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Tyrosine kinase inhibitors for acute respiratory failure due to non-small-cell lung cancer involvement in intensive care unit

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To the Editor:

Lung cancer remains the main cause of death due to cancer in occidental countries ¹ and the most common cause of solid cancer that requires admission to the intensive care unit (ICU) ². Patients with advanced-stage of non-small-cell lung cancer (NSCLC) have high mortality rates in ICU ^{2,3}. In the last two decades, targeted therapies revolutionized the treatment of patients with lung cancer outside the ICU. Since the outbreak of Tyrosine Kinase Inhibitors (TKI) as effective agents for NSCLC with an Epidermal Growth Factor Receptor (EGFR) mutation, the median overall survival for these patients exceed 3 years ⁴. Unlike cytotoxic chemotherapy, the fast efficacy and the lower toxicity of targeted therapies led some oncologists and intensivists to use them as rescue therapy for ICU patients ^{3,5-7} leading to the so-called Lazarus syndrome ⁸. We sought to investigate the outcomes of patients with NSCLC involvement responsible for acute respiratory failure and for whom TKI agents were initiated in ICU.

Methods

We performed a national multicenter retrospective case series with the participation of the Groupe de Recherche en Réanimation Respiratoire en Onco-Hématologie. Patients with NSCLC admitted to the ICU for acute respiratory failure due to NSCLC involvement between 2009 and 2019 were included in the study if a TKI was initiated during ICU stay. Cases were identified using hospital-pharmacies records. We collected demographic and clinical data in charts. All charts were reviewed to confirm NSCLC accountability in the acute respiratory failure. Vital status was assessed at the time of study completion (August 2019). The primary outcome was overall survival 90 days after ICU admission, estimated by the Kaplan-Meier method. Exploratory univariate analysis was performed to seek potential factors of ICU survival. Ethical committee of Avicenne Hospital approved the study (CLEA-2018-66).

Results

Thirty-two patients admitted to a total of 14 ICUs throughout France were included. Patients' characteristics are presented in Table 1. Twenty-one (66%) had never smoked. The most frequent histological type was adenocarcinoma (n=23, 72%) and a majority had metastatic cancer (n =22, 69%) corresponding to Stage IV lung cancer. The remaining 10 (31%) patients had Stage III lung cancer. Among the 32 patients, 24 (75%)

had evidence of oncologic driver with actionable mutation. Epidermal Growth Factor Receptor mutation was the most common oncologic driver identified (n=17, 53%). Lung cancer computed tomographic (CT) presentation were pneumonic type adenocarcinoma (n=17, 53%), lymphangitic carcinomatosis (n =10, 31%) and miliary carcinomatosis (n =5, 16%).

During the ICU stay, 17 (53%) patients required invasive mechanical ventilation (IMV), 17 (53%) catecholamine infusion, 2 (6%) renal replacement therapy and one (3%) extracorporeal membrane oxygenation. Mean SAPS2 was 40 +/-14. In addition to TKI, 23 (72%) patients received steroids (beyond 0.5 mg/Kg/day), and 3 (9%) patients were treated with chemotherapy during ICU stay. We did not report significant toxicity of TKI. This treatment was continued during the whole ICU stay for all patients. All patients received the appropriate daily dose of TKI drug, 18 (56%) through nasogastric tube and other with oral administration. Decision of withholding or withdrawal life sustaining therapies was taken at ICU admission for 3 (9%) patients and for 12 (37%) during ICU stay.

Twenty (63%) patients were discharged alive from ICU. Among the 17 patients who received IMV, 8 (47%) were discharged alive from ICU. There was no difference in ICU survival between patients naïve of cancer treatment at ICU admission and those who were already treated with chemotherapy before ICU. Of the 24 patients with evidence of oncologic driver, 17 (71%) were discharged alive from ICU. Exploratory univariate analysis showed that documentation of an oncologic driver, adenocarcinoma histological type and lymphangitic carcinomatosis CT presentation were associated with ICU survival.

Sixteen deaths had been observed by day 90. The Kaplan-Meier estimate of overall survival at day 90 was 50.0% (95%confidence interval, 35.4-70.7) (Figure 1). Eight patients were still alive one year after ICU admission and 3 were lost to follow-up (alive at D-143, D-216 and D-194). Moreover, among the 17 patients requiring IMV, 6 were alive after 90 days and 4 one year after ICU admission (one was lost to follow-up, alive at day 216).

Discussion

In this multicenter case series, survival of patients with NSCLC involvement responsible for acute respiratory failure and for whom TKI agents were initiated in ICU was better than previously reported. In

the work of Chen et al.⁹, 24 patients received TKI in ICU for naïve NSCLC. However, only one patient had an EGFR mutation and ICU mortality did not differ between TKI treatment group and best supportive care group (50%). In the *Lung Cancer in Critical Care* (LUCCA) study³, day-90 mortality of NSCLC patients with advanced or metastatic disease admitted to the ICU was high (70%) in the absence of TKI treatment initiation. Our data suggest that survival at day 90 (50%) is better when TKI treatment is initiated with evidence of oncologic driver.

Administration of anti-cancer treatment in ICU should be preceded by an extensive discussion between intensivists, oncologists, family and patients¹⁰. These treatments require the ability to reassess the decision of life sustaining therapies towards palliative care in case of unfavorable course. Despite some limited studies, less is known about prediction of TKI treatment success. Adenocarcinoma being the most common histological type associated to the presence of an oncologic driver, interpretation of univariate analysis should be view with caution. Interestingly, all the 10 patients with lung lymphangitic carcinomatosis on CT at ICU admission survived after TKI administration during ICU stay.

This study has several limitations. First, the sample size was small. The population of the study being scarce in the ICU, larger prospective studies require international collaboration. Secondly, we did not assess pharmacological issues. Indeed, drug volume of distribution in ICU patients is frequently increased implying that TKI treatment could be under-dosed.

This case series showed that in the context of NSCLC involvement responsible for acute respiratory failure, the use of TKI treatment should not be refrained in patients with actionable oncologic driver admitted to the ICU.

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Guarantor: Stephane Gaudry is the guarantor of the content of the manuscript, including data and analysis

Author's contribution: This is an investigator-initiated multicenter study led by SG and YTL. All the investigators mentioned as co-authors gathered the data. YA performed the data-management. The statistical

analysis was performed by AO. The paper was written by YTL, BD and SG. The paper was submitted to all the co-authors who made substantial contributions and agreed to submit to *Chest*.

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Role of the sponsors: None

Other contributions: We performed a national multicenter retrospective study with the participation of the GRRROH (Groupe de Recherche en Réanimation Respiratoire en Onco-Hématologie)

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Table1: Characteristics, management of the patients

	All patients n=32	ICU survivors * n=20	ICU nonsurvivors n=12	P
CHARACTERISTICS OF PATIENTS				
Age, yr, mean ± SD	59 ± 14	56 ±16	64 ±7	0.10
Female sex, n (%)	20 (62)	13 (65)	7 (58)	0.70
Smoking status, n (%)				0.80
Patients who had never smoked	21 (66)	12 (60)	9 (75)	
Patients who quit smoking	8 (25)	6 (30)	2 (17)	
Smoking patients	3 (9)	2 (10)	1 (8)	
ECOG performance status, n (%)				1.00
0	7 (22)	4 (20)	3 (25)	
1	12 (37)	8 (40)	4 (33)	
2	7 (22)	4 (20)	3 (25)	
3	6 (19)	4 (20)	2 (17)	
Histological subtype, n (%)				0.006
Adenocarcinoma	23 (72)	18 (90)	5 (42)	
Non-adenocarcinoma	9 (28)	2 (10)	7 (58)	
Metastatic status, n (%)				0.10
Number of metastatic organs _≥ 2	22 (69) 7 (22)	16 (80) 4 (20)	6 (50) 3 (25)	
Oncologic Driver, n (%)	24 (75)	17 (85)	7 (58)	0.04
EGFR	17 (53)	12 (60)	5 (42)	
ALK	4 (12)	2 (10)	2 (17)	
ROS	3 (9)	3 (15)	0 (0)	
Chest CT-scan pattern				0.001
Lymphagitis	10 (31)	10 (50)	0 (0)	
Miliary	5 (16)	4 (20)	1 (8)	
Pneumonic type adenocarcinoma	17 (53)	6 (30)	11 (92)	
Chemotherapy before TKI introduction, n (%)	7 (22)	4 (20)	3 (25)	1.00
SAPS II at ICU admission, mean ± SD	40 ± 14	39 ± 10	42 ±19	0.60
MANAGEMENT IN THE ICU				
TKI molecule, n (%)				0.60
Erlotinib	13 (41)	9 (45)	4 (33)	
Gefitinib	4 (12)	3 (15)	1 (8)	
Crizotinib**	8 (25)	5 (25)	3 (25)	
Osimertinib	6 (19)	2 (10)	4 (33)	
Erlotinib and Gefitinib	1 (3)	1 (5)	0 (0)	
Respiratory support, n (%)				
High flow oxygen therapy	17 (53)	10 (50)	7 (58)	0.60
Non-invasive mechanical ventilation	11 (34)	5 (25)	6 (50)	0.20
Invasive mechanical ventilation	17 (53)	8 (40)	9 (75)	0.05
Neuromuscular blockers	11 (34)	5 (25)	6 (50)	0.20
Inhaled nitric oxide	5 (16)	1 (5)	4 (33)	0.05
Prone position	7 (22)	3 (15)	4 (33)	0.40
ECMO-VV	1 (3)	0 (0)	1 (8)	0.40
Vasopressor support, n (%)	17 (53)	4 (20)	9 (75)	0.004
Renal replacement therapy, n (%)	2 (6)	0	2 (17)	0.10

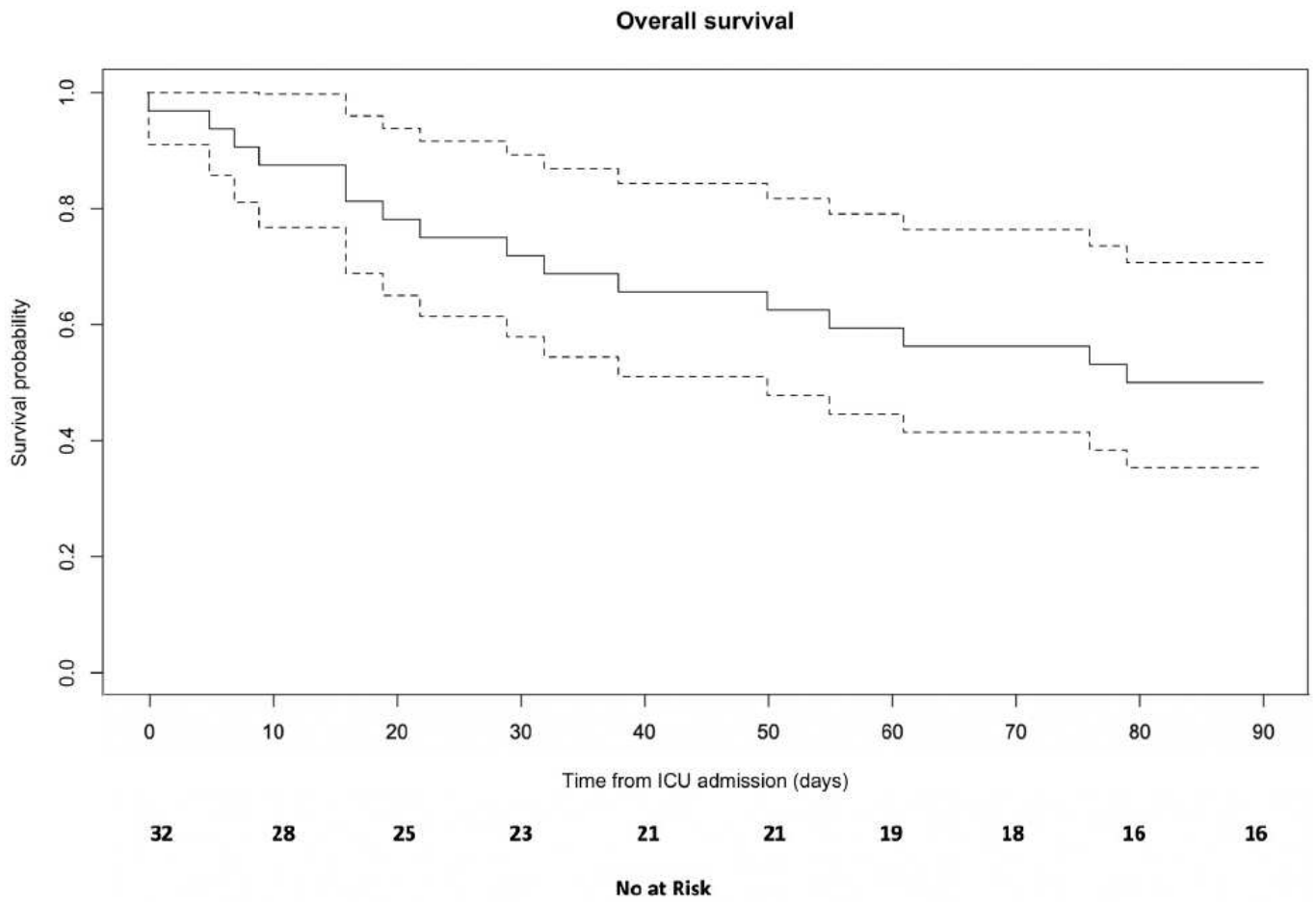
Definition of abbreviations: ICU: Intensive Care Unit, ECOG: Eastern Cooperative Oncology Group, EGFR: Epidermal Growth Factor Receptor, ALK: Anaplastic Lymphoma Kinase, ROS: Reactive Oxygen Species, TKI: Tyrosin Kinase inhibitor, SAPS: Simplified Acute Physiology Score, ECMO-VV: Extracorporeal Membrane Oxygenation Venovenous, SD: Standard Deviation

* The groups (ICU survivors and ICU non survivors) were compared by Chi-2 or Fisher exact tests, as appropriate for categorical variables, and student t-tests for quantitative variables (with normality hypotheses tested by normality graph)

** Among 8 patients receiving crizotinib, 3 had ROS-1 rearrangement, 4 had ALK fusion and one was treated in 2017 with crizotinib because of c-MET amplification in a sarcomatoïd lung tumor.

FIGURE 1: Probability of survival 90 days after ICU admission

Kaplan-Meier curve of the probability of survival from ICU admission to day 90



ICU = intensive care unit

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