Three-Year Overall Survival of Advanced Stage ALK-Positive NSCLC at a Single Clinical Setting in Indonesia

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INTRODUCTION

Lung cancer is regarded as a primary contributor to cancer-related mortality on a global scale, with non-small cell lung cancer (NSCLC) accounting for a striking 84% of cases. Within Indonesia, lung cancer holds the leading position among men and ranks fifth among women, marking it as the deadliest malignancy with a significant impact, representing 13.2% of cancer-related deaths [1,2]. In 2007, the fusion of the anaplastic lymphoma kinase (ALK) gene with echinoderm microtubule-associated protein-like 4 (EML4) was unveiled by Soda et al. [3], offering a potential molecular target for cancer therapy in NSCLC patients. The occurrence of this ALK fusion was quite uncommon, appearing in only 5–6% of NSLC subjects, predominantly among the younger population with onset and being never or light smokers [4].

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ABSTRACT

Background: ALK-positive Non-Small Cell Lung Cancer (NSCLC) is a rare condition predominantly observed in much younger non-smokers with adenocarcinoma histology, often accompanied by brain metastases. Despite its unique features, there is a lack of data concerning the treatment of ALK-positive NSCLC in Indonesia. Therefore, this study represented the first attempt to document the treatment landscape for ALK-positive NSCLC in the country. The available ALK inhibitors included crizotinib, alectinib, brigatinib, and lorlatinib, and none of these were listed under the Indonesian Universal Health Coverage as of September 2022. This study aimed to characterize survival outcomes of ALK-positive NSCLC patients treated within a specialized thoracic oncology practice in Indonesia.

Methods: The retrospective observational cohort study drew secondary data from medical records of ALK-positive NSCLC patients treated at a private thoracic oncology clinic. Data were collected retrospectively, spanning from December 2019 to December 31, 2022. Exclusion criteria included incomplete data, untreated ALK-positive NSCLC, cases at stage I-III, or diagnoses made after August 2021. The observation period extended up to 36 months, although several patients exceeded 48 months, with one individual currently boasting a 96-month survival.

Results: A total of 15 patients with ALK-positive NSCLC were selected as the respondents in this study. The median age stood at 50.8 years, predominantly female, and diagnosed with adenocarcinoma. Predominant sites of metastasis included pleural effusion and brain metastases, and preliminary 36-month survival rates reached 73.3%. The 1-year survival rate was recorded at 100%, while the 2-year overall survival (OS) stood at 80%, aligning closely with global ALK inhibitors clinical trial data.

Conclusions: This study provided the first-ever dataset indicating an ALK-positive profile within a singular thoracic oncology clinic in Indonesia. Despite the accessibility constraints of treatments, ALK-positive patients showed comparable total survival to pivotal clinical trial data. This preliminary dataset shed light on the profile and treatment of ALK-positive NSCLC in the country.
Recent years have witnessed the emergence of tyrosine kinase inhibitors (TKIs) as a front-line therapy for ALK-positive NSCLC, a breakthrough that has led to significant advancements in patient care. Several of these inhibitors have gained approval and become accessible in the medical landscape of Indonesia. This cohort of ALK inhibitors comprises the first-generation crizotinib, the second-generation alectinib and brigatinib, and the third generation lorlatinib after the Indonesian Food and Drug Authority approval in 2016, 2019, 2020 and 2022, respectively. However, as of September 2022, none of these inhibitors have yet received approval within the Indonesian Universal Health Coverage system for reimbursement [5]. Existing reviews consistently showed that ALK inhibitors have yielded marked improvements in both progression-free survival and overall survival when compared to systemic chemotherapy [6-8]. This study marks the first endeavor to explore survival rates of ALK-positive NSCLC patients treated with ALK inhibitors within the Indonesian private healthcare sector. The focus is to present a collection of cases involving ALK-positive NSCLC, where treatment with these inhibitors was administered in real-world clinical scenarios. By delving into the characteristics of the patients, this study aims to foster a deeper understanding and formulate more robust therapeutic strategies.

METHODS

This observational retrospective cohort study was conducted at a single thoracic oncology clinic in Indonesia, centered on subjects with advanced-stage ALK-positive NSCLC undergoing treatment with ALK inhibitors. The study spanned from 2019 to December 31, 2022, aiming to focus on documenting all instances of ALK-positive NSCLC cases treated with ALK inhibitors, a rarity within the Indonesian context. Among the subjects, 5 patients participated under the aegis of the Special Access Scheme (SAS) for alectinib before its official approval in the country. The identification of ALK-positivity was grounded in ALK immunohistochemistry analysis drawn from histopathological samples. The primary outcome of this study focused on the 1-year survival rate among patients receiving ALK inhibitors (across all treatment lines). Potential confounders considered involved unreported dates of decease, accessibility of later-generation ALK inhibitors in Indonesia, medication availability, and instances of treatment interruption due to prohibitive costs. The calculation of overall survival (OS) was determined from the point of diagnosis to the date of demise or the cut-off point of data in December 2022. Following the complexities in gauging treatment sequences, this study did not assess Progression-Free Survival (PFS). Additionally, due to varying time frames, calculations were confined to a 3-year survival span among subjects. Inclusion criteria included all ALK-positive NSCLC diagnoses preceding August 31, 2021, and treatment with ALK inhibitors in any sequence. Meanwhile, exclusion criteria consisted of incomplete data, untreated ALK-positive NSCLC cases, stage I-III diagnoses, or diagnoses made after August 31, 2021. The evaluation of untreated ALK-positive NSCLC was precluded due to the absence of recorded data. This study presented the most extensive collections of data on NSCLC patients treated with ALK inhibitors within a single practice, predating the inclusion of these inhibitors under Universal Health Coverage. Data were collected from medical records, subsequently organized using Microsoft Excel, and analyzed through IBM SPSS version 25. Ethical approval for this observation was granted by the Ethics Committee, as outlined below.

RESULTS

A comprehensive dataset was obtained from 15 individuals diagnosed with ALK-positive NSCLC, all predating August 31, 2021, and undergoing ALK inhibitor treatment across various lines of therapy (Table 1). Among these subjects, a majority were female (60%) and had no history of smoking (86.7%). The average age at the point of diagnosis stood at 50.87 years, with ages ranging from 25 to 68 years. Regarding histology, adenocarcinoma accounted for the vast majority, while squamous cell carcinoma accounted for the smallest percentage (6.7%). Staging at the point of diagnosis was predominantly IV (100.0%). In terms of locations of metastases, brain metastasis and pleural effusion were observed in 46.7% and 80.0% of patients, respectively. The dataset allowed for a comprehensive observation of survival rates among patients receiving ALK inhibitors (across all treatment lines). Potential confounders considered involved unreported dates of decease, accessibility of later-generation ALK inhibitors in Indonesia, medication availability, and instances of treatment interruption due to prohibitive costs. The calculation of overall survival (OS) was determined from the point of diagnosis to the date of demise or the cut-off point of data in December 2022. Following the complexities in gauging treatment sequences, this study did not assess Progression-Free Survival (PFS). Additionally, due to varying time frames, calculations were confined to a 3-year survival span among subjects. Recent years have witnessed the emergence of tyrosine kinase inhibitors (TKIs) as a front-line therapy for ALK-positive NSCLC, a breakthrough that has led to significant advancements in patient care. Several of these inhibitors have gained approval and become accessible in the medical landscape of Indonesia. This cohort of ALK inhibitors comprises the first-generation crizotinib, the second-generation alectinib and brigatinib, and the third generation lorlatinib after the Indonesian Food and Drug Authority approval in 2016, 2019, 2020 and 2022, respectively. However, as of September 2022, none of these inhibitors have yet received approval within the Indonesian Universal Health Coverage system for reimbursement [5]. Existing reviews consistently showed that ALK inhibitors have yielded marked improvements in both progression-free survival and overall survival when compared to systemic chemotherapy [6-8]. This study marks the first endeavor to explore survival rates of ALK-positive NSCLC patients treated with ALK inhibitors within the Indonesian private healthcare sector. The focus is to present a collection of cases involving ALK-positive NSCLC, where treatment with these inhibitors was administered in real-world clinical scenarios. By delving into the characteristics of the patients, this study aims to foster a deeper understanding and formulate more robust therapeutic strategies.

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Table 1. Patients characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (%)</th>
<th>Mean (SD) / Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td></td>
<td>50.8 (12.30)</td>
</tr>
<tr>
<td>Survival (months)</td>
<td></td>
<td>(Range 15–96 months)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Year 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 Year 80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 Years 73.3%</td>
</tr>
<tr>
<td>History of smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (13.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (86.7)</td>
<td></td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>14 (93.3)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>1 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Staging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>15 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Sites of metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain metastasis</td>
<td>7 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>12 (80.0)</td>
<td></td>
</tr>
</tbody>
</table>

N: number of patients; SD: standard deviations; IQR: interquartile range
squamouous cell carcinoma was evident in only a solitary case. All the respondents were initially diagnosed with stage IV lung cancer at the onset of the study. Among the prevailing metastatic sites, pleural effusion held the highest prevalence at 80%, closely followed by brain metastases at 46.7%.

A total of 3 subjects initiated their treatment journey with doublet chemotherapy as first-line therapy, with ALK status pending. Subsequently, these patients progressed to treatment with crizotinib, alectinib, and lorlatinib respectively. About 12 individuals commenced their treatment with a first-line ALK inhibitors, and alectinib was the predominant choice (7; 58.3%), followed by crizotinib (4; 30%), and ceritinib (1; 0/8%). Following the disease progression, both brigatinib and lorlatinib were used as further treatment options, having recently secured approval by the Indonesian Food and Drug Authority in 2020 and 2022 respectively. A total of 1 subject has shown ongoing survival, having undergone more than 5 treatments. This case was significant for a favorable intracranial response to brigatinib exceeding 19 months. The positive outcome was achieved after progression on crizotinib, alectinib, and lorlatinib respectively. The recorded 1-year survival rate reached 100%, while the 2-year overall survival stood at 80%. Furthermore, the 3-year overall survival rate was observed to be 73.3%, closely aligning with data gleaned from global ALK inhibitors clinical trials (Figure 1).

**DISCUSSION**

ALK-positive NSCLC was characterized by its rarity, often afflicting younger individuals who are typically non-smokers or light smokers. This stood as the first recorded instance of survival among ALK-positive NSCLC patients treated with ALK inhibitors in Indonesia. Previous reviews have consistently shown a median age of 55 years among these patients [9,10]. The analysis results showed that the average age at diagnosis was lower, measuring 50.87 years. This observed pattern of early onset in ALK-positive NSCLC within the Indonesian context likely resonated with a higher prevalence of genetic alterations [2]. The results mirrored those of a study by Shaw et al. [11], involving 141 subjects, which highlighted a strong correlation between ALK rearrangement and a history of never or light smoking. This aligned seamlessly with this study, wherein a substantial 86.7% of the patients were identified as never smokers. However, this analysis refrained from further classifying the smoker cohort into light or heavy smokers, abstaining from compounding potential data complexities. The prevalence of ALK rearrangement across smokers and non-smokers has been variably documented in multiple investigations, hinting at an absence of a direct association between these two variables [12–15]. Factors such as modest sample sizes and potential disparities in ethnic backgrounds might play contributory roles in these discrepancies. A significant proportion of subjects lacking a smoking history could be characterized molecularly by an actionable oncogenic mutant kinase, thereby fostering the rationale for targeted therapies, including ALK inhibitors [16]. Global investigations have consistently established a parallel incidence of ALK-positivity among men and women [9]. Within the broader NSCLC population, a divergence emerged, with a substantially higher proportion of men testing positive for ALK (23%) compared to women (9%) [11]. The analysis results showed that 60% of the subjects were women, wherein only 1 woman (11.1%) and a solitary man (20%) possessed a smoking history.

Adenocarcinomas represented the prevailing cancer subtype in ALK-positive NSCLC patients, occasionally interwoven with reports of squamous cell carcinoma cases. At diagnosis, the majority of ALK-positive subjects presented with advanced disease, indicative of the
inherent aggressiveness of the disease. This collective backdrop underscored the critical need for instituting lung cancer screening and early detection programs within Indonesia. Brain and hepatic metastases were characteristics of ALK-positive NSCLC, often coupled with pericardial and pleural effusion [17]. While ALK was naturally expressed in the testes, small intestine, and central nervous system, the occurrence of intracranial metastases remained enigmatic [18]. This study comprised subjects diagnosed with stage IV NSCLC, and 12 out of these individuals exhibited pleural effusions, while hepatic metastases remained absent [19]. Almost all the respondents manifested NSCLC with ALK-positivity, with nearly half of these cases being accompanied by brain metastases. This observation correlated with results from a substantial population study indicating that 23.2% of 1,127 NSCLC subjects ultimately developed brain metastases [20]. Furthermore, epidemiologic data including 947 ALK-positive subjects unveiled a 28% incidence of brain metastases merely 88 days after primary diagnosis. Common risk factors for brain metastases included age below 60 years and an adenocarcinoma histological subtype. Adenocarcinomas exhibited a higher likelihood of brain metastasis compared to squamous cell and large-cell carcinomas [21]. In this study, 14 out of 15 subjects presented with adenocarcinoma, of which 7 experienced brain metastases. The results also indicated that a single patient with squamous cell carcinoma did not develop brain metastases, and ALK-positive NSCLC manifested a poor prognosis. A cohort study documented an escalating incidence of brain metastases in subjects with NSCLC and ALK-positivity across the year, initially 23.8%, followed by 45.5%, and 58.4% after 1, 2, and 3 years [22].

The median overall survival time derived from this study aligned closely with the results from global investigations endeavors. A 1-year survival rate of 100% was observed, with the 2-year overall survival at 80%, and the 3-year overall survival amounted to 66.7%. This observation mirrored the outcomes of global clinical trials involving ALK inhibitors [22–30]. A total of 5 subjects were able to access alectinib through a SAS, and the majority of the respondents turned to chemotherapy within the framework of Universal Health Coverage (UHC) for subsequent therapeutic interventions. Multiple factors converged to shape the overall survival rates of certain subjects. Firstly, individuals underwent doublet chemotherapy as a second-line subsequent therapy due to the unavailability of ALK inhibitors under the Universal Health Coverage scheme before September 2022. Secondly, the recent approval of a newer generation of these inhibitors contributed to the outcomes. This investigation stood as the pioneering attempt to expound upon the one-year overall survival rate of ALK-positive NSCLC patients subjected to ALK inhibitors treatment within a real-world, single private healthcare context in Indonesia. The limitations of this study included the inability to capture data related to PFS, the intricate sequences of treatments, and specifics regarding adverse events and treatment interruptions resulting from limited access and availability of later-generation ALK inhibitors.

CONCLUSIONS

This study underscored the congruence between the characteristics of ALK-positive NSCLC subjects within the broader global data trends. These traits included youthfulness, non-smoking history, and a predominant adenocarcinoma histological type. The analysis results showed that the initial range of survival spanned from 15 months to an impressive 96 months. A total of 1-year survival rate reached 100%, while the 2-year overall survival stood at 80%, and the 3-year overall survival rate at 73.3%. These survival rates closely paralleled the outcomes documented in global clinical trials of ALK inhibitors. The study effectively mirrored the impact of the inhibitors treatment within a private healthcare context, predating the introduction of newer ALK inhibitors in Indonesia and their subsequent inclusion within the framework of National Universal Health Coverage. Furthermore, the availability and accessibility of later-generation inhibitors, administered as treatment modalities, might exert a substantial influence on the overall survival outcomes highlighted in this study.

DECLARATIONS

Competing interest
The authors declare no competing interest in this study.

Ethics approval and consent to participate
This observation was approved by the Ethic Committee of Faculty of Medicine University of Indonesia (KET 334/UN2/F1/ETIK/PPM.00.02/2021) and MRCCC Siloam Hospital Jakarta (001/EA/KEPKK/RSMRCCC/VIII/ 2021).

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REFERENCES