) for the targeted therapy group, and 62.5% (15/24) for the BSC group (p = 0.656). The median in-hospital
survival times were 48, 39, and 19 days for patients in the chemotherapy, EGFR-TKI, and BSC groups, respectively (p = 0.034) (Figure 2). There were no significant differences in ICU survival (28 days vs. 48 days, p = 0.374) or in-hospital survival (39 days vs. 48 days, p = 0.269) between the EGFR-TKI and chemotherapy groups.

After adjusting for clinical factors and patient management (sex, smoking status, histologic type, metastasis sites, mechanical ventilator use, systemic anticancer therapy, and DNR orders), the multi-variant analysis for ICU survival showed that patients receiving chemotherapy (HR, 0.202; p = 0.012) and mechanical ventilation (HR, 0.270; p = 0.022) were significantly associated with longer ICU survivals (Table 3). The multi-variant analysis for hospital survival showed that patients receiving chemotherapy (HR, 0.443; p = 0.083) appeared to have relatively longer hospital survival than BSC group. However, DNR orders (HR, 4.516; p = 0.001) were significantly associated with shorter hospital survival times.

Table 4 shows the treatment side effects and regimens. Patients who received chemotherapy, especially platinum-based regimens, had higher risks of grade 3 or 4 neutropenia (10/24, 41.6%) and thrombocytopenia (5/24, 20.8%) than did patients in the EGFR-TKI group. Nevertheless, three patients (3/24, 12.5%) in the EGFR-TKI group had suspicious gefitinib-related interstitial pneumonitis.

**Discussion**

This is the first study to specifically focus on the outcomes of different anticancer strategies of treatment-naive lung cancer (including SCLC and NSCLC) patients admitted to the ICU. Therapy involving either chemotherapy or EGFR-TKIs might provide better ICU and in-hospital survival times than BSC for these patients. Moreover, among patients requiring mechanical ventilation, those who received chemotherapy in the ICU seemed to have higher weaning rates than did those receiving EGFR-TKIs and BSC. However, patients receiving chemotherapy and targeted therapy in the ICU also have higher risks of treatment-related side effects, but not mortality, than those receiving BSC.
Table 3. Multivariate analysis of clinical factors associated with intensive care unit survival of treatment-naïve lung cancer patients

| Clinical factors | No. of patients | Median ICU survival (days) | Univariate analysis | Multivariate analysis | Median Hospital survival (days) | Univariate analysis | Multivariate analysis |
|------------------|-----------------|-----------------------------|---------------------|----------------------|-----------------------------|---------------------|----------------------|
| Anticancer therapy |                 |                             |                     |                      |                             |                     |                      |
| Best supportive care | 24              | 11                          | 0.011               | 1.000                | 19                          | 0.034               | 1.000                |
| EGFR-TKI          | 24              | 28                          | 0.394 (0.143–1.085) | 0.072                | 39                          | 0.610 (0.263–1.412) | 0.248                |
| Chemotherapy      | 24              | 48                          | 0.202 (0.058–0.699) | 0.012                | 48                          | 0.443 (0.177–1.111) | 0.083                |
| Gender            |                 |                             |                     |                      |                             |                     |                      |
| Female            | 16              | 59                          | 0.063               |                      | 54                          | 0.159               |                      |
| Male              | 56              | 24                          | 3.310 (0.771–14.209) | 0.107                | 37                          | 2.397 (0.778–7.383) | 0.128                |
| Smoking status    |                 |                             |                     |                      |                             |                     |                      |
| Never smoker      | 25              | 39                          | 0.286               |                      | 48                          | 0.478               |                      |
| Smoker            | 47              | 23                          | 1.445 (0.463–4.507) | 0.526                | 34                          | 1.069 (0.441–2.590) | 0.883                |
| Histologic type   |                 |                             |                     |                      |                             |                     |                      |
| SCLC              | 14              | 23                          | 0.993               |                      | 40                          | 0.377               |                      |
| NSCLC             | 58              | 28                          | 0.728 (0.225–2.357) | 0.597                | 38                          | 0.804 (0.317–2.039) | 0.645                |
| Metastasis sites  |                 |                             |                     |                      |                             |                     |                      |
| 0–1               | 23              | 23                          | 0.586               |                      | 45                          | 0.372               |                      |
| 2–4               | 49              | 27                          | 1.243 (0.489–3.157) | 0.648                | 37                          | 1.581 (0.753–3.321) | 0.226                |
| Mechanical ventilator use |     |                             |                     |                      |                             |                     |                      |
| No                | 25              | 12                          | 0.038               |                      | 40                          | 0.824               |                      |
| Yes               | 47              | 28                          | 0.270 (0.088–0.827) | 0.022                | 38                          | 0.495 (0.206–1.188) | 0.115                |
| Sepsis event      |                 |                             |                     |                      |                             |                     |                      |
| No                | 19              | 11                          | 0.530               |                      | 13                          | 0.037               |                      |
| Yes               | 53              | 27                          | 5.519 (0.489–54.453) | 0.172                | 34                          | 3.589 (0.834–15.443) | 0.086                |
| DNR order in ICU  |                 |                             |                     |                      |                             |                     |                      |
| No                | 29              | 54                          | 0.020               |                      | 101                         | <0.001              |                      |
| Yes               | 43              | 22                          | 2.302 (0.584–9.078) | 0.234                | 26                          | 4.516 (1.792–11.382) | 0.001                |

Abbreviations: CI: confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; ICU, Intensive care unit; NSCLC, non-small cell lung cancer; TKI, tyrosine-kinase inhibitor; SCLC, small cell lung cancer; DNR, do not resuscitate

Table 4. Chemotherapy and targeted therapy for 48 treatment-naïve lung cancer patients treated in the intensive care unit

| Cancer cell type | Side effects recorded in ICU | Median ICU hospitalization (days) | Univariate analysis | Multivariate analysis |
|------------------|-----------------------------|----------------------------------|---------------------|---------------------|
| SCLC (n = 11)    | Neutropenia Grade 3/4 | Anemia Grade 3/4 | Thrombocytopenia Grade 3/4 | GI toxicity Grade 3/4 | Skin toxicity Grade 3/4 | Acute kidney injury | Treatment-related IP | Death in ICU | Death in hospital |
|                 |                            |                            |                    |                     |                     |                      |                    |             |                   |
| Etoposide + cisplatin (n = 6) | 5 | 1 | 3 | 0 | 2 | 0 | 0 | 0 | 0 | 3 | 5 |
| Etoposide + carboplatin (n = 5) | 4 | 1 | 4 | 1 | 2 | 2 | 0 | 0 | 0 | 0 | 1 |
| Etoposide + vinristine (n = 1) | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Carboplatin + pemetrexed (n = 1) | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Carboplatin + pemetrexed + bevacizumab (n = 1) | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Gemcitabine (II)/cisplatin + pemetrexed (n = 1) | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Cisplatin + gemcitabine (n = 1) | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Cisplatin + docetaxel (n = 2) | 0 | 2 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 |
| Paclitaxel/gemcitabine (n = 2) | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Docetaxel (n = 2) | 0 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Gemcitabine (n = 1) | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Vinorelbine (n = 1) | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| EGFR-TKI therapy (n = 24) | Gefitinib (n = 16) | 0 | 16 | 0 | 0 | 0 | 1 | 0 | 0 | 3 | 8 |
| Erlotinib (n = 6) | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Gefitinib/erlotinib (n = 2) | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |

Abbreviations: EGFR, epidermal growth factor receptor; ICU, Intensive care unit; IP, interstitial pneumonitis; GI, Gastrointestinal; NSCLC, non-small cell lung cancer; TKI, tyrosine-kinase inhibitor; SCLC, small cell lung cancer

Decisions regarding the type and timing of anticancer therapy for the subject subpopulation are extremely complex, and only limited data exist regarding their impact [15,16,22,23]. Generally, lung cancer patients with poor PS are precluded from chemotherapy; BSC or palliative care is usually considered for these patients [13,24]. A few studies have suggested that immediate chemotherapy may be
beneficial for selected critically ill cancer patients with newly diagnosed malignancies [16,25,26]. For example, chemotherapy might benefit selected newly diagnosed SCLC patients with cancer-related respiratory failure in the ICU, allowing relatively early extubation and ICU discharge [15].

In the present study, multivariate analysis revealed that lung cancer patients receiving chemotherapy might have longer ICU and in-hospital survivals than patients receiving BSC, regardless of histologic type or disease metastasis. Mechanical ventilation was also more common among patients in the treatment groups and was associated with longer ICU survival. In contrast, patients with DNR orders were more common in the BSC group than in the chemotherapy group and were associated with diminished ICU and hospital survival. Lung cancer patients receiving various first-line chemotherapies, in the ICU, also demonstrated better weaning rates than those receiving EGFR-TKIs and only BSC. The higher weaning rate associated with chemotherapy might be attributed to the highly chemoresponsive characteristics of treatment-naïve SCLC patients (n=8) and some NSCLC patients (n=2), similar to previously reported indications that combined full-code management and cancer chemotherapy might have short-term survival benefits for selected lung cancer patients [16,24−27]. Further study is warranted to evaluate the impact of chemotherapy and ICU support on long-term outcomes, quality of life, and cost effectiveness for this patient subgroup.

Patients with poor PS who receive chemotherapy also have higher risks of treatment-related toxicities [28]. We found that the most common grade 3 or 4 toxic effects noted in the chemotherapy group were neutropenia (41.6%), thrombocytopenia (20.8%), and gastrointestinal toxicity (20.8%), similar to the general population of patients undergoing platinum-based chemotherapy for NSCLC [29] and SCLC [30]. The optimal chemotherapy regimen and dose for critically ill lung cancer patients has not been previously evaluated, and prospective clinical trials are needed to clarify the present findings.

Although there are studies reporting the poor prognosis of cancer patients requiring intensive care and mechanical ventilation support [8-12], based on the previous reports [15−16,25-26] and our findings, we suggest that treatment-naïve lung cancer patients could be considered as a distinct subgroup which might benefit from immediate chemotherapy, especially those with highly chemosensitive tumor (such as SCLC) presenting with cancer-related organ failures. Besides, NSCLC patients with wild-type EGFR or unknown mutation status, chemotherapy could be an effective treatment with relatively rapid response compared with targeted therapy [13].

Identifying the genetic mutation present in NSCLC patients is critical for targeted therapies [31,32], which are effective (improved progression-free survival, response rates, and quality of life relative to chemotherapy) in lung adenocarcinoma patients harboring the EGFR mutation [33,34]. Previous studies reported that first-line EGFR-TKIs provide greater clinical benefit to extremely poor PS NSCLC patients with short life expectancies than does BSC [35,36]. Others indicated that targeted molecular agents could be considered for use in cancer patients with extremely poor PS, even when they are receiving critical care [23]. In our study, critically ill lung cancer patients receiving EGFR-TKIs had better ICU and hospital survival than did BSC patients. Furthermore, significant differences in ICU and hospital survivals were not noted between the EGFR-TKI and chemotherapy groups. This observation might be attributed to the heterogeneity of lung cancer patients (SCLC and NSCLC patients) in the chemotherapy group and that most EGFR-TKI group NSCLC patients had wild type EGFR or an unknown molecular status. However, only one patient harboring positive EGFR mutation (Exon 19 Deletion) who required mechanical ventilation in EGFR-TKIs group was liberated from MV support and the majority of patients (16 of 17) in EGFR-TKI group harboring wild type EGFR mutation or an unknown molecular status who required MV support all were failure to wean from mechanical ventilation. These results were consistent with Hsia et al [37] that EGFR-TKIs for stage IV NSCLC patients requiring MV did not lead a better weaning outcome. In addition, three patients (3/24, 12.5%) in the EGFR-TKI group demonstrated gefitinib-related interstitial pneumonitis, consistent with previous reports that patients with poor PS might be more prone to drug toxicity than those with good PS, even in patients receiving targeted agents [38].

In this study, we were unable to determine the molecular mutation status of all patients due to their vulnerability to the invasive specimen collection procedures and possible some rare EGFR mutations could not be detected in the early period of targeted therapy era without sensitive detection methods (such as next-generation sequencing) [39-40]. Since this is a retrospective study that we could not clearly identify the decision criteria of using EGFR-TKIs for critically ill NSCLC patients without EGFR mutations. We supposed that clinicians might expect the benefits of EGFR-TKIs on the status of nonsmokers and non-squamous NSCLC, East Asian patients [41] with possible undetected less common EGFR mutations [39,40].
In our study, one patient with EGFR mutation-positive NSCLC received gefitinib had partial response and successfully weaned from MV and the other EGFR mutation-positive patient received best supportive care. In contrast, we found that up to 54.2% (13 of 24) patients in EGFR-TKI group with wild type EGFR mutation or unknown mutation status stopped using EGFR-TKIs due to disease progression and treated related interstitial pneumonitis. Only 2 patients with wild type EGFR mutation received EGFR-TKIs had partial response and one patient with an unknown mutation status had stable disease. Thus, the strategy of administering EGFR-TKIs to critically ill NSCLC patients should be carefully interpreted with only limited evidences [23,35-37]. Our findings suggest EGFR-TKIs therapy for NSCLC patients should be used according to the molecular status even under critical condition, which would be a better choice [13, 33-35]. Further research is warranted to evaluate the impact of various targeted therapies for critically ill NSCLC patients with known mutation status.

In real-world practice, the risks and benefits of administrating anticancer therapies for treatment-naïve, lung cancer patients requiring intensive care usually be evaluated by oncologists and intensivists to identify the patients who are most likely to have favorable outcomes. Besides, the further communication among medical team and the patients or the families is also very important, which especially focuses on informing the possible complications and discussing the satisfaction of their long-term quality of life [42]. Based on the previous studies [15,16,22-27,33-38,42] and our findings, we suggest that treatment-naïve lung cancer can be treated with chemotherapy under critical condition for some selected patients, particularly those with SCLC or wild-type EGFR/unknown mutation status NSCLC and patients who required MV support but without DNR order. In addition, we also suggest that EGFR-TKIs could be only considered for the critically ill lung cancer patients with positive EGFR mutations.

The present study has several limitations. First, we analyzed a small number of highly selected, critically ill lung cancer patients with multiple complex confounding factors in a single-center, observational study. Thus, generalization of our findings will require further large-scale investigation. Second, data from patients with various types of lung cancer were pooled, possibly clouding the separate chemotherapeutic benefits for critically ill NSCLC and SCLC patients. Third, the benefit of anticancer therapies in ICU should be cautiously interpreted because of the retrospective nature of this study with selection bias and the possible treatment related adverse events may have been missed from the coding problems. Fourth, we could not evaluate patient clinical responses following treatment, due to their high mortality rates.

Conclusions

In conclusion, for newly diagnosed, critically ill lung cancer patients, chemotherapy and targeted therapy might provide short-term survival benefits and might be considered for selected patients. Further studies are needed to evaluate the benefits of combined ICU management and immediate anticancer therapy for treatment-naïve lung cancer patients.

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Competing Interests

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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