Clinics in Oncology

Research Article
Published: 17 Oct, 2020

Second *versus* First-Generation Tyrosine Kinase Inhibitors in Lung Adenocarcinoma after Chemotherapy Progression

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Abstract

Objective(s): The aim of the present study was to assess the benefit of afatinib compared with gefitinib after chemotherapy progression in patients with advanced stage Epidermal Growth Factor Receptor (*EGFR*)-mutated lung adenocarcinoma.

Methods: This was a retrospective single-center study that analyzed the disease-free survival of advanced stage *EGFR*-mutated lung adenocarcinoma that was treated with Tyrosine Kinase Inhibitors (TKIs) as a second or third-line treatment after chemotherapy. The study included patients with *EGFR*-mutated lung adenocarcinoma that was pathologically confirmed between 2011 and 2016 at the "Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío" (INER). The primary endpoint was progression-free survival after TKIs as a second or third-line treatment.

Results: We included 61 patients, among whom 24 (39.3%) received afatinib and 37 (60.6%) received gefitinib. The median progression-free survival for patients treated with afatinib was 11 months, which was significantly longer compared with those treated with gefitinib (8 months).

Conclusion: We found better progression-free survival in those treated with afatinib as a second or third-line treatment after chemotherapy compared with gefitinib, with similar results in response rate.

Keywords: Epidermal growth factor receptor mutation; Non-small-cell lung cancer; Afatinib; Gefitinib; Progression-free survival; Lung adenocarcinoma; Chemotherapy; Tyrosine kinase inhibitor

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Received Date: *24 Sep 2020*
Accepted Date: *14 Oct 2020*
Published Date: *17 Oct 2020*

Citation:
Rodríguez-Cid JR, Arroyo-Hernandez M, Flores-Mariñelarena RR, Castro-Lopez CJ, Alatorre-Alexander JA, Martínez-Barrera L, et al. Second versus First-Generation Tyrosine Kinase Inhibitors in Lung Adenocarcinoma after Chemotherapy Progression. Clin Oncol. 2020; 5: 1746.

Introduction

Lung cancer is associated with the highest mortality rate in the world [1-3]. More than 85% of patients present with an advanced stage disease at diagnosis this result in a poor prognosis [4]. Without treatment, lung cancer has a median survival rate of less than 6 months. The current standard treatment is chemotherapy (response rate, 40%) [5], but the constant discovery of common oncogenes such as mutations in Epidermal Growth Factor Receptor (*EGFR*) and KRAS, which have an overall prevalence of 15% to 25% and 10% to 35%, respectively [6], has resulted in new potential target therapies over time [7,8].

Oncogenes have multiple functions in tumor maintenance. For example, the *EGFR* mutation activates a kinase cascade that counteracts the apoptosis mechanisms and thereby enhanced its proliferation [9]. *EGFR* is highly expressed on the surface of Non-Small Cell Lung Cancer (NSCLC), but few tumors show a mutation in the *EGFR* gene. The deletions from exon 19 and point mutations in exon 21 (mutation L858R) represent 85% to 90% of the *EGFR* mutations in

lung cancer. Regardless of the age group, the *EGFR* mutation is found more frequently in tumors from female patients without exposure to tobacco smoke (defined as less than 100 cigars in their life time) that have adenocarcinoma histology, but it can also be detected in patients who are active smokers [10].

Current patients with *EGFR*-mutated NSCLC can be treated with Tyrosine Kinase Inhibitors (TKIs) [11-13]; the first-generation of this type of drugs includes gefitinib and erlotinib, bind in a reversible way and block the *EGFR* gene signaling pathway, while afatinib, a second-generation TKI bind irreversibly [14,15]. Wider-spectrum activities from the second-generation TKIs and their irreversible mechanism of action have been associated with better tumor growth inhibition compared with first-generation drugs. Different studies have been performed that compare TKIs and chemotherapy with superior results for Progression-Free Survival (PFS) and overall survival for those patients in the TKI study arm, establishing TKIs as a first-line treatment in patients who were diagnosed with advanced-stage *EGFR*-mutated NSCLC [16-23].

At diagnosis, metastasis to the Central Nervous System (CNS) was reported in up to 25% of the patients who were diagnosed with NSCLC [24], but 44% to 63% of patients with NSCLC were reported to have cerebral involvement [25]. These patients are usually excluded from clinical trials because of their negative impact on survival rates [26]. Patients with CNS invasion without treatment report an average survival of 1 month from diagnosis, 2 months with glucocorticoid treatment, and 2 to 5 months with radiotherapy to the brain [27]. However, findings in phase III trials such as the LUX-Lung 3 trial, which compared afatinib and cisplatin-pemetrexed or the LUX-Lung 6 that compared afatinib with platinum-based chemotherapy as a first-line treatment including patients with *EGFR*-mutated NSCLC with, brain metastasis. They found improvement in PFS in the afatinib group compared with other treatments [28,29]. The improvement was similar to that in other studies where patients with brain metastasis were excluded because of their poor prognosis [15,30], which supports the inclusion of patients with CNS metastasis in the present study.

LUX-Lung 7 was the first multicenter, international, randomized study that compared first (gefitinib) and second-generation (afatinib) *EGFR* TKIs as first-line treatment in patients who were diagnosed with *EGFR*-mutated lung adenocarcinoma without previous TKI treatment. A PFS of 11 months was reported in the afatinib group compared with 10.9 months in patients who were treated with gefitinib (p=0.017). The mean time to treatment failure of 13.7 months (95% CI 11.9 to 15) with afatinib versus 11.5 months (95% CI 10.1 to 13.1) with gefitinib (p=0.0073) [15]. There was a reduction in the risk of death with a median overall survival of 3.4 months longer for afatinib (27.9 months) compared with gefitinib (24.5 months), although this difference was not statistically significant [31].

In Mexico, access to oncological treatment has multiple limitations such as economic and socio-demographic factors, and access to the health system issues, which hinders the use of TKIs as a first-line treatment. This exemplifies common problems that were raised in developing countries where a wide range of treatments are not always accessible, resulting in a suboptimal treatment and, as a consequence, disease progression.

The present study aims to describe the benefit of treatment with TKIs (first and second generation) as a second or third-line treatment in patients with advanced lung adenocarcinoma *EGFR* mutated.

Methods

This retrospective study was performed at the Thoracic Oncology and Radiology departments at the "Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío" (INER), in Mexico City. The study design was approved by INER's Institutional Ethics Board in accordance with the Declaration of Helsinki, Fortaleza Brazil 2013. Because this is a retrospective review of clinical records, not all patients were able to grant informed consent for multiple reasons, but the information was reported as a group and patient confidentiality was maintained. The inclusion criteria were as follows: Patients over 18 years old with a histopathological diagnosis of *EGFR*-mutated lung adenocarcinoma, Eastern Cooperative Oncology Group performance status (ECOG) 0-3 at the beginning of the treatment with afatinib or gefitinib as a second or third-line between November 2011 and May 2016, and an advanced clinical stage. Exclusion criteria were as follows: Patients who stopped TKI treatment; patients who were previously treated with TKIs; and patients who underwent surgery in the previous 4 weeks (Figure 1). The primary endpoint was the PFS with afatinib or gefitinib as a second or third-line treatment.

The following clinical and pathological variables were reviewed: Gender, age, smoking, exposure to wood smoke, ECOG, TNM initial clinical stage, metastasis sites, previous radiotherapy treatment, adverse effects from TKI (evaluated by the common terminology criteria for adverse events version 4.03) [32], PFS, and response based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria [33], as assessed by the radiologist in our group using a computed tomography scan. The radiologist was blinded to the treatment that was received by the patient, as well as their survival rate.

EGFR gene analysis was performed using the Therascreen *EGFR* RGQ PCR kit version 2 by Qiagen™ (Valencia, CA, USA) on the biopsy samples obtained by video-assisted thoracoscopy to confirm the presence of the most frequent somatic mutations. SPSS version 24.0 (IBM Corp., Armonk, NY, USA) was used for the analysis. The variables were expressed as the median, or as the total number, percent, Hazard Ratio (HR) and 95% Confidence Interval (CI). Univariable and multivariable survival analyses were performed using a logistic regression model, PFS was determined using a Kaplan Meier plot. The criterion for statistical significance was $p<0.05$. All financial-related issues were absorbed by the investigation group from the study.

Results

One hundred twenty patients were identified with a diagnosis of lung adenocarcinoma from November 2011 to May 2016, and only 61 patients met the study entry criteria. Overall, 18 patients were male (29.5%) and 43 were female (70.5%). The average age in years was 59.74 (Standard Deviation (SD) 12.44) years with a range of 35 to 89 years. Most patients denied smoking (72.1%), but 45.9% indicated exposure to wood smoke with an average time of 56.87 hours/year. At the beginning of the TKI treatment, 30 patients (49.1%) had ECOG 1, 18 patients (29.5%) had ECOG 0, ten patients (16.4%) had ECOG 2 and three patients (5%) had ECOG 3. The most prevalent metastasis site among our study population was bone (25 patients, 41%) and pleura (24 patients, 39.3%).

There were of 47 (77%) patients who received TKIs treatment

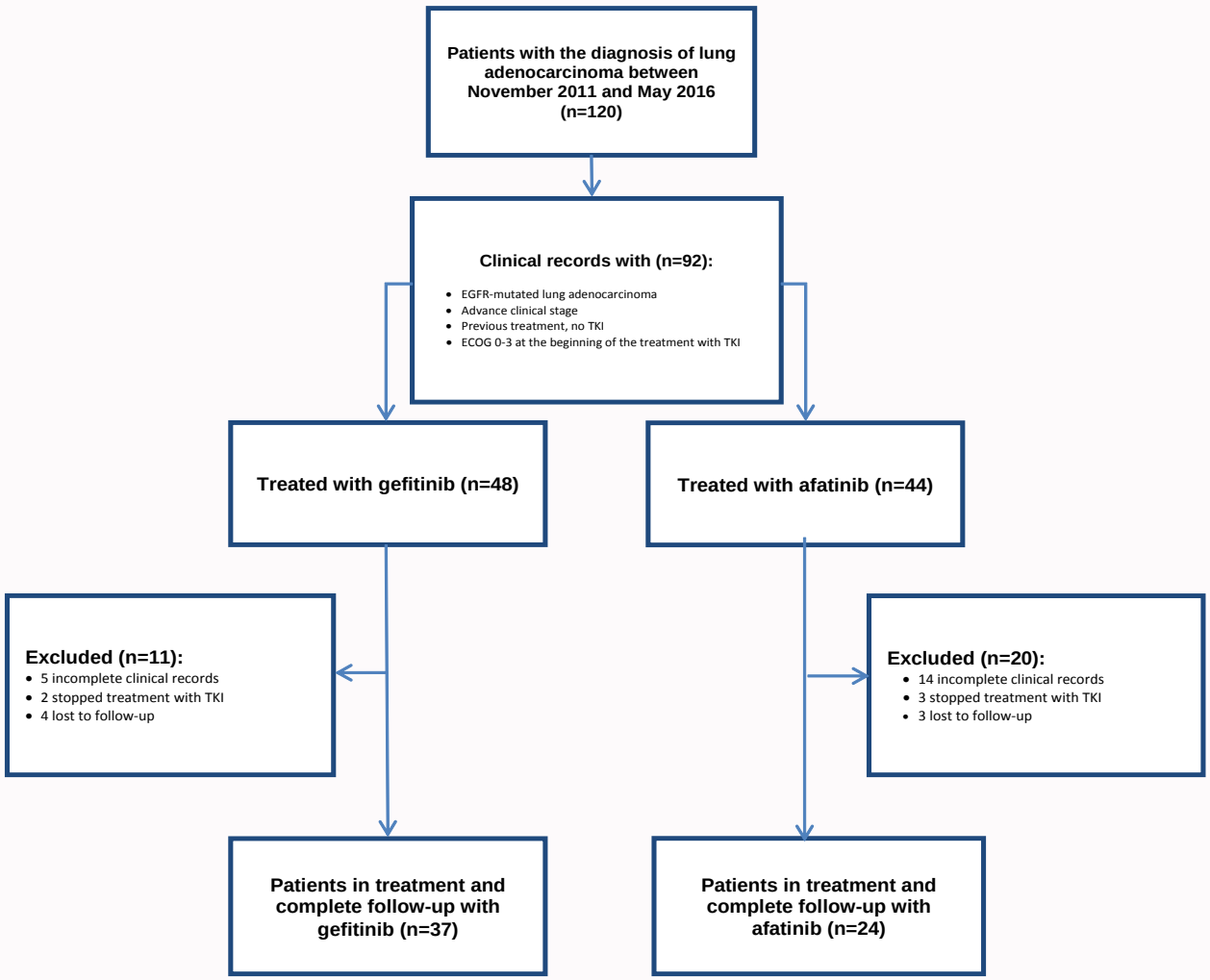

Figure 1: Flow diagram of the study population.
TKI: Tyrosine Kinase Inhibitor; EGFR: Epidermal Growth Factor Receptor; ECOG: Eastern Cooperative Oncology Group performance status

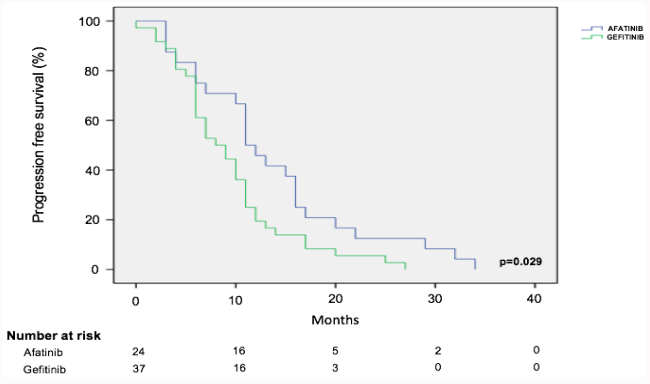

Figure 2: Progression-free survival, for patients treated with afatinib compared with gefitinib.

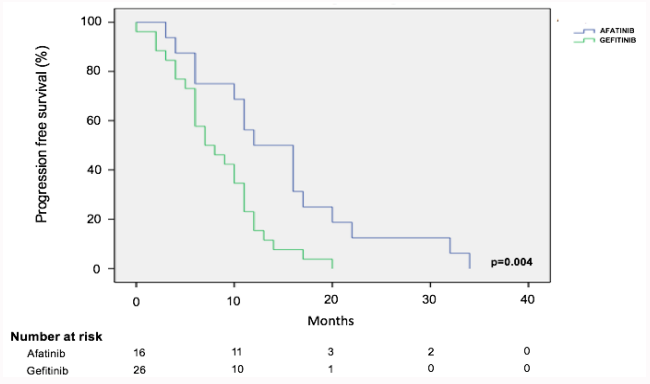

Figure 3: Progression-free survival, in female patients treated with afatinib compared with gefitinib.

as a second-line treatment and 14 (23%) as a third-line treatment. Regardless of the second- or third-line treatment, 24 (39.3%) patients received afatinib and 37 (60.6%) patients received gefitinib in the overall study population. In the afatinib group, 16 (66.6%) patients received this TKI as a second-line treatment and eight (33.3%) patients received it as a third-line treatment. Among those in the gefitinib group, 34 (91.8%) patients received it as a second-line and three (8.1%) patients received it as a thir d-line treatment.

The most common adverse reactions in both groups were diarrhea (63.9%), rash (55.73%), gastrointestinal manifestations (32.8%), mucositis (13.1%), neuropathy (8.2%) and urinary symptoms (1.6%). Table 1 lists the characteristics of the study population based on to the use of gefitinib or afatinib.

Table 1: Characteristics of 61 patients with *EGFR*-mutated lung adenocarcinoma based on treatment with afatinib or gefitinib.

	Afatinib (n=24)	Gefitinib (n=37)
Age, mean (± SD)	59.7 (± 12.4)	60.3 (± 11.2)
Gender		
Female, n (%)	16 (66.6)	27 (72.97)
Male, n (%)	8 (33.3)	10 (27.02)
Smoking status		
Current, n (%)	6 (25)	11 (29.7)
Smoking index, pack year (min.–max., ± SD)	2.2 (0–28 ± 6.61)	2.6 (0–43 ± 7.99)
Wood Smoke		
Exposed, n (%)	8 (33.3)	20 (54.05)
Wood smoke index, hours year (min-max., ± SD)	41.1 (0–240 ± 69.20)	67.1 (0–671 ± 142.44)
ECOG		
0, n (%)	4 (16.6)	14 (37.8)
1, n (%)	12 (50)	18 (48.6)
2, n (%)	5 (20.8)	5 (13.5)
3, n (%)	3 (12.5)	0
4-5, n (%)	-	-
Initial clinical stage		
IIA, n (%)	-	1 (2.7)
IIIB, n (%)	2 (8.3)	-
IV, n (%)	24 (91.6)	36 (97.2)
Previous treatment		
Previous radiotherapy, n (%)	8 (33.3)	4 (10.8)
CNS metastases, n (%)	9 (37.5)	4 (10.8)
Other metastasis sites		
· Bone, n (%)	10 (41.6)	15 (40.5)
· Contralateral lung, n (%)	3 (12.5)	10 (27.02)
· Adrenal glands, n (%)	3 (12.5)	1 (2.7)
· Lymph nodes, n (%)	3 (12.5)	13 (35.1)
· Pleura, n (%)	6 (25)	18 (48.6)
· Liver, n (%)	10 (41.6)	1 (2.7)
Adverse reactions		
Diarrhea, n (%)	19 (79.1)	20 (54.05)
Rash, n (%)	15 (62.5)	19 (51.3)
Gastrointestinal, n (%)	10 (41.6)	10 (27.02)
Mucositis, n (%)	7 (29.1)	1 (2.7)
Urinary symptoms, n (%)	1 (4.1)	0 (0)
Neuropathy, n (%)	3 (12.5)	2 (5.4)

CNS: Central Nervous System; SD: Standard Deviation; EGFR: Epidermal Growth Factor Receptor; ECOG: Eastern Cooperative Oncology Group performance status

The best objective response to treatment, based on RECIST 1.1 for both groups, was 37 patients (61.7%) with a partial response, 17 (28.3%) patients with stable disease, three patients (5%) with a complete response and three patients (5%) with disease progression. In the afatinib group, there were two patients (8.3%) with a complete response, thirteen patients (54.2%) with a partial response, three patients (12.5%) with disease progression and six patients (25%) with ongoing stable disease. For the gefitinib group, just one patient (2.8%) had a complete response, 24 patients (66.7%) had a partial response, 11 patients (30.6%) had stable disease, and no patients reported disease progression (Table 2).

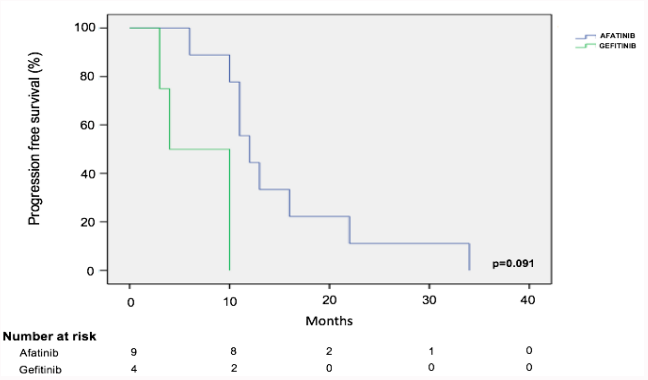

Figure 4: Progression-free survival, of patients with central nervous system metastases treated with afatinib compared with gefitinib.

Table 2: Best objective response to treatment by RECIST 1.1 on afatinib and gefitinib group.

RECIST 1.1 (p=0.871)	AFATINIB N. (%)	GEFITINIB N. (%)
Complete	2 (8.3)	1 (2.8)
Partial	13 (54.2)	24 (66.7)
Progression	3 (12.5)	0 (0)
Stable	6 (25)	11 (30.6)

RECIST: Response Evaluation Criteria in Solid Tumors

In the univariate analysis, patients with CNS metastases at diagnosis (p=0.015) and at different ECOG stages (p=0.011) showed a statistically significant difference for those who received afatinib. When the multivariate logistic regression model was performed (age, gender, ECOG performance status, smoking index, wood smoke index, CNS metastases, previous radiotherapy, and RECIST), no statistical significance was found regarding response to treatment. However, a significant difference was found in terms of mortality (p=0.001) and time to progression (p=0.029) for patients treated with afatinib.

The median PFS for patients treated with afatinib was significantly higher (11 months) compared with patients treated with gefitinib (8 months; HR=0.48, p=0.011, 95% CI 0.11 to 0.84) (Figure 2). We also found a significantly higher PFS in women (p=0.004) and a tendency toward a higher PFS in patients with CNS metastases (p=0.091) for the group treated with afatinib, as shown in Figure 3 and Figure 4.

The PFS of those treated with a TKI as a second-line treatment was also compared with that of those who received a TKI as a third-line treatment, and no significant differences were found. The PFS compared between afatinib as a second-line treatment, afatinib as third-line treatment, gefitinib as second-line treatment and gefitinib as third-line treatment showed no statistical significance.

Discussion

Previous studies have shown the superiority of treatment with TKIs on PFS compared with chemotherapy, but this was not shown when TKIs were used as a second or third-line treatment. Although a significant difference was found between using afatinib or gefitinib as a second or third-line treatment, there was no significant difference when afatinib and gefitinib groups were compared by the line of

treatment. This could result from a sample size effect.

A greater number of patients with CNS metastasis were found in the afatinib group. However, there was no significant difference in the multivariate analysis, and this may suggest that having CNS metastasis at the beginning of treatment did not influence PFS and mortality.

Other studies that are similar to the present study were performed in 2017 by Zheng et al. [34] where they investigated the effect of first-line and second-line *EGFR* TKIs in 18 patients treated with erlotinib, 30 patients treated with gefitinib, and 27 patients treated with icotinib as second-line treatment, and they showed a median PFS of 7.6 months. Miyawaki et al. [35] assessed the efficacy of erlotinib as a second or third-line treatment after chemotherapy regimens for elderly patients (38 patients, age ≥ 70 years), and they reported PFS of 7.8 months in patients with an *EGFR* mutation. Additionally, the characteristics of the population that was enrolled into the Lux-Lung 7 study [15,31] included patients with ECOG 0 or 1 and at least one measurable lesion, in accordance with RECIST 1.1, and adequate general function. Because the characteristics of the populations in the aforementioned studies are similar to those of patients included in our study and because the Lux-Lung 7 study mentioned a comparison of the same medications, we considered these studies to be a reference. We obtained similar results that support the use of TKIs and show that they have similar benefit as a second or third-line treatment.

Although the results obtained suggest the possibility of using TKIs to treat potential patients who received previous chemotherapy, it is still necessary to deal with the economic limitation that suggests that there is a lack of access to these drugs nationwide. This study forms the basis for performing a broader, prospective longitudinal study that reflects in detail the consequences of delayed TKI use.

The retrospective nature of our study limits the ability to control variables such as follow-up dates and data that were obtained during the clinical consultation. Thus, the loss of information may have resulted in the exclusion of some patients from the study. If we had established an exact date to perform the computed tomography of the thorax to evaluate the response based on RECIST 1.1, we would have been able to compare the response to treatment by imaging within the same period of time in all patients. Another limitation of the study focuses on the lack of homogeneous grading of drug toxicity by removing the precision when comparing toxicity between afatinib and gefitinib.

Thus, the use of TKIs that are applied as a second or third-line treatment showed similar results to the Lux-Lung 7 study, including improved PFS where first-line treatment was indicated. Because of the characteristics of the population that received TKIs at INER where different in terms of socio-demographic, cultural, and economic issues, the results obtained from this study can be extrapolated to developing countries. There is currently no high powered study that documents the effectiveness of treatment with TKIs that are not a first-line treatment in developing countries, so obtaining good results for the prognosis and survival of patients who are treated with TKIs as a second or third-line treatment suggests that they can be used despite a common history of chemotherapy in countries without access to oncological therapies.

More toxicity was observed in the afatinib group compared with the gefitinib, and a more homogeneous method of grading adverse effects is required to correlate the adverse events correctly with the drug administration.

Although this study has a retrospective design, it will serve as the basis to perform a larger, prospective longitudinal study that reflects in detail the consequences of delayed TKI use.

Acknowledgment

The authors would like to thank the Department of Thoracic Oncology from the "Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío" for the supervision and general administrative support to this study.

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