Original Article

Characteristics of progression to tyrosine kinase inhibitors predict overall survival in patients with advanced non-small cell lung cancer harboring an *EGFR* mutation

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Background: Non-small cell lung cancer (NSCLC) harboring EGFR-sensitizing mutations has a distinct biology and heterogeneous clinical behavior. We evaluated the characteristics to progression such as clinical patterns of progression (dramatic, gradual, and local) with the prognosis of NSCLC patients treated with tyrosine kinase inhibitors (TKIs).

Methods: We reviewed 123 advanced-NSCLC patients with an EGFR-sensitizing mutation treated with TKIs (gefitinib, erlotinib and afatinib). We assessed patients according to clinical factors and progression pattern to TKIs at three centers.

Results: For all patients, 58.5%, 31.7% and 9.8% harbored exon19 deletion, exon21 L858R mutation and other-sensitivity mutations, respectively. Median progression-free survival (PFS) was 8.8 months (95% CI: 7.9–9.7). Sixty percent of patients were asymptomatic. Dramatic-progression was the most frequent pattern (50.4%), followed by gradual-progression (32.5%), and local-progression (17.1%). Median overall survival (OS) was 23.1 months (95% CI: 17.4–28.9). In the univariate analysis, factors associated to a longer OS included pattern [gradual-progression (32.1), dramatic (19.5) and local (18.8 months), P=0.008], and the time to progression to TKI [>12 months (38.5), 6-12 months (19.1), <6 months (9.6), P<0.001]. Multivariate analysis showed that only time to progression to TKI was independently associated to OS and PFS.

Conclusions: Factors at TKI progression associated to a longer OS can define a subset of patients who may benefit from continued TKI therapy, as well as from local-ablative therapy in progression sites, especially in patients without T790M or who lack access to third-generation TKI.

Keywords: Lung adenocarcinoma; exon 19; gefitinib; afatinib; patterns of progression; epidermal growth factor receptor (EGFR)

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Introduction

Lung cancer is the leading cause of cancer-related deaths in the world, it is often diagnosed at a late stage and survival with traditional first-line chemotherapy platinum-based regimens is generally poor (1,2). Currently, molecular testing for patients with advanced-stage lung adenocarcinoma is a routine activity, which aims to define the most optimal treatment strategy (3,4). Prognosis for advanced stage disease has improved in the past 20 years with tyrosine kinase inhibitors (TKIs) in patients with epidermal growth factor receptor (*EGFR*) mutation, nevertheless, uncommon mutations are associated with poor prognosis (5,6). Non-small cell lung cancer (NSCLC) harboring *EGFR*-sensitizing mutations has a distinct biology with improved patient survival compared to other subtypes of lung cancer. Somatic mutations in *EGFR* have been demonstrated as the most important biomarker in predicting the clinical outcome for NSCLC patients treated with EGFR-TKIs (3,7). In randomized phase III trials, treatment of NSCLC patients who present an activating *EGFR* mutation with EGFR-TKIs was associated with a longer progression-free survival (PFS), higher radiographic response rates and improved quality of life when compared to treatment with standard first-line platinum-based chemotherapy, in addition to being cost effective (8-10). However, despite a dramatic initial response, almost all patients treated with EGFR-TKIs eventually develop acquired resistance to these drugs with a median time to disease progression of 10–14 months (5,8,9,11-15). The Response Evaluation Criteria in Solid Tumors (RECIST) has been used as a standard method for assessing response and defining progression in cancer patients receiving treatment (15). However, there is more evidence every day, which suggests that continuing treatment beyond radiographic progression could confer an advantage, especially in patients treated with targeted therapy or immunotherapy (16). Treatment guidelines for NSCLC recommend continued use of TKI and local therapy after disease progression in asymptomatic patients. This strategy mirrors experience in other tumors, particularly *HER2*-amplified breast cancer, in which it is also recommended continuing anti-HER2 therapy despite disease progression (17).

Several studies have evaluated the impact of patterns of progression after treatment with TKIs showing that continued EGFR-TKI treatment after progressive disease (PD) prolongs survival time compared to patients who switch to cytotoxic chemotherapy in a select population (18). Yang *et al.* (19) separated the pattern of progression after treatment with EGFR-TKI (erlotinib or gefitinib) as dramatic, gradual, and local progression. Their results show that patients with a gradual progression have better results in PFS and could represent a subset of patients who benefit from continuing TKIs rather than switch to cytotoxic chemotherapy. They also suggest that chemotherapy is better for the dramatic group with rapid tumor increment, and that patients with local progression benefit from continued therapy with TKIs and local treatment.

Using the criteria established by Yang to define models of progression to TKIs, we performed a retrospective analysis of patients treated with gefitinib, erlotinib or afatinib. The purpose of the current study was to evaluate patterns of progression in patients who received TKIs, and additionally assess the relationship between these progression patterns and clinical outcome in *EGFR*-mutated NSCLC patients.

Methods

Patients

We retrospectively collected clinical information from patients with histologically confirmed metastatic NSCLC, treated from June 2009 to December 2015 in three oncology centers of Latin America (Mexico, Costa Rica and Colombia). We examined patients with advanced NSCLC harboring activating EGFR mutation who were treated with EGFR-TKI in the first or second-line setting, and who showed radiological progression after treatment with EGFR-TKIs. We confirmed PD using the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1).

Progression patterns at the time of initial EGFR-TKIs failure

We used the criteria established by Yang (19) to define models of disease progression for TKI-treated NSCLC patients based on three clinical factors: the duration of disease control, evolution of tumor burden (rapid: *vs.* minor), and clinical symptoms. A detailed description is presented in *Figure 1*.

Statistical analysis

For descriptive purposes, continuous variables were summarized as arithmetic means and SDs, whereas categorical variables were expressed as frequencies

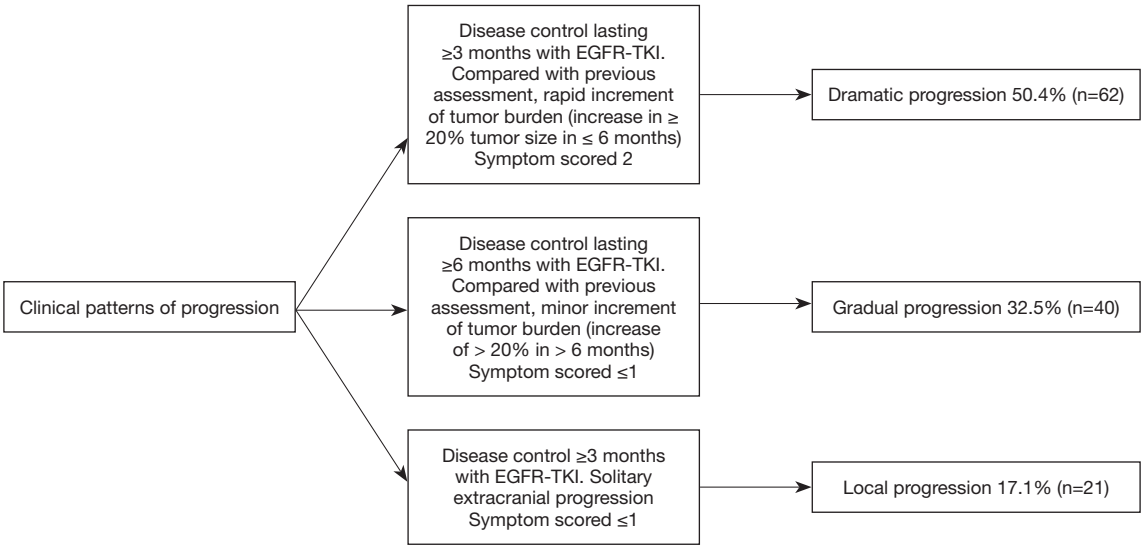

Figure 1 Clinical patterns of progression to tyrosine kinase inhibitors.

and proportions. The χ^2 or Fisher exact test were used for assessing the statistical significance of clinical and biochemical parameters. All continuous variables were dichotomized according with the median for PFS and OS analyses. PFS was defined as the time from first dose of EGFR-TKI to the first documentation of PD, or death from any cause or lost to follow up. Time to progression was defined as the time from first dose of EGFR-TKI to the first documentation of PD. Overall survival (OS) was calculated from first dose of EGFR-TKI to the last visit or death from any cause. The Kaplan-Meier method was used to estimate survival curves. The log-rank test was used to compare survival curves among patient groups. The multivariate Cox proportional hazards regression was used to evaluate independent prognostic factors associated with PFS or OS. All statistical tests were two-sided and P<0.05 was deemed to be statistically significant. SPSS software (version 22; SPSS; Chicago, IL, USA) was used for data analysis.

Results

Patient characteristics

From June 2009 to December 2015, 123 patients with advanced NSCLC were analyzed at three Latin America (Mexico, Costa Rica and Colombia) oncology centers. Overall, 63.4% of patients were female and the mean age was 59.9 years (±12.7). Most patients were never-smokers (72.4%) and the Eastern Cooperative Oncology Group performance status (ECOG) was 0–1 in 69.9%. Histological examination revealed adenocarcinoma in 120 (97.6%) patients. All patients demonstrated an activating *EGFR* mutation, the main mutation detected was exon 19 deletion (58.5%), while the L858R mutation was detected in 39 patients (31.7%). These patients had been treated with TKIs in the first (42.3%) or second-line (57.7%) setting, following chemotherapy.

Patient characteristics according to clinical patterns of progression in relation to PFS

For all the studied population, 62 patients developed dramatic progression (50.4%), 40 patients had gradual progression (32.5%) and 21 patients presented local progression (17.1%). Demographic, clinical and pathological characteristics from patients were similar among the three progression pattern groups. However, patients with dramatic progression were more likely to have a worse ECOG performance status (≥2) in comparison with patients with gradual or local progression (P=0.012). At the time of progression, 39.8% of the patients were symptomatic, most symptomatic patients were in the group of dramatic progression (48.4%), while fewer patients were in the gradual progression (30.0%) or local progression (33.3%), however, this difference was not statistically significant (P=0.144) (*Table 1*).

The median PFS was 8.8 months for all patients (95%

Table 1 General characteristics of patients by pattern of progression to TKIs (n=123)

Variable	Total (n=123)	Dramatic progression (n=62)	Gradual progression (n=40)	Local progression (n=21)	P
Gender					0.878
Female	78 (63.4)	38 (61.3)	26 (65.0)	14 (66.7)	
Male	45 (36.6)	24 (38.7)	14 (35.0)	7 (33.3)	
Age (yrs)					
Mean (SD)	59.9 (±12.7)	61.5 (±12.2)	58.1 (±14.9)	58.8 (±9.0)	0.394
<60	52 (42.3)	23 (37.1)	19 (47.5)	10 (47.6)	
60+	71 (57.7)	39 (62.9)	21 (52.5)	11 (52.4)	0.503
History of smoking					0.898
Never	89 (72.4)	44 (71.0)	29 (72.5)	16 (76.2)	
Smoker	34 (27.6)	18 (29.0)	11 (27.5)	5 (23.8)	
ECOG (CR)					0.012
0–1	86 (69.9)	36 (58.1)	34 (85.0)	16 (76.2)	
≥2	37 (30.1)	26 (41.9)	6 (15.0)	5 (23.8)	
Stage					0.551
III	8 (6.5)	3 (4.8)	4 (10.0)	1 (4.8)	
IV	115 (93.5)	59 (95.2)	36 (90.0)	20 (95.2)	
Brain metastases					
Absent	41 (69.6)	24 (65.6)	10 (50.0)	74 (64.5)	0.336
Present	18 (30.4)	12 (34.5)	10 (50.0)	41 (35.5)	
Lung metastases					0.110
Absent	32 (54.3)	27 (75.9)	10 (50)	69 (60.2)	
Present	27 (45.7)	9 (24.1)	10 (50)	46 (39.8)	
Pleura metastases					0.303
Absent	41 (69.6)	22 (62.1)	17 (83.3)	80 (69.9)	
Present	18 (30.4)	14 (37.9)	3 (16.7)	35 (30.1)	
Lymphatic nodes metastases					0.283
Absent	47 (80.4)	34 (93.1)	18 (88.9)	99 (86.0)	
Present	12 (19.6)	2 (6.9)	2 (11.1)	16 (14.0)	
Liver metastases					0.902
Absent	46 (78.3)	29 (79.3)	17 (83.3)	92 (79.6)	
Present	13 (21.7)	7 (20.7)	3 (16.7)	23 (20.4)	

Table 1 *(continued)*

Table 1 *(continued)*

Variable	Total (n=123)	Dramatic progression (n=62)	Gradual progression (n=40)	Local progression (n=21)	P
Adrenal glands metastases					0.220
Absent	54 (91.3)	36 (100.0)	18 (88.9)	108 (93.5)	
Present	5 (8.7)	0 (0)	2 (11.1)	7 (6.5)	
Bone metastases					0.307
Absent	37 (63.0)	24 (65.5)	9 (44.4)	69 (60.2)	
Present	22 (37.0)	12 (34.5)	11 (55.6)	46 (39.8)	
Other metastases					0.241
Absent	56 (95.7)	34 (93.1)	17 (83.3)	106 (92.5)	
Present	3 (4.3)	2 (6.9)	3 (16.7)	9 (7.5)	
Histology					0.721
Adenocarcinoma	120 (97.6)	61 (98.4)	39 (97.5)	20 (95.2)	
Other NSCLC	3 (2.4)	1 (1.6)	1 (2.5)	1 (4.8)	
EGFR mutation type					0.957
Del 19	72 (58.5)	37 (57.9)	23 (57.5)	12 (57.1)	
L858R	39 (31.7)	20 (32.3)	13 (32.5)	6 (28.6)	
Other	12 (9.8)	5 (8.1)	4 (10.0)	3 (14.3)	
Line of TKI					0.139
1st line	52 (42.3)	27 (43.5)	20 (50.0)	5 (23.8)	
2nd line	71 (57.7)	35 (56.5)	20 (50.0)	16 (76.2)	
Type of TKI					0.307
Gefitinib	27 (22.0)	11 (17.7)	10 (25.0)	6 (28.6)	
Erlotinib	64 (52.0)	31 (50.0)	24 (60.0)	9 (42.9)	
Afatinib	32 (26.0)	20 (32.3)	6 (15.0)	6 (28.6)	
Symptoms at progression					0.144
Asymptomatic	74 (60.2)	32 (51.6)	28 (70.0)	14 (66.7)	
Symptomatic	49 (39.8)	30(48.4)	12 (30.0)	7 (33.3)	
Time to progression to TKI					0.139
<6 months	40 (32.5)	22 (35.5)	9 (22.5)	9 (42.9)	
6–12 months	43 (35.0)	23 (37.1)	12 (30.0)	8 (38.1)	
>12 months	40 (32.5)	17 (27.4)	19 (47.5)	4 (19.0)	

Data are shown as number (%). SD, standard deviation; yrs, years; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

CI, 7.9–9.7 months). The univariate analysis did not show differences in PFS by gender, age, smoking status, ECOG performance status, clinical stage, or *EGFR* mutation type (*Table 2*). Baseline factors associated to a longer PFS in the univariate analysis included line of TKI treatment [first (11.1, 95% CI: 7.2–14.8) *vs.* second-line (8.1, 95% CI: 6.3–9.8), P<0.001] and time to progression to TKI [<6 months (3.8, 95% CI: 2.8–4.9), 6-12 months (8.9, 95% CI: 8.3–9.4), >12 months (22.0, 95% CI: 18.1–26.0); P<0.001]. In the multivariate analysis the only two factors independently associated with PFS were disease stage (HR: 0.4, 95% CI: 0.2–0.9; P=0.027) and time to progression to TKI (HR: 0.01, 95% CI: 0.0–0.03; P<0.001) (*Table 2*).

Factors at progression associated with a longer PFS included type of progression pattern [gradual (10.4, 95% CI: 7.3–13.5) *vs.* local (7.4, 95% CI: 3.6–11.2), *vs.* dramatic, P=0.039] and symptoms at progression [asymptomatic (9.8, 95% CI: 7.3–12.4), *vs.* symptomatic (6.9, 95% CI: 4.7–9.1), P=0.001] (*Figure 2A,B*).

Patient characteristics according to clinical patterns of progression in relation to OS

Median overall survival (OS) was 23.1 months (95% CI: 17.4–28.9). The univariate analysis did not show differences in OS by gender, age, smoking status, ECOG performance status, clinical stage, NSCLC histology, EGFR mutation type, nor by line or type of TKI (*Table 3*). Factors associated to a longer OS included pattern of progression [gradual progression (32.1, 95% CI: 23.7–40.4) *vs.* dramatic (19.5, 95% CI: 10.2–28.7) and local (18.8, 95% CI: 12.9–24.8 months), P=0.008] (*Figure 3A*), symptoms at the time of progression [asymptomatic (27.1, 95% CI: 16.6–37.7) *vs.* symptomatic (19.6 months, 95% CI: 10.8–28.4), P=0.084) (*Figure 3B*), and the time to progression to TKI [>12 months (38.5, 95% CI: 26.0–50.9), 6–12 months (19.1, 95% CI: 13.7–24.5) <6 months (9.6, 95% CI: 3.9–15.1), P<0.001] (*Figure 3C*). The latter factor was the only independent factor associated to a longer OS in the multivariate analysis (HR: 0.01, 95% CI: 0.00–0.03; P<0.001) (*Table 3*).

Additionally, a subgroup analysis which exclusively analyzed patients with exon 19 deletion revealed that a gradual pattern of progression to TKI was associated with a longer OS [gradual (32.8, 95% CI: 4.3–25.3), *vs.* local (32.4, 95% CI: 18.9–45.9) *vs.* dramatic (14.8, 95% CI: 4.3–25.3), P=0.008) (*Figure 4A*). However, this was not the case for patients harboring an exon21 L858R and other sensitizing mutations [gradual (22.4, 95% CI: 14.7–40.1) *vs.* local (14.5, 95% CI: 9.8–19.1), vs dramatic (22.7, 95% CI: 18.1–27.3), P=0.331) (*Figure 4B*).

Discussion

Molecular targeted therapies [erlotinib (5,20,21) gefitinib (8,9,11,22), afatinib (12,13,23,24)], have improved PFS in *EGFR*-positive lung cancer patients. Interestingly, epidemiological reports have shown a higher *EGFR* mutation prevalence in our study population (25,26). This can be explained by different exposure factors associated such as wood smoke exposure (27), high prevalence of chronic tuberculosis infection (28) and ethnicity (29). However, despite spectacular initial response to EGFR-TKIs, most patients eventually develop resistance to treatment and, subsequently, radiological and/or clinical progression.

In our study, in agreement with previous reports, we showed that patients with a dramatic pattern of progression were more likely to have a worse prognosis. This suggests that these patients may develop more aggressive resistance mechanisms. Hispanic patients undergoing re-biopsy show different mechanisms of acquired resistance, including the substitution of methionine for threonine at position 790 (T790M) in 47.1% of cases (14,30). However, PIK3CA and *EGFR* amplification is higher in Hispanics compared to other populations (14). Recently, Oya *et al.* described the progression pattern in patients with T790M mutation. In this study, response to EGFR-TKI, a duration of response greater than 6 months and single progression were associated with the development of T790M mutation (31). Our data showed that the median OS was significantly better in the group of patients with a sustained response which lasted for more than 12 months. This could be explained because a longer exposure to a TKI confers the time to develop a resistance mutation. Following this observation, previous studies have shown slower cell growth and favorable outcomes in patients with acquired resistance to EGFR-TKI associated to T790M mutations (32-35).

Suspending TKI therapy in patients who progress may not always be the best course, as it may result in accelerated tumor growth and precipitation of symptoms (36). Riely *et al.* (37) showed that patients who have responded for more than 6 months to erlotinib or gefitinib could benefit from continuing treatment despite documented progression of disease by RECIST criteria. Discontinuing treatment will result in worsening of lung cancer related symptoms, increase in tumor size and tumor fluorodeoxyglucose (FDG) uptake, a phenomenon described as "tumor flare". In these

Table 2 Univariate and multivariate analyses of the baseline factors associated with PFS of patients

Variable	Univariate		Multivariate	
	Median (95% CI)	P	HR (95% CI)	P
Overall	8.8 (7.9–9.7)			
Sex				
Female	8.9 (7.6–10.1)			
Male	8.7 (7.9–9.4)	0.648		
Age (yrs)				
<60	8.5 (7.5–9.6)			
60+	9.1 (7.9–10.3)	0.101	1.1 (0.7–1.6)	0.793
History of smoking				
Never	8.9 (7.8–10.1)			
Smoker	8.7 (7.4–10.0)	0.672		
ECOG (CR)				
0–1	8.9 (7.9–10.0)			
≥2	8.7 (7.6–9.8)	0.567		
Stage				
III	8.5 (1.4–15.5)			
IV	8.8 (7.9–9.8)	0.165	0.4 (0.2–0.9)	0.027
Brain metastases at diagnosis				
Absent	8.5 (7.3–9.7)			
Present	6.5 (4.7–8.3)	0.455		
Histology				
Adenocarcinoma	8.9 (7.9–9.8)			
Other NSCLC	3.8 (3.6–4.1)	0.056	0.9 (0.3–3.1)	0.896
EGFR mutation type				
Del 19	8.5 (6.6–10.5)			
L858R	8.9 (7.5–10.2)			
Other	8.9 (7.8–10.1)	0.757		
Line of TKI				
1st line	11.1 (7.2–14.8)			
2nd line	8.1 (6.3–9.8)	<0.001	0.8 (0.7–1.6)	0.862
Pattern of progression to TKI				
Dramatic	8.1 (6.5–9.7)			
Gradual	10.4 (7.3–13.5)			
Local	7.4 (3.6–11.2)	0.039	0.8 (0.6–1.0)	0.080
Symptoms at progression				
Asymptomatic	9.8 (7.3–12.4)			
Symptomatic	6.9 (4.7–9.1)	0.001		
Time to progression to TKI				
<6 months	3.8 (2.8–4.9)			
6–12 months	8.9 (8.3–9.4)			
>12 months	22.0 (18.1–26.0)	<0.001	0.01 (0.0–0.03)	<0.001

SD, standard deviation; yrs, years; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

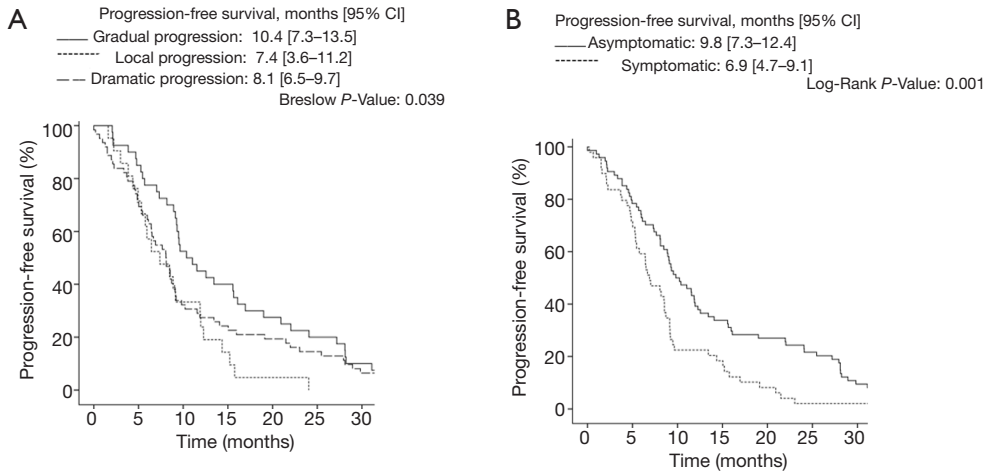

Figure 2 Kaplan-Meier Curves for progression-free survival, according to pattern of progression (A) and symptoms at progression (B) to tyrosine-kinase inhibitors.

Table 3 Univariate and multivariate analysis of the OS of patients

Variable	Univariate analysis		Multivariate analysis	
	Median (95% CI)	P	HR (95% CI)	P
Overall	23.1 (17.4–28.9)		–	–
Gender		0.923		
Female	24.1 (17.5–30.8)		–	–
Male	19.8 (10.5–29.1)		–	–
Age (yrs)		0.992		
<60	23.8 (16.8–30.7)		–	–
60+	22.7 (12.6–32.7)		–	–
History of smoking		0.740		
Never	23.1 (16.4–29.9)		–	–
Smoker	25.4 (19.4–31.5)		–	–
ECOG (CR)		0.806		
0–1	23.8 (17.1–30.4)		–	–
≥2	19.6 (5.6–33.5)		–	–
Stage		0.524		
III	19.1 (14.9–23.2)		–	–
IV	23.8 (17.6–29.9)		–	–
Present	22.7 (15.1–30.3)		–	–

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Univariate analysis		Multivariate analysis	
	Median (95% CI)	P	HR (95% CI)	P
Histology		0.179		
Adenocarcinoma	23.8 (16.7–30.8)			
Other NSCLC	19.1 (NR)		0.6 (0.2–1.9)	0.396
EGFR mutation type		0.433		
Del 19	24.9 (13.9–30.0)		–	–
L858R	27.1 (16.5–37.7)		–	–
Other	23.9 (12.2–26.7)		–	–
Line of TKI		0.370		
1	27.1 (11.3–42.9)		–	–
2	18.9 (17.8–20.1)		–	–
3+	24.9 (18.4–31.5)		–	–
Pattern of progression to TKI		0.008*		
Dramatic	19.5 (10.2–28.7)			
Gradual	32.1 (23.7–40.4)			
Local	18.8 (12.9–24.8)		0.8 (0.6–1.0)	0.082
Symptoms at progression		0.084*		
Asymptomatic	27.1 (16.6–37.7)			
Symptomatic	19.6 (10.8–28.4)		1.4 (0.9–2.0)	0.129
Time to progression to TKI		<0.001		
<6 months	9.6 (3.9–15.1)			
6–12 months	19.1 (13.7–24.5)			
>12 months	38.5 (26.0–50.9)		0.01 (0.00–0.03)	<0.001

*, Breslow-test, otherwise Log-rank Test. SD, standard deviation; yrs, years; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; BSC, best supportive care; HR, hazard-ratio.

patients TKI reintroduction produced stabilization or improvement in symptoms and reduction in tumor FDG uptake (37). However, it is important to dissect which patients would benefit from continued therapy.

Several studies have attempted to correlate the pattern of progression to EGFR-TKIs with clinical outcomes (38). Gandara *et al.* (39) proposed three subtypes of progression according to the site and mechanisms of acquired resistance: (I) central nervous system sanctuary PD, (II) oligo-PD and (III) systemic PD. In this classification oligo-PD was defined as new lesions, or growth of existing lesions, in a localized area (maximum four sites). However, it does not consider other clinical variables, or time to progression. In a Japanese study (40) which included 104 patients with *EGFR* mutated NSCLC treated with TKIs and evidence of PD, the oligo progression and asymptomatic status were significantly associated with clinical outcome after failure of EGFR-TKIs, regardless of subsequent treatment. However, the analysis included 9 patients with carcinomatous meningitis as oligo-progression. These patients are widely recognized for representing a subgroup of poor prognosis. Data from the univariate analysis of our study populations allows us to present two specific subgroups of patients with improved OS: patients with gradual progression

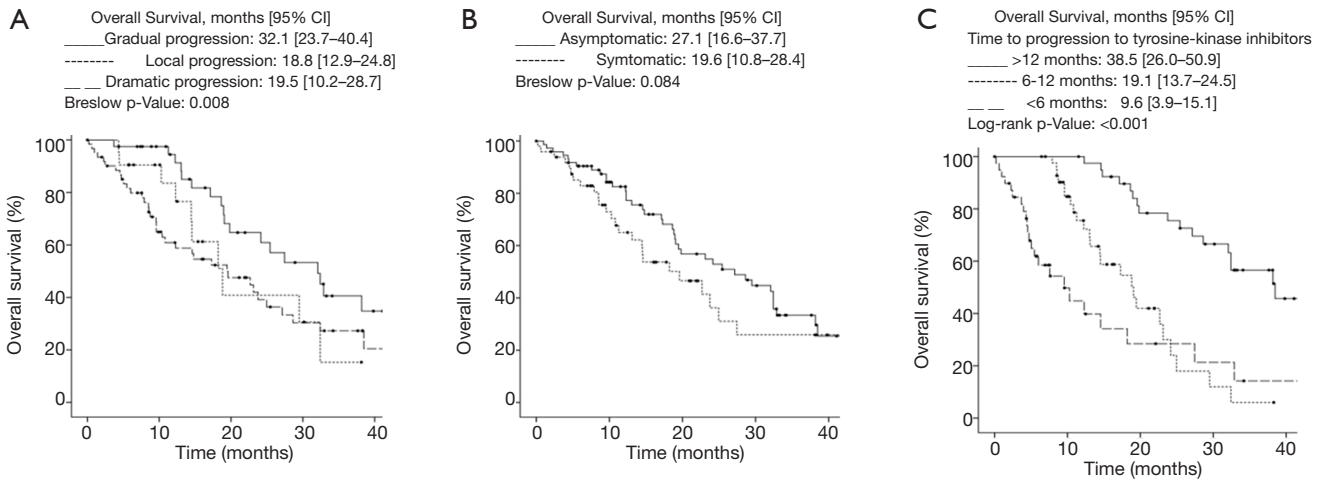

Figure 3 Kaplan-Meier curves for overall survival (OS) according to pattern of progression (A), symptoms at progression (B) and time to progression (C) to tyrosine-kinase inhibitors.

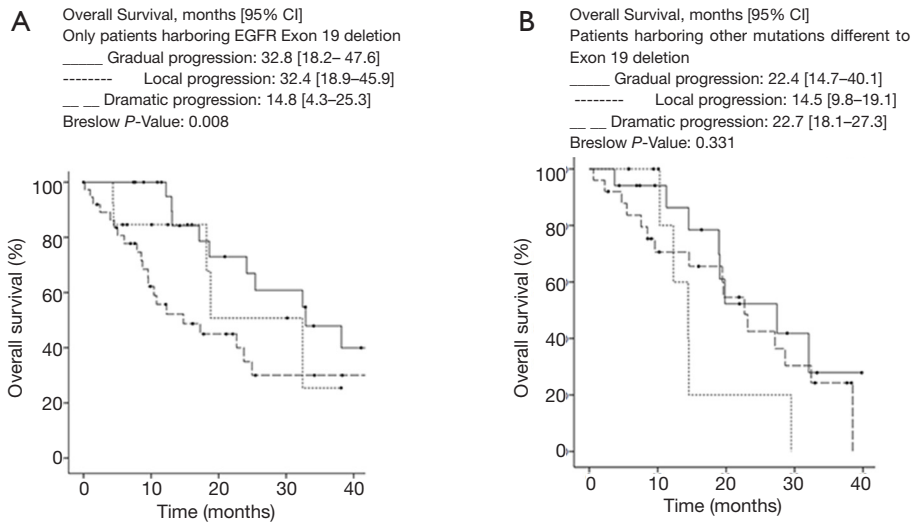

Figure 4 Kaplan-Meier curves for subgroup analysis of overall survival, according to pattern of progression to tyrosine-kinase inhibitors and mutation subtype.

and patients with a time to progression to TKI of at least 12 months. This last characteristic was the only statistically significant independent factor associated with a longer OS in the multivariate analysis (41).

In the AURA 3 trial, osimertinib showed to be more effective than combination platinum-based chemotherapy in patients with T790M-positive NSCLC after disease progression with first-line EGFR-TKI therapy (42), becoming a standard of treatment in this group of patients. However, although the benefit of osimertinib is overwhelming, half of the patients will not be candidates (T790M-negative) and others will not have access to the drug (43). Our data helps identify a subset of patients treated with TKIs who are likely to benefit from continuing treatment beyond progression, local ablative treatment and close surveillance, especially in countries where access to third-generation TKIs is limited. The ASPIRATION (Asian Pacific trial of Tarceva® as first-line in EGFR mutation) trial demonstrated the efficacy of first-line treatment with erlotinib, and showed that treatment continuation is

feasible beyond progression. This is helpful in delaying treatment with chemotherapy, thus avoiding unnecessary toxicity, in patients with good response to TKI, longer time to progression or good ECOG at the time of PD (18). Therefore, it is expected that patients with slow progression might benefit from this strategy. Patients who have dramatic progression have rapid functional impairment, therefore, identification of this subgroup of patients is important to avoid delaying further treatment.

This is the largest reported series that evaluates the details of progression patterns and prognosis to treatment with EGFR-TKIs for advanced NSCLC in patients harboring an *EGFR* mutation. This work has inherent limitations due to its retrospective design, including the lack of a control arm and the small number of patients included, which might condition the sensibility of the multivariate analysis. However, future studies, which seek to evaluate TKI treatment beyond progression, might consider progression characteristics and patterns, in order to better identify patients who might reap more benefit from continuing TKI therapy.

Conclusions

Acquired resistance to TKIs is the common scenery for EGFR-mutated patients receiving targeted therapy. Our data suggests that the pattern of progression and time to TKI response are relevant factors to be considered at the time of progression to TKI, especially in countries with restrictions to molecular tests and limited health resource. These results are aimed at improving the selection of patients who are candidates for a therapeutic switch or re-challenge. However, validation of these results is required with randomized prospective clinical trials. Data from studies evaluating osimertinib conclude this is a feasible first-line treatment, and these concepts may be applied in patients treated with third-generation therapy in the first-line setting. These results would facilitate the development of therapeutic strategies beyond PD diagnosis after first-line EGFR-TKI treatment failure.

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Footnote

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Ethical Statement: The protocol was approved by a central ethical and scientific committee in the National Cancer Institute in Mexico City (approval number 011/012/ICI, CB/678).

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