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Outcome of Patients with Lung Adenocarcinoma Harboring Common and Rare Epidermal Growth Factor Receptor Mutations in Response to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

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ABSTRACT

Background: Approximately 10-40% of patients with adenocarcinoma have somatic mutations in the epidermal growth factor receptor. The presence of the common activating epidermal growth factor receptor mutations (DEL 19/L858R) is closely associated with sensitivity to reversible tyrosine kinase inhibitors. Conversely, rare mutations (G719X/L861Q/768I/T790M/Exon 20 insertion) have usually been associated with resistance to epidermal growth factor receptor tyrosine kinase inhibitors and poorer prognosis. **Methods:** We conducted a literature review up to January 2015 using PubMed and Embase to identify phase II and III randomized trials and case series that assessed first-line epidermal growth factor receptor tyrosine kinase inhibitor therapy versus standard platinum-based chemotherapy regimens in previously untreated patients with positive epidermal growth factor receptor mutation advanced lung adenocarcinoma with uncommon epidermal growth factor receptor mutations and response to epidermal growth factor receptor tyrosine kinase inhibitors, and compared them with our previous study to determine differences in response rates as well as clinical factors among patients with common and rare mutations. **Review:** Overall, in patients with epidermal growth factor receptor mutations, women have shown a better progression-free survival to epidermal growth factor receptor tyrosine kinase inhibitors compared to men,

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and also, rare epidermal growth factor receptor mutations are more frequent in high-grade adenocarcinomas than in low-grade tumors. We report a significant number of patients with epidermal growth factor receptor mutations; most of the studies refer to the status of the mutation, but only a few of them report the type of mutation. Concerning common mutations, these studies report a longer progression-free survival with epidermal growth factor receptor tyrosine kinase inhibitors versus chemotherapy (9.2-13.6 vs. 4.6-6.9 months; $p < 0.001$). However, progression-free survival for uncommon mutations with epidermal growth factor receptor tyrosine kinase inhibitors versus standard chemotherapy was lower (1.4-3.9 vs. 5.1-5.9 months, respectively), with no significant difference. **Conclusion:** Our findings suggest that due to their low response rates and short progression-free survival in response to epidermal growth factor receptor tyrosine kinase inhibitors, only patients with uncommon epidermal growth factor receptor mutations should receive platinum-based chemotherapy as first-line treatment. Consequently, epidermal growth factor receptor tyrosine kinase inhibitors could be reserved as a second- or third-line treatment. (J CANCEROL. 2015;2:56-63)
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Key words: EGFR mutation. EGFR tyrosine kinase inhibitor. Adenocarcinoma lung cancer. Deletion exon 19. L858R mutation. Uncommon mutations.

INTRODUCTION

Lung cancer is the main cause of cancer-related mortality worldwide, accounting for 1.6 million deaths in 2012 alone[1]. This disease has a poor prognosis due in part to late-stage diagnosis, overall five-year survival rates of 15-16%[2-4], and a response rate of 30% to platinum-based chemotherapy (standard initial treatment)[5]. Non-small cell lung cancer (NSCLC) is the main type of lung cancer present in patients, and its histology includes: squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, with the latter being the most common subtype[4].

Since the last decade, the identification of driver mutations within lung cancer tumors has turned treatment towards these specific mutations. In 2004 the epidermal growth factor receptor (EGFR) gene, a membrane-bound receptor tyrosine kinase (TK) that regulates cell growth, was identified. The EGFR receptor activates after binding to the peptide growth factors of the EGF family; upon ligand binding and after dimerization, the ErbB receptors auto- and trans-phosphorylate tyrosine residues[6]. Thus, EGFR driver mutations result in a receptor with deregulated signaling, driving cell growth with a cellular dependence on EGFR receptor TK signaling, which in turn is strongly associated with therapeutic sensitivity to tyrosine kinase inhibitor (TKI) drugs (Fig. 1)[7-9].

Approximately 10-40% of patients with lung adenocarcinoma have somatic mutations in the EGFR, and its frequency varies according to ethnicity and some unique and molecular biological characteristics[10]. It was identified to be more likely that female patients, non-smokers, lepidic and acinar adenocarcinoma subtypes, individuals exposed to wood-smoke, and Asians (50%) present these mutations[3,11]. Additionally, the percentage of EGFR mutations is higher in Latin Americans (26%) than Caucasians (15%)[12].

The EGFR TKIs, gefitinib and erlotinib, marked a turning point for the treatment of NSCLC patients with driver mutations. These are orally administered agents that bind at the catalytic cleft of EGFR in competition with adenosine triphosphate (ATP), suppressing EGFR phosphorylation and downstream signaling[6]. Considering that the EGFR pathway promotes tumor growth and progression by stimulating cancer cell proliferation, invasion, and metastasis, as well as inhibiting apoptosis, the use of these agents is a logical step for targeting this pathway[7,11,13].

It is known that EGFR-TKIs have better results in EGFR-positive mutation status patients due to the

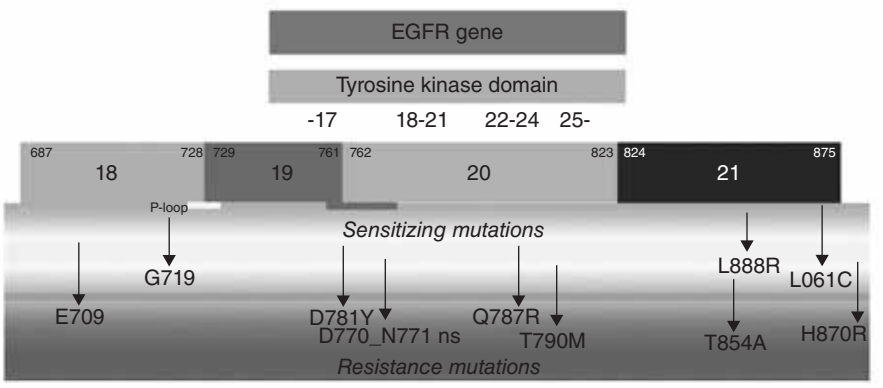

Figure 1. Graphic representation of epidermal growth factor receptor somatic mutations within exons 18-21 of the tyrosine kinase domain of the gene (arrows). The most common sensitizing (light grey background) and resistance (dark grey background) mutations are represented *(modified with permission from Massarelli, et al. Lung Cancer. 2013;80:235-41).*
EGFR: Epidermal growth factor receptor.

association of its presence to the sensitivity to reversible EGFR-TKIs. Patients with these common mutations display EGFR-TKI response rates of approximately 70%, a median progression-free survival (PFS) of approximately 9-12 months, and overall survival (OS) rates that may exceed 20-32 months[14-17]. However, the impact of these drugs is not well established for the outcome of patients harboring rare EGFR mutation status.

We conducted a review of the literature including phase II/III randomized clinical trials and case series in which previously untreated patients with advanced NSCLC were prospectively randomized to receive either EGFR-TKIs or standard chemotherapy. The purpose of the analysis was to define clinical factors as well as differences in response rates, such as OS and PFS, in advanced NSCLC associated with common and rare EGFR mutations, and compare them with our previous report[18].

METHODS

We conducted a search in PubMed and Embase for English-language studies published from database inception to January 2015. The search strategy aimed to identify phase II/III randomized trials and case series assessing first-line EGFR-TKIs therapy versus standard platinum-based chemotherapy regimens in previously untreated patients with advanced lung adenocarcinoma and EGFR mutation.

The search terms included: “phase III”, “phase II”, “advanced” or “metastatic lung adenocarcinoma”, “EGFR common mutations” and “EGFR uncommon mutations”. The literature search identified 1,466 records, from which 118 were considered potentially relevant. Ten clinical trials and case series were selected, including a total sample size of 1,959 EGFR-mutated patients that compare mutation types and response to TKIs[18-27].

The main outcomes used for comparison were: PFS, defined as the length of time during and after the treatment that a patient lives with the disease but it does not get worse, and OS, defined as the length of time from the date of the start of treatment that patients diagnosed with the disease are still alive. Both were identified regarding advanced NSCLC patients with common and rare EGFR status mutation treated with either first-line chemotherapy or EGFR-TKIs.

Table 1. Phase III clinical trials, overall and progression-free survival regarding epidermal growth factor receptor common mutations, chemotherapy versus epidermal growth factor receptor-tyrosine kinase inhibitors

Trial Common Mutations (DEL 19/L858R)	EGFR-TKI	(n)	PFS to CT (months)	PFS to EGFR TKI (months)	p	OS to CT (months)	OS to EGFR TKI (months)	p
EURTAC (2012)[22]	Erlotinib	173	5.2	9.7	< 0.001			
TORCH (2012)[23]	Erlotinib	760	6.9	9.7	< 0.001	18.1	32.5	< 0.001
OPTIMAL (2011)[24]	Erlotinib	165	4.6	13.1	< 0.001			
Maemondo, et al. (2010)[25]	Gefitinib	230	5.4	10.8	< 0.001	23.6	30.5	< 0.001
WJTOG3405 (2010)[26]	Gefitinib	177	6.3	9.2	< 0.001			
LUX-Lung 3 (2012)[27]	Afatinib	345	6.9	13.6	< 0.001	21.1	33.3	< 0.001
LUX-Lung 3 (2012)[28]	Afatinib	364	5.6	11.0	< 0.001	18.4	31.4	< 0.001

OS: overall survival; PFS: progression-free survival; CT: chemotherapy; EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor.

Table 2. Case series: progression-free and overall survival in common and uncommon mutation patients comparing chemotherapy versus epidermal growth factor receptor-tyrosine kinase inhibitors

Trial	(n)	Common mutations (DEL 19/L858R)	Uncommon mutations (G719X/L861Q/768I/T790M/ Exon 20 insertion)	p
Arrieta, et al. (2014)[29]	188			
– PFS to CT		6.5	5.1	0.042
– PFS to TKI		16.5	3.9	< 0.001
– OS to CT/TKI		37.3	17.4	< 0.001
Watanabe, et al. (2014)[30]	225		(G719X/L861Q)	
– PFS to CT		5.4	5.9	0.847
– PFS to TKI		11.4	2.2	< 0.001
– OS to CT		28.0	22.8	0.358
– OS to TKI		29.3	11.9	< 0.001
Wu, et al. (2011)[31]	627		Exon 20 insertion	
– PFS to TKI		8.5	1.4	< 0.001
– OS to TKI		19.6	4.8	< 0.001

OS: overall survival; PFS: progression-free survival; CT: chemotherapy; EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor.

REVIEW

Progression-free survival

Table 1 shows the selected phase III clinical trials comparing PFS to either TKI or chemotherapy regarding EGFR common mutations. As seen in these studies, patients with common mutations who received TKIs showed a better PFS than patients who received standard chemotherapy (9.2-13.6 vs. 4.6-6.9 months, respectively; $p < 0.001$).

When we compared uncommon mutations in case series, the PFS in the TKI-chemotherapy group was lower than the PFS seen with standard chemotherapy (1.4-3.9 vs. 5.1-5.9 months, respectively), with no statistical differences; nevertheless, PFS comparisons between common and uncommon mutations with EGFR-TKIs showed a significant difference (8.5-16.5 vs. 1.4-3.9 months; $p < 0.001$) (Table 2). In our previous study, median PFS in common mutations was 16.6 months (95% CI: 12-21.1) vs. 3.9 months (95% CI: 1.9-5.9) in rare mutations ($p < 0.001$).

Overall survival

In phase III clinical trials, the patients with common mutations treated with EGFR-TKIs showed a longer OS compared to those who received standard chemotherapy (30.5-33.3 vs. 18.1-23.6 months; p < 0.001) (Table 1). Data from case series where common versus uncommon mutations to EGFR-TKIs were compared, showed common mutations had a longer OS while still different between each subgroup of uncommon mutations (19.3-29.3 vs. 4.8-11.9 months, respectively; p < 0.001) (Table 2). In our previous trial we found an important difference in median PFS between patients with a deletion in exon 19 and those with the exon 21 L858R mutation (21.4; 95% CI: 11.4-31.4 vs. 13.9; 95% CI: 8.3-19.5, respectively; p = 0.006). Nonetheless, differences between OS were not statistically significant.

DISCUSSION

Similar results were reported in a randomized phase II study in patients with mutated EGFR, which compared erlotinib versus erlotinib plus bevacizumab, showing that patients with the exon 19 deletion had a better PFS than those with the L858R mutation[28]. Moreover, a pooled analysis of two phase III studies (LUX-Lung 3 and LUX-Lung 6) showed that patients with common EGFR mutations had improved OS if treated with afatinib when compared to third-line standard chemotherapy; this difference was particularly more prominent in patients with exon 19 deletion compared with patients with exon 21 mutation[29].

Information describing the sensitivity and resistance of rare mutations to EGFR-TKIs is limited. A study carried out by Maemondo, et al. compared chemotherapy versus gefitinib in Asian NSCLC patients with EGFR mutations, finding a PFS of 10.8 months with gefitinib; however, only 6.1% of patients with rare EGFR mutations were included[22]. A phase III study compared afatinib versus cisplatin plus pemetrexed as first-line treatment for NSCLC patients with EGFR mutations; in this trial, only 11.3% of the patients presented rare mutations. The PFS was 11.14 months in all patients using afatinib. However, PFS in patients with rare mutations was not reported, suggesting a decreased sensitivity of patients with rare mutations to EGFR-TKIs[24]. In a recent study published by Watanabe, et al., gefitinib versus chemotherapy in NSCLC patients with the uncommon EGFR G719X and L861Q mutations was compared[26]. The OS was significantly shorter among patients with uncommon EGFR mutations (G719X or L861Q) compared with the OS of those with common EGFR mutations (12 vs. 28.4 months; p = 0.002). The PFS in the chemotherapy group to common and uncommon mutations was not statistically significant (5.4 vs. 5.9 months, respectively; p = 0.847), but in the TKI group the PFS for common versus uncommon mutations was 11.4 vs 2.2 months, respectively (p < 0.001). This study also considered OS to chemotherapy in common and uncommon mutations (28 vs. 22.8 months, respectively; p = 0.358); on the other hand, when we searched for the OS to TKI in the common and uncommon mutations, the OS was statistically significant (29.3 vs. 11.9 months, respectively; p < 0.001) (Table 2). Although this study considers uncommon mutations, it only compares two types (G719X, L861Q), considered “sensitizing mutations”. In our previous study, we found that the most frequent mutations were exon 19 and L858R deletions (Table 3), similarly to those previously reported[12,14]. Only 20.5% of all patients had rare mutations, with G719X being the most frequent in this group; among the patients with EGFR mutations, this mutation has a prevalence ranging from 1 to 4%[30]. We also found complex mutations in 8% of patients, although 6.9% had a combination of common EGFR mutations according to the other studies.

According to our previous findings, high-grade micropapillary and solid histology are the only clinical factors associated with a higher frequency of rare or complex mutations. To the best of our knowledge, no trial has reported this association. However, it is known from different series validating the new classification of adenocarcinomas that the

Table 3. Epidermal growth factor receptor mutational profile of lung adenocarcinoma patients[29]

Variable	Frequency
Type of EGFR mutations	
– Common mutations	
• Deletion exon 19 or exon 21 L858R	150 (79.5%)
– Rare mutations.	38 (20.4%)
• Rare single mutations	23 (12.4%)
• Rare complex mutations	15 (8.0%)
• Rare complex mutations with Del exon 19 or exon 21 L858R	13 (6.9%)
• Rare complex mutations without Del exon 19 or exon 21 L858R	1 (1.1%)
EGFR common mutations	
– Exon 19 (Deletion)	105 (55.8%)
– Exon 21 (L8585R)	45 (23.9%)
EGFR rare mutations	
– Sensitizing mutations	
• Exon 18 (G719X)	11 (5.9%)
• Exon 21 (L861Q)	2 (1.1%)
– Intermediate Sensitivity	
• Exon 20 (S768I)	5 (2.7%)
– Non-sensitizing mutation	
• Exon 20 (T790M)	5 (2.7%)
• Exon 20 insertion	0 (0%)
EGFR rare complex mutations	
– Exon 18 G719X and exon 20 S768I	1 (0.5%)
– Exon 19 Deletion and exon 20 T790M	3 (1.6%)
– Exon 19 Deletion and exon 20 S768I	2 (1.1%)
– Exon 19 Deletion and exon 21 L858R	3 (1.6%)
– Exon 20 S768I and exon 20 T790M	1 (0.5%)
– Exon 20 S768I and exon 21 L858R	1 (0.5%)
– Exon 20 T790M and exon 21 L858R	3 (1.6%)
– Exon 20 S768I, exon 20 T790M and exon 21 L858R	1 (0.5%)
KRAS mutation	
– Negative	184 (97.9%)
– Positive	4 (2.1%)

EGFR: epidermal growth factor receptor.

prognosis is worse in patients bearing high-grade histology tumors, such as micropapillary or solid tumors, during the early stages of disease[31-35]. We found that 49% of EGFR mutations were related to wood-smoke exposure, an association that we have previously reported. Wood-smoke exposure is a risk factor that is almost exclusive to developing countries; it is estimated that up to 16% of households in some places in Mexico use this type of fuel for heating and cooking[3].

Previous studies have shown that patients with common mutations, such as EGFR mutation in exon 20, tend to have a lower response rate to EGFR-TKIs. Wu, et al. reported a 25% response rate in 23 patients with EGFR exon 20 mutation using gefitinib[36]. Similarly, when the same group of researchers compared the response to EGFR-TKIs based on the types of mutation, they showed that the response rates were 74.1% in patients with single classical mutations, 60% in patients with uncommon mutations in combination with deletions in exon 19 or L858R, 20% in patients with uncommon mutations without concurrent deletion in exon 19 or L858R, and 0% in patients with an insertion in exon 20[27]. We obtained similar results, confirming the reports that patients with rare mutations (single or complex) have lower response rates (32.4%) compared to those with common mutations (63.8%). Consistent with the results from the Watanabe[26] and Wu studies[27], our previous study[18] also shows a better PFS and OS in patients with single common mutations than in patients with uncommon mutations. In our PFS and OS analysis we did not include a classical EGFR mutation associated with resistance (T790M), whose exact resistance mechanism has not yet been clarified and whose clinical impact has not been systematically investigated in any study to date[37]. These mutations may interfere with the site where TKIs bind[38]. Despite the lack of differences in the frequency of common mutations in both genders, we found a longer PFS in females using EGFR-TKIs in this study. Moreover, without an increase in response rate, it is known that females have better prognoses than males, possibly due to hormonal influence or greater tolerance to chemotherapy[39]. However, this is the first report associating females with better PFS using EGFR-TKIs. The only factor associated with OS was the type of mutation in this population (i.e., common or rare). Differences between common and rare mutations in PFS using EGFR-TKIs were deemed as important because of their impact on OS.

Due to the low frequency of non-common mutations and the heterogeneity of the types of mutations, this warrants the need for a meta-analysis of the relationship between the type of mutation and the response between prognosis and the type of EGFR mutations to help guide the choice of therapy for NSCLC with EGFR mutations.

CONCLUSION

In patients with EGFR mutations, it has been demonstrated that women have better PFS to EGFR-TKIs compared to men, and that rare EGFR mutations are more frequent in high-grade adenocarcinomas than in low-grade tumors. Our review included a significant number of patients with EGFR mutations; most of the studies informed about the status of this mutation, but only few also reported the type of mutation. Our findings suggest that only patients with rare EGFR mutations should receive platinum-based chemotherapy as a first-line treatment due to their low response rates and short PFS in response to EGFR-TKIs. Consequently, EGFR-TKIs could be reserved as a second- or third-line treatment. We are waiting for the subgroup analysis and meta-analysis for uncommon mutations regarding the clinical trials before mentioned.

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