The impact of erlotinib use in non-small-cell lung cancer patients treated in a private reference general hospital and in a private cancer clinic from 2005 to 2011

O impacto do uso do erlotinibe em pacientes portadores de neoplasia de pulmão de não pequenas células tratados em um hospital geral de referência e clínica particular de oncologia no período de 2005 a 2011

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ABSTRACT

Objective: To report the demographic data and clinical outcomes of non-small-cell lung cancer patients exposed to erlotinib in any line of treatment. **Methods:** This was a retrospective cohort study of non-small-cell lung cancer patients from a reference general hospital and a private oncology clinic, who received erlotinib from 2005 to 2011. Statistical analysis was performed and we evaluated demographic data and response to treatment, by correlating the results of this first cohort published in Brazil with results of current literature. **Results:** A total of 44 patients were included; 65.9% were diagnosed with adenocarcinoma, and 63.6% had metastatic disease. The mean age was 63.3 years. The median follow-up was 47.9 months. Epidermal growth factor receptor mutation screening was performed in 22.7% of patients (n=10), with mutation present in 30% of patients. The median overall survival was 46.3 months, and there was a higher probability of survival at 60 months for females compared to males (29.4% *versus* 15.8%; p=0.042). The other variables did not present significant statistical difference. **Conclusion**: We collected the largest cohort of patients with non-small-cell lung cancer who have used erlotinib in Brazil to date, and demonstrated that outcomes of patients treated at our clinic during the study period were consistent with the results of current literature in similar patients.

Keywords: Carcinoma, non-small cell lung; Genes, erbB-1; Receptor, epidermal growth factor; Protein kinase inhibitors; Antineoplastic agents

RESUMO

Objetivo: Relatar as características demográficas e a evolução de pacientes com neoplasia de pulmão de não pequenas células que receberam erlotinibe em qualquer linha de tratamento. **Métodos:** Coletamos retrospectivamente dados de pacientes portadores de neoplasia de pulmão de não pequenas células que receberam erlotinibe em qualquer linha de tratamento em um hospital geral de referência e em uma clínica particular de oncologia em São Paulo, no período de 2005 a 2011. Foi realizada a análise estatística e foram avaliados aspectos demográficos e resposta ao tratamento estabelecido, correlacionando os resultados dessa primeira coorte publicada no Brasil com resultados da literatura vigente. **Resultados:** Foram avaliados 44 pacientes, dos quais 65,9% eram portadores de adenocarcinoma e 63,6% tinham doença metastática. A média de idade foi de 63,3 anos. O seguimento mediano foi de 47,9 meses. A pesquisa de mutação do receptor do fator de crescimento epidérmico foi realizada em 22,7% dos pacientes (n=10), resultando positiva em 30% dos avaliados. A sobrevida global mediana foi de 46,3 meses, e observou-se uma probabilidade maior de sobrevida em 60 meses para o grupo feminino, quando comparado ao grupo masculino (29,4% *versus* 15,8%; p=0,042). As demais variáveis não apresentaram diferença estatística significativa. **Conclusão:** Coletamos a maior sequência de pacientes com neoplasia de pulmão de não pequenas células que fizeram uso de erlotinibe no Brasil até a data vigente e demonstramos que a evolução dos pacientes tratados no período avaliado teve resultados concordantes com os da literatura vigente em pacientes semelhantes.

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Descritores: Carcinoma pulmonar de células não pequenas; Genes erbB-1; Receptor do fator de crescimento epidérmico; Inibidores de proteínas quinases; Antineoplásicos

INTRODUCTION

Lung cancer is the primary cause of death by cancer in men and women worldwide.[1] In Brazil, it is estimated that approximately 16,400 new cases of lung cancer in men were found in 2014. In 2011, the gross mortality rate by lung cancer in the country was 14.54 per 100 thousand men.[2] Non-small-cell lung cancer (NSCLC) accounts to 80% of lung neoplasms, and the World Health Organization classification divides it according to histology. The main types are adenocarcinoma, squamous cell carcinoma, large-cell carcinoma.[3]

The standard treatment for advanced NSCLC (clinical stage IIIb or higher) is based on chemotherapy with platinum (combinations of two drugs), or target-drugs, depending on the presence or not of mutations present in the neoplastic cell.[4-6]

The epidermal growth factor receptor (EGFR) has tyrosine kinase action and regulates apoptosis, angiogenesis and cellular adhesion. Superexpression or aberrant expression of the EGFR (HER1) can be found in some cases of NSCLC, most commonly in non-smoking patients with adenocarcinoma.[7-9]

Erlotinib is a selective of EGFR tyrosine kinase inhibitor. It reduces autophosphorylation of EGFR in intact tumor cells and the proliferation of the EGFR-dependent cell, blocking the start of the cellular cycle in the G1 phase. It was approved by the Food and Drug Administration for treatment of locally advanced or metastatic NSCLC in 2004. Monotherapy with this drug proves to be effective and more active for patients with NSCLC and mutated EGFR.[10-12]

The use of erlotinib has been shown to be effective in the treatment of NSCLC with mutated EGFR, thus rousing great interest in factors for a better response and better survival. Various factors have been studied related to the greater or lesser efficacy of the medication. The presence of mutations such as EGFR and the Kirsten rat sarcoma viral oncogene, known as KRAS, as well as the skin rash when initiating the medication in patients with non-mutated EGFR, demographic factors such as Asian race, presence or absence of smoking are considered independent factors for response to erlotinib.[13-15]

Patients with EGFR-activating mutations, such as L858R in exon 21 and deletions in exon 19, show improvement in symptoms and a higher response rate with the use of erlotinib. Investigation of the EGFR mutation is essential for the decision to initiate use of erlotinib, and its absence is justified only by the impossibility of performing it, such as, for example, due to scarcity of material. This mutation was found with greater frequency in non-smoking patients with the adenocarcinoma histological subtype, which, presented with greater sensitivity to gefitinib and erlotinib in one study.[5,7,8,10,15,16]

The skin rash also showed a direct relation with response to medication, increasing the objective response and affording greater survival in patients without the EGFR mutation, but not in patients with mutations. Elderly patients also benefited from the use of erlotinib, but at the cost of greater toxicity, even though it is tolerable in most cases.[13,17-21]

The subgroup of patients that potentially have greatest benefit from the medication includes those with greatest prevalence of EGFR mutations: Asian patients, of the female gender, with adenocarcinoma subtype, and non-smokers.[7-10,13,22-24]

The KRAS gene mutation showed an inverse relation with the response to erlotinib, as well as with the non-coexistence with the EGFR mutation. Treatment with erlotinib in patients with mutated KRAS resulted in worse survival in comparison with the control group, suggesting a possible reduction of responsiveness to erlotinib in the presence of the said mutation.[8,10,19]

OBJECTIVE

To analyze and describe a series of patients with non-small cell lung cancer treated with erlotinib during a period prior to the mandatory investigation of the epidermal growth factor receptor mutation before use of this medication, including retrospective data of overall survival since the diagnosis of metastasis, and histological characteristics and demographic characteristics of the group.

METHODS

We retrospectively collected data from patients with NSCLC who had received erlotinib in any line of treatment in a private reference general hospital and in a private oncology clinic in São Paulo, during the period of 2005 to 2011.

The sample comprised 44 patients. This was a retrospective cohort study, with median follow-up of 47.9 months.

Patients were selected according to the following inclusion criteria: patients with histologically confirmed NSCLC treated in a private reference general hospital and in a private oncology clinic in São Paulo during the period from January 1st, 2005, to December 31st, 2011; 18 years of age or more; use of erlotinib for at least one day; receive erlotinib in any line of treatment.

EGFR mutation investigation was not a criterion for the use of erlotinib, since at the time of the study, this mutation was not mandatory for the use of the medication. The research was conducted in accordance with the personal evaluation of each patient's treating physician.

Exclusion criteria included: patients less than 18 years of age; patients with other active neoplasms, except non-melanoma skin cancer; patient whose physician responsible for the medical record did not work at the organizations, or had not authorized review of the record.

The criterion for disease progression, stable disease, or complete or partial response was based on the personal evaluation of the attending physician of each patient.

Statistical analysis

Statistical analysis of the sample was done by means of absolute and relative frequencies, measures of central tendency (mean and median), and dispersion (standard deviation, minimum, and maximum).

For analysis of overall survival in 60 months, Kaplan-Meier test was used, and the comparison between curves was made by the log-rank test. Overall survival was calculated between the date of diagnosis of metastases until the last status (alive or dead).

For statistical analyses, the Statistical Package for Social Sciences, version 17 for Windows was used.

A descriptive level of 5% ($p \leq 0.050$) was adopted for statistical significance.

Table 1. Demographic and clinical characteristics

Category	n (%)
Sex	
Female	22 (50.0)
Male	22 (50.0)
Age, years	
≤60	22 (50.0)
>60	22 (50.0)
Ethnicity*	
White	33 (75.0)
Non-white	11 (25.0)
History of neoplasm	
Yes	5 (11.9)
No	37 (88.1)
Smoker	
Yes	14 (33.3)
No	28 (66.7)
Histological type	
Adenocarcinoma	29 (65.9)
Epidermoid carcinoma	8 (18.2)
Large-cell carcinoma	2 (4.5)
Others	5 (11.4)
Clinical staging at diagnosis	
IA	3 (6.8)
IIB	1 (2.4)
IIIA	6 (13.6)
IIIB	6 (13.6)
IV	28 (63.6)
Status at the time of analysis	
Alive and with disease in remission	1 (2.3)
Alive and with disease in activity	2 (4.5)
Alive and with stable disease	8 (18.2)
Death with unknown relationship	5 (11.4)
Death by cancer	26 (59.1)
Death by other causes	2 (4.5)
Total	44 (100.0)

* There are unknown values.

RESULTS

Forty-four patients were evaluated, 65.9% of them diagnosed with adenocarcinoma, and the majority of patients (63.6%) had stage IV neoplasms at the first visit. The characteristics of patients, tumors, and the first treatment are displayed on table 1. All patients were treated at a private organization.

History of neoplasm was reported in five patients, including thyroid cancer (papillary) in one patient; bronchioalveolar cancer in one patient; cervical cancer in one patient; breast and colon cancer in one patient.

The mean age of these patients was 63.3 years (standard deviation of 11.3 years), median of 61.1; minimum 43.5, and maximum, 86.5 years. Median follow-up was 47.9 months, varying from 6.78 to 95.69 months, as of the date of the pathological study until the final status. In the overall survival analysis, the median time was 46.3 months, varying from 6.6 to 144.8 months.

In the overall survival analysis, a statistically significant difference was noted between sexes (Table 2).

There was a greater probability of 60-month survival for the female group when compared to the males (29.4% *versus* 15.8%; p=0.042). The other variables showed no statistically significant difference (Figures 1 and 2).

Table 2. Overall survival, as per demographic and clinical characteristics

Variable	Cases (n)	Deaths (n)	Overall survival (%)			p value
			12 m	36 m	60 m	
Overall survival	44	33	95.5	81.1	23.3	-
Sex						
Female	22	17	95.5	95.5	29.4	0.042
Male	22	16	95.5	65.8	15.8	
Age (years)						
≤60	22	14	95.5	85.1	22.3	0.288
>60	22	19	95.5	77.3	23.2	
Ethnicity						
White	33	25	93.9	84.8	21.3	0.995
Non-white	11	8	100.0	66.3	26.5	
Smoking						
Yes	14	8	100.0	83.6	*	0.847
No	28	23	92.9	78.1	21.6	
Comorbidities						
Yes	21	17	95.2	85.4	18.3	0.953
No	21	14	95.2	75.3	14.3	
Histological type						
Carcinoma + other	15	13	93.3	73.3	16.3	0.304
Adenocarcinoma	29	20	96.6	85.2	26.7	
Clinical staging at diagnosis						
IA and IIB	4	3	100.0	75.0	0.0*	0.253
IIIA and IIIB	12	9	100.0	75.0	0.0	
IV	28	21	92.9	84.7	33.1	

*No patient of this group reached 60 months of survival. Kaplan-Meier test.

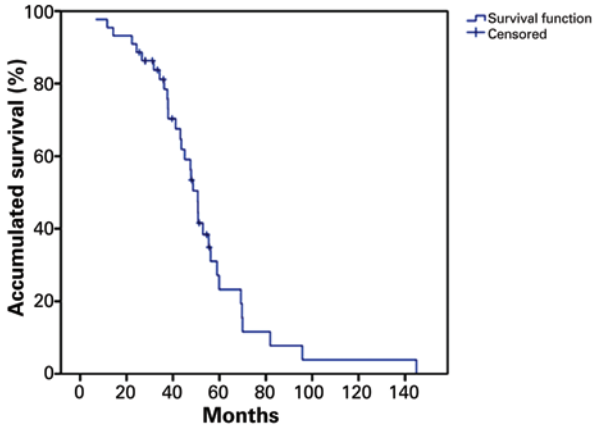

Figure 1. Overall survival (%) in months. Kaplan-Meier test

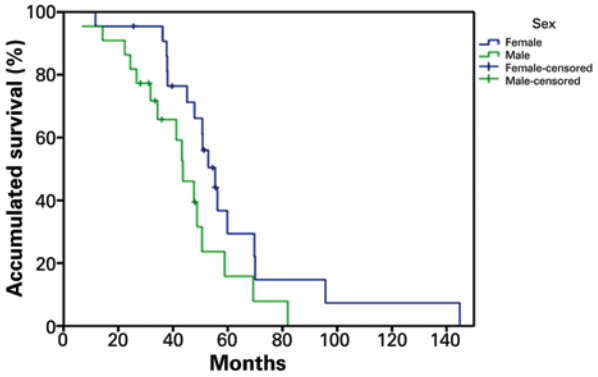

Figure 2. Overall survival (%) in months, per gender. Kaplan-Meier test

EGFR mutation investigation was done in only 22.7% of the patients (n=10), with a positive result in 30% of the patients evaluated, as is seen on table 3.

Table 3. Patients tested for mutation of the cellular receptor of the epidermal growth factor receptor

EGFR	n	Investigated (%)	Total patients (%)
Mutated	3	30.0	6.8
Non-mutated	7	70.0	15.9
Total investigated	10	100.0	22.7
EGFR not known	34	-	77.3
Total patients	44	-	100

EGFR: epidermal growth factor receptor.

In the analysis of time to treatment failure analysis, a mean of 169.3 days (standard deviation of 144.9) was noted, with a median of 125 days, minimum time of 19 and maximum of 533 days. As to use of erlotinib in different lines, there was no statistically significant difference (p=0.745) in survival. The probabilities of survival in 60 months were for the first, second, and third lines of treatment, 17.1%, 41.6%, 29.6%, and 37.5% (Table 4), respectively.

Table 4. Patients who used erlotinib, according to lines of treatment and their respective survivals

Lines of treatment	Cases n (%)	Deaths (n)	Survival 60 months* (%)
First	7 (15.9)	6	17.1
Second	20 (45.5)	11	41.6
Third	9 (20.5)	8	29.6
Fourth	8 (18.2)	8	37.5
Total	44 (100.0)	33	

*Kaplan-Meier test.

DISCUSSION

We conducted a retrospective study in NSCLC patients submitted to the use of erlotinib, treated in a private reference general hospital and a private oncology clinic in São Paulo during the period of January 2004 to December 2011, with a median follow-up of 47.9 months.

In our study we found a greater probability of survival in 60 months for patients of the female gender when compared to the male group (29.4% *versus* 15.8%; p=0.042). EGFR investigation was performed on a small portion of the patients (n=10; 22.7%), and mutation was present in 6.8% of the total number of patients (n=3; 30%). The use of erlotinib was made in patients not selected as to the EGFR status for most of the patients, since this investigation was not demonstrably necessary for the use of this medication at that time.

We found five patients with history of neoplasm. A hypothesis for such a high number is that the institutions where the study was carried out are reference centers for the treatment of neoplasms, and we expected to find patients with a personal and familiar history of neoplasms.[25]

In these patients we observed a median survival of 46.3 months, varying from 6.6 to 144.8 months, that is, a little bit above the median found in literature in patients with NSCLC using erlotinib who were not selected as to EGFR.[15] We also noted a statistically significant difference between genders, with a greater probability of survival in 60 months for the female group (29.4% *versus* 15.8%; p=0.042). We should point out that such results include patients not selected as to their EGFR mutation status, since this analysis was not yet proved essential for the use of the medication in the period when the patients were treated.

In our study, the use of erlotinib in different treatment lines did not show a statistically significant difference (p=0.745) in terms of survival. More patients used the second or subsequent lines of treatment, since use as first line therapy was established after the beginning of erlotinib sales. The apparent greater survival in second line treatment compared to the first line did not show statistical significance considering the low number of patients.

Despite the findings, our study had limitations related to its retrospective nature and the small number of patients, impeding greater statistical significance. It is important to point out the lack of information as to the EGFR mutation status in the majority of patients, which has a great influence on the response to the treatment concerned.

CONCLUSION

Our study included the largest sequence published in Brazil to date, including patients with non-small-cell lung cancer who used erlotinib. It demonstrated that the clinical progression of patients treated in our clinic and hospital, during the period analyzed, had results that agreed with those of current literature in similar patients.

Given the importance of the data presented and limitations, we plan to carry out a new follow-up of these patients as well as of new patients who used erlotinib for non-small-cell lung cancer in the following years. The reason is we will have a growing number of patients who used this medication in the subsequent years when the drug was more widely present in the country.

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