Short Communications

Prevalence of EGFR Mutations and Clinico-Pathological Characteristics of Chilean Lung Cancer Patients

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Abstract

   Background: Lung cancer (LC) is the second leading cause of cancer death in Chile, causing >3,000 deaths every year. Epidemiological LC data in Chile is scarce and scattered. Here, we aimed to quantify the prevalence of Epidermal Growth Factor Receptor (EGFR) gene mutations in a Chilean cancer center. These data may identify individuals that could benefit from targeted therapies such as Tyrosine Kinase Inhibitors (TKIs). **Methods:** A total of 1,405 Biopsies from 1,381 LC patients were retrospectively analyzed retrieving clinical data from EGFR mutants including age, gender, histological type, smoking habits and type of EGFR mutation. We also analyzed overall survival (OS) rates. **Results:** From all patients 21.7% had clinically relevant EGFR mutations, and a median age at diagnosis of 65 years. Most were female (64%), classified as adenocarcinomas (94.5%), and non-smokers/light smokers (93.1%). The most prevalent mutation was exon-19 deletions (50.6%) followed by Leucine-to Arginine 858; OS was 15 months. Clinical follow-up information was available for 83 patients. The use of TKIs in these patients significantly improved OS. **Conclusion:** The prevalence of EGFR mutations in the studied population was 21.7%, comparable to other countries in Latin America. The most frequent EGFR mutation was exon-19 deletion, OS in this group was 15 months, and TKIs significantly improved OS.

Keywords: Lung cancer- overall survival- EGFR mutants- tyrosine kinase inhibitors

Introduction

   Worldwide, lung cancer (LC) is the leading cause of cancer death. Only in 2015, a total of 1.8 million cases were diagnosed causing 1.5 million deaths (Raez et al., 2017); LCs can be subdivided into two categories: small cell lung cancers (SCLC) or non-small cell lung cancers (NSCLC). The vast majority (80-85%) of cases is categorized as NSCLCs (Jänne et al., 2005), and during the last decade, studies have identified a subgroup of NSCLC patients that harbor Epidermal Growth Factor Receptor (EGFR) gene mutations. These patients also display a positive response to targeted therapies such as Tyrosine Kinase Inhibitors (TKIs), increasing patient survival rates. The majority of these EGFR-activating mutations (90%) correspond to the Leucine-to-Arginine substitution at position 858 (L858R) in exon 21 and exon-19 gene deletions (Han et al., 2017). Another relevant mutation is Threonine-to-Methionine substitution at position 790 (T790M); although studies report its frequency is rather low in untreated patients, it is present in almost 50% of TKI- resistant NSCLC cases, suggesting a role in TKI-acquired resistance (Westover et al., 2018). Other clinically relevant mutations include exon-20 insertions and Glycine substitutions at position 719 (G719X) in exon 18.

   Most epidemiological studies on the prevalence of EGFR mutations have been conducted in Europe and North America. In sharp contrast, studies in Latin America are scarce. In general, these studies have documented striking differences across geographic areas and/or ethnic groups (Midha et al., 2015). Indeed, the prevalence of EGFR somatic mutations in Asian NSCLC patients is about 60%, compared to 10-15% in Caucasians (Tan et al., 2016).

   In Chile, LC is responsible for more than 3,000 deaths every year and currently ranks as the second leading cause of cancer mortality. Despite this, the prevalence of EGFR mutants in the Chilean population remains largely unknown. Herein, we report the prevalence of EGFR gene mutations within a group of 1,385 Chilean LC patients in the Cancer Center at the Red de Salud UC-CHRISTUS. A total of 300 patients displayed EGFR mutations. Reported mutations include those with clinical relevance such as L858R, T790M, G719X, exon-19 deletions, or exon-20 insertions. We also report basic demographic characteristics of patients with EGFR mutations including

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age, gender, histological type and smoking habits.

Materials and Methods

Patient biopsies and medical records

This is a descriptive cross-sectional study that involved a total of 1,405 studied biopsies from 1,381 patients diagnosed with LC over the period 2010-2017. Patients were diagnosed at the Red de Salud UC-CHRISTUS. Clinical data including age at diagnosis, gender, histological type, smoking habits and EGFR mutations were extracted from medical records or biopsy reports. Histological type and EGFR status were determined by pathologists using standard techniques and two DNA amplification kits: 1) the ARMS (Amplification Refractory Mutation System) kit by QIAgen (Cat #ID874101), or 2) the cobasTM system (Cat # 07248563190) from Roche Diagnostics, following manufacturer's protocol.

Study approval

The institutional review board and the ethics committee at the Pontificia Universidad Catolica de Chile (PUC) approved this research on resolution #17-100-400-5 dated on November 7th, 2017. All patients were anonymized and no sensitive data were collected for the purpose of this study. The study adhered to the Declaration of Helsinki and Good Clinical Practice guidelines.

Data analysis

Survival rates were calculated using date of diagnosis (biopsy) until the last date of clinical follow up or the date of death for every patient. Clinical data, survival rates along with EGFR status were used for statistical analysis in GraphPad Prism v 7.0. Overall survival data were analyzed using the Kaplan Meier method and statistical significance was set at p=0.05.

Results

Prevalence of EGFR mutations in Chilean LC patients

A total of 1,405 biopsies from 1,381 LC patients were accessed and analyzed for this study. Within this group 703 were female (50.91%) and 678 males (49.09%), median age at diagnosis was 65 years (range: 19-90). According to biopsy reports, 21.7% (300 out of 1,385) of these patients had clinically relevant EGFR mutations.

Clinico-pathological characteristics of EGFR mutants

Median age at diagnosis of EGFR mutants was 65 years (range: 31-85). A summary of clinico-pathological characteristics of these patients is presented in Table 1. In general, activating EGFR mutations are significantly more frequent in females and non-smokers (Jänne et al., 2005; Tseng et al., 2017). As expected, EGFR mutants were predominantly female (64%) and classified as non-smokers or light smokers (93.1%). As there is no consensus on a cutoff value that defines a category for "light smoker", we opted for the criteria established by the National Lung Screening Trial that set the limit at less than 30 cigarette packs per year (Aberle et al., 2011). Also as
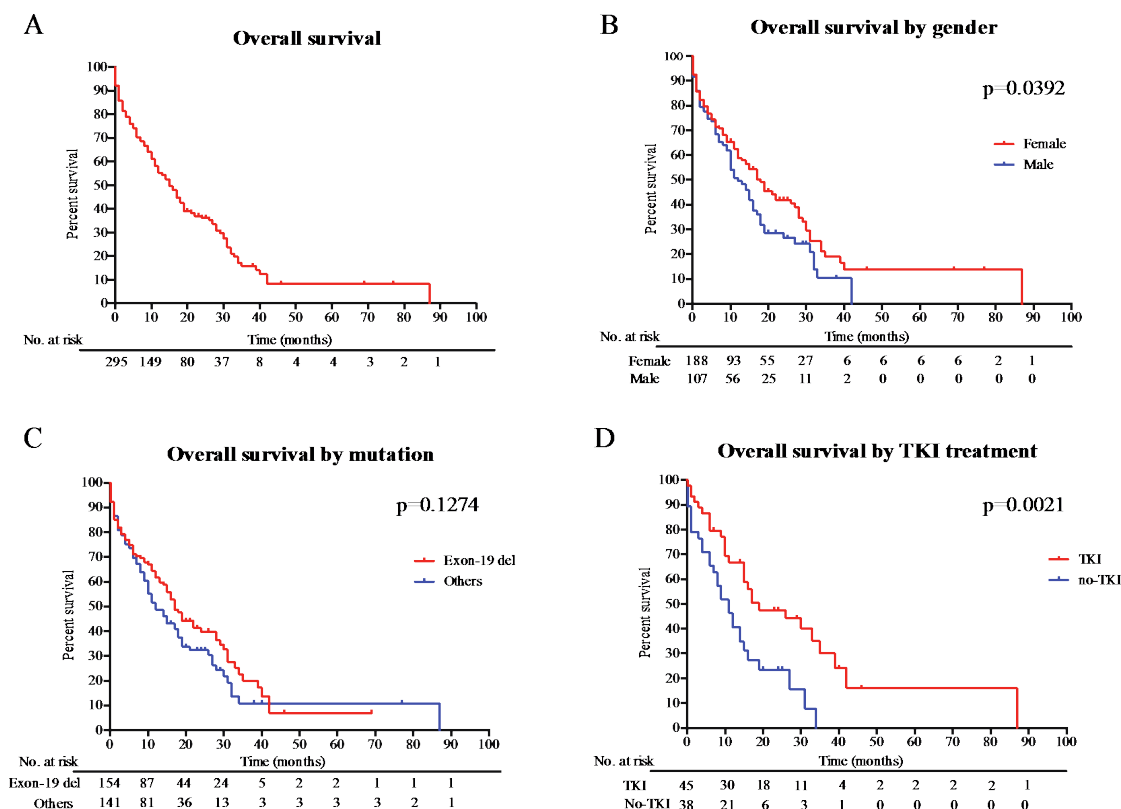

Figure 1. OS Rates in EGFR Mutants. A. Kaplan-Meier curve for all EGFR mutants (n=295). B. Kaplan-Meier curve for female and male LC patients (n=295). C. Kaplan-Meier curve for EGFR mutations, comparing exon-19 deletion against other mutations screened (n=295). D. Kaplan-Meier curve for patients with clinical follow-up that did (TKI) or did not receive TKI treatment (no-TKI), (n=83).

EGFR Mutations Prevalence in Chilean Lung Cancer Patients

Table 1. Basic and Clinico-Pathological Characteristics of Patients with EGFR Mutations

Variable	n (%)
Analyzed biopsies	308
Total patients	300 (100)
Gender†	300 (100)
Male	108 (36.0)
Female	192 (64.0)
Histological type	111 (100)
Adenocarcinoma	105 (94.5)
Squamous	3 (2.7)
Adeno-squamous	3 (2.7)
EGFR mutations†	300 (100)
Exon-19 deletion	155 (50.6)
L858R	89 (28.9)
T790M de novo	5 (1.6)
Exon-20 insertion	9 (2.9)
G719X	10 (3.2)
Other	32 (12.7)
Smoking habits	87 (100)
Non-smoker/light smoker	81 (93.1)
Heavy smoker	6 (6.8)

†, 5 patients had gender and biopsy-reported; EGFR mutation data but no other information in their medical records (n = 295).

expected, most patients had NSCLC (Jänne et al., 2005) adenocarcinomas (94.5%) and the most frequent EGFR mutation was exon-19 deletion (50.6%), followed by L858R (28.9%), similar to other studies in LA that report a 47.1% and 37.3% for exon-19 deletion and L858R, respectively (Arrieta et al., 2015).

Survival rates in EGFR mutants

Next, as shown by (Figure 1) we analyzed OS rates in EGFR mutants with complete medical records (n=295) according to gender and type of EGFR mutation. Please note that 5 patients were excluded from survival analyses due to missing data (see Table 1). Median OS rates for the entire group of 295 patients harboring EGFR mutations, including patients at all stages of disease (I through IV), was 15 months (Figure 1A). Unfortunately only a small fraction of patients had clinical follow up data (28.1%, 83 out of 295); within this group, 45 received TKI treatment (54.2%, 45 out of 83). Therefore, a significant percentage of patients were probably undertreated, alternatively they received unspecified treatment or palliative care, this could partially explain the observed discrepancy in OS after comparison with other studies, this is further discussed in the next section. Then, we calculated OS according to gender (Figure 1B). As expected (Tseng et al., 2017), median OS in females was 18 months compared to 12 months among males (Log Rank p=0.0392).

Figure 1C shows that median OS for patients with exon-19 deletions was 17 months compared with 12 months for other mutations (Log Rank p=0.1274). Finally, as shown in Figure 1D, patients that received TKI treatment had significantly better OS rates (Log Rank p=0.0021, median OS: 19 months versus 11 months).

Discussion

Like most malignancies, LC is a highly heterogeneous disease. Accordingly, previous reports have demonstrated the prevalence of EGFR is highly heterogeneous across geographical regions and ethnic groups (Midha et al., 2015; Steuer et al., 2016). Recent studies suggest LC is public health concern in LA with an incidence still on the rise (Raez et al., 2018). Also, several reports suggest a high prevalence of EGFR mutants among Asians, that ranges from 50 to 60% (Shi et al., 2014). In contrast, the prevalence is much lower in Caucasians fluctuating between 10-15% (Tan et al., 2016). Within LA the highest prevalence of EGFR mutants is found in Peru (37.0-51.1%) (Arrieta et al., 2015; Lopez-Chavez et al., 2016), followed by Mexico (34.3%) (Arrieta et al., 2015), Costa Rica (31.4%) (Arrieta et al., 2015), Panama (27.3%) (Arrieta et al., 2015), Colombia (24.7%) (Arrieta et al., 2015), Uruguay (18.3%) (Steuer et al., 2016) and Argentina (14.4%) (Arrieta et al., 2015). Accordingly, the prevalence reported here for Chile (21.7%) is comparable to those in LA. We speculate that the observed differences in prevalence of EGFR mutants within LA could be attributed to the genetic composition in each individual country; indeed, Peru has the second largest population of Asian descent in LA surpassed only by Brazil (Lopez-Chavez et al., 2016). In contrast, a population of European descent dominates other countries with lower prevalence of EGFR mutants including Argentina, Uruguay and Chile (Berois et al., 2017; Eyheramendy et al., 2015).

Our analyses on patient survival showed a trend towards better OS in patients with exon-19 deletions versus other EGFR alterations (Figure 1C). Indeed, Previous studies have demonstrated that, among all EGFR mutations, exon-19 deletions are associated to better outcomes compared to other alterations (Choi et al., 2018). However, the observed differences in our study did not reach statistical significance, as explained above this could be due to undertreated patients that did not receive TKI treatments derived from its high cost. Recently, two large phase III clinical trials on EGFR mutation+ NSCLC patients compared afatinib as TKI treatment versus cisplatin-based chemotherapy plus pemetrexed (LUX-Lung 3) or gemcitabine (LUX-Lung 6) and demonstrated that TKI improved median OS by 12.1 and 13 months respectively in patients with exon-19 deletions (Yang et al., 2015). Unfortunately, while the results of our study validate the above-mentioned studies, methodological differences limit the extent of these results.

The arrival of EGFR targeted therapies has significantly improved the survival of NSCLC patients in recent decades (Choi et al., 2018). Despite this, the access to targeted therapies in Chile has been somewhat limited, mainly due to its high costs (Skinner et al., 2018). Our study here renders an estimated prevalence of EGFR mutations in the Chilean population and therefore it might help to delineate public policies in order to rationalize

the use of TKIs in patients that carry EGFR mutations, improving their clinical outcomes.

Given the descriptive cross-sectional nature of this study, it has certain limitations. First, medical records and biopsy reports for some patients were incomplete and information in some cases was missing or not available. Second, EGFR mutation analyses were performed at the Red de Salud UC-CHRISTUS, however many patients received treatment and/or clinical follow up at different institutions. Consequently, information for these patients could not be retrieved. For the purposes of this study, we assumed that the date of diagnosis was the same as the date of the biopsy; therefore OS rates were estimated using the date of diagnosis and the date of death at the national identification system in Chile. Finally, and perhaps the most critical limitation of our study clinical follow up and treatment information were only available for 83 out of 300 patients. Within this group, 45 received TKI treatment, which might explain some of our findings.

To the best of our knowledge, this is the first report on the prevalence of EGFR mutations in Chilean NSCLC patients. The reported 21.7% of EGFR mutations is comparable to other countries in LA. Importantly, this study might help to rationalize the use of EGFR targeted therapies in patients that carry EGFR mutations in Chile. Other patient characteristics assessed, including gender, histological type, frequency of EGFR mutations and response to TKIs were also similar to previously published studies. Future prospective studies in the Chilean population shall further expand our findings.

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